Headwinds in Breast Cancer Research: The Case for Pragmatic Radiotherapy De-escalation Studies

Lior Z. Braunstein, MD[1]; Melissa P. Mitchell, MD, PhD[2]; Atif J. Khan, MD[3]; William M. Sikov, MD[4]; Eleftherios P. Mamounas, MD[5]; Thomas B. Julian, MD[6]; and Norman Wolmark, MD[7]

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The Iterative Nature of Cancer Therapy

The evolution of cancer treatment is a continuous process of multidisciplinary refinement: Therapeutic gains achieved by one modality often render previously essential treatments less critical or even obsolete. This iterative paradigm is evident across oncology. Radical mastectomy gave way to breast-conserving surgery (BCS) when combined with radiotherapy, which itself may be dispensable in selected patients; in rectal cancer, chemoradiation is now routinely withheld among responders to neoadjuvant therapy, and some forego resection entirely following immunotherapy; and manifold pediatric oncology studies have focused on de-escalation to reduce long-term morbidity while maintaining disease control. These transitions did not occur through spontaneous consensus but through deliberate scientific inquiry that challenged established practices, often through rigorously designed single-arm studies when randomization proved impractical or ethically challenging.

Underlying de-escalation research in breast cancer is the premise that, as systemic therapies improve and become more effective at controlling disease, incremental benefits of local-regional treatments may diminish to the point at which their toxicity, cost, and inconvenience outweigh their marginal outcomes.

This concept is not novel. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis[1] demonstrated that although post-lumpectomy radiotherapy reduces relative risk of local recurrence by approximately 50%, the absolute benefit varies substantially. When systemic therapy has reduced local recurrence to exceptionally low levels, the absolute benefit of radiotherapy necessarily becomes negligible.

Multiple landmark trials have successfully established radiotherapy omission as standard practice in carefully selected low-risk populations, such as older patients with small, hormone receptor-positive breast tumors,[2,3] or patients with "good-risk" ductal carcinoma in situ.[4] The single-arm LUMINA,[5] IDEA,[6] and PRECISION[7] trials used molecular profiling to further identify low-risk luminal A tumors (T1N0), for which radiotherapy could be safely omitted with low local recurrence rates. These studies fundamentally altered perception because they recognized that treatment standards must evolve in parallel with advances in patient selection, systemic therapy, and our understanding of tumor biology.

Successful single-arm de-escalation studies share critical design features distinguishing them from hypothesis-generating pilot studies: rigorous patient selection criteria defining specific low-risk populations with high pretest confidence, prespecified endpoints and statistical thresholds for acceptability, adequate sample sizes and follow-up duration, robust safety monitoring, and compelling biological rationale grounded in contemporary treatment understanding.

Several de-escalation trials have anticipated randomization challenges: DESCARTES[8] evaluates radiotherapy omission among patients achieving pathologic complete response (pCR) post-neoadjuvant therapy, recognizing that such responders represent a biologically favorable cohort. ROSALIE[9] examines radiotherapy omission among node-negative patients

undergoing lumpectomy and achieving pCR, using a pragmatic single-arm design that acknowledges the difficulties of randomly assigning patients away from established treatment (Table 1).

The question before us is not whether such evolution should occur, but rather how we design and execute studies capable of generating the essential evidence necessary to inform these transitions, particularly when studies encounter formidable headwinds.

The HERO Trial: A Case Study in De-escalation Challenges

NRG-BR008, known as the HERO trial (Human Epidermal Growth Factor Receptor 2 [HER2] Radiation Optimization),[10] exemplifies both the scientific rationale for treatment de-escalation as well as the practical challenges imperiling such research.

HER2-positive breast cancer treatment has been transformed by targeted therapies. The APT trial[11,12] demonstrated a 7-year locoregional recurrence-free survival of 99.0% among patients with small, node-negative HER2-positive tumors treated with adjuvant paclitaxel and trastuzumab, who underwent breast-conserving therapy plus radiotherapy. Confirmatory results from ATEMPT[13] showed a 5-year invasive disease-free survival of 97%. These outcomes rival or exceed those of any breast cancer subtype studied to date.

APT also illustrates the nuances of treatment optimization. Often cited as a de-escalation study, APT actually represented treatment *escalation* for approximately 19% of patients with pT1a tumors (who typically received no systemic therapy), and treatment de-escalation for the remaining 81% with larger tumors (who typically received more intensive regimens such as taxotere, carboplatin, and herceptin or doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab). Notably, the randomized adjuvant trastuzumab trials had not specifically included the smaller, node-negative population, and thus the intensity of systemic therapy these patients received in practice often reflected clinical extrapolation rather than established evidence. Despite this mixed approach (or perhaps because of it), APT established a new standard of care through a single-arm design, demonstrating that nonrandomized studies with rigorous selection criteria, prespecified endpoints, and compelling biological rationale can fundamentally alter practice.

If one accepts the multiply reproduced EBCTCG meta-analysis findings that adjuvant radiotherapy approximately halves the risk of local recurrence,[1] then the APT cohort might have experienced a <4% local recurrence rate had radiotherapy been omitted, a modest absolute increment that might be acceptable to many patients, given the burdens of radiotherapy. These burdens are substantial: systemic costs ranging upwards of $10,000 US dollars per course; logistical challenges of daily treatment during multiple weeks disproportionately affecting patients with limited transportation, inflexible employment, or caregiving responsibilities; and toxicities including fatigue, skin changes, breast pain, and rare but serious risks of cardiopulmonary injury and secondary malignancies.

HERO was initially conceived as a focused, single-arm phase II study of radiotherapy omission in this favorable population (low-risk HER2-positive cancer)—a design mirroring pragmatic approaches from APT and emerging international trials.[8,9] However, following extensive peer review and discussion with National Cancer Institute (NCI) stakeholders, HERO was redesigned as a phase III randomized noninferiority trial because of appropriate concerns on whether a single-arm design would be truly practice changing or whether physicians and patients would require a randomized trial to accept omission as a viable option. This redesign fundamentally altered the feasibility calculus.

The final design compared standard radiotherapy to observation among patients with T1-2N0, HER2-positive disease (primary tumor ≤3 cm with initial BCS or pCR after neoadjuvant therapy for lesions ≤5 cm) following BCS and HER2-targeted systemic therapy.

Initial accrual proved challenging, reflecting difficulties common to de-escalation trials: provider reluctance to randomly assign patients away from standard treatment, patient anxiety about omitting established therapy, and time required for socialization of novel concepts within the clinical community.

Despite accelerating engagement, HERO was closed in mid-2025 following NCI/Cancer Therapy Evaluation Program reconsideration of feasibility projections, operational constraints, and competing resource demands. Although investigators believed the recent accrual trajectory suggested potential for successful completion, the responsible parties ultimately determined that continued support was not feasible given the resource constraints facing the cooperative group system.

De-escalation Dilemma: Barriers to Progress

The challenges facing HERO are neither unique nor unpredictable; they reflect fundamental structural barriers that systematically impede research that questions established paradigms. Understanding these barriers is essential for designing future studies and implementing systemic reforms for evidence generation when the underlying science is sound but randomization proves impractical.

Provider hesitancy represents a major obstacle. The Hippocratic principle of "do no harm" manifests as risk aversion when omitting standard treatments. Physicians comfortable prescribing regimens with considerable toxicity and uncertain benefit paradoxically resist studies evaluating treatment omission in populations for whom the incremental benefit is demonstrably small. This asymmetry reflects cognitive biases deeply embedded in medical culture: Acts of commission feel safer than acts of omission, even when evidence suggests equivalence. Medicolegal concerns

TABLE 1. Trials Discussed

Year	Title of Study/Citation/Link	Type	Results/Description	NCT No.
2011	EBCTCG (Early Breast Cancer Trialists' Collaborative Group)[1]	Meta-analysis of 17 trials	Demonstrated that although post-lumpectomy radiotherapy reduces relative risk of local recurrence by approximately 50%, absolute benefit varies substantially. When systemic therapy has reduced local recurrence to exceptionally low levels, the absolute benefit of radiotherapy necessarily becomes negligible. Adjuvant radiotherapy approximately halves risk of local recurrence	NA
2023	LUMINA[5]	Single-arm radiotherapy omission on the basis of Ki-67	Used molecular profiling to identify low-risk luminal A tumors (T1N0), for which radiotherapy could be safely omitted with low local recurrence rates. Fundamentally altered perception because investigators recognized that treatment standards must evolve in parallel with advances in patient selection, systemic therapy, and our understanding of tumor biology	NCT01791829
2024	IDEA (Individualized Decisions for Endocrine Therapy Alone)[6]	Single-arm radiotherapy omission on the basis of OncotypeDX RS	Used molecular profiling to identify low-risk luminal A tumors (T1N0), for which radiotherapy could be safely omitted with low local recurrence rates. Fundamentally altered perception because investigators recognized that treatment standards must evolve in parallel with advances in patient selection, systemic therapy, and our understanding of tumor biology	NCT02400190
2023	PRECISION (Profiling Early Breast Cancer for Radiotherapy Omission)[7]	Single-arm radiotherapy omission on the basis of PAM50/Prosigna	Used molecular profiling to identify low-risk luminal A tumors (T1N0), for which radiotherapy could be safely omitted with low local recurrence rates. Fundamentally altered perception because investigators recognized that treatment standards must evolve in parallel with advances in patient selection, systemic therapy, and our understanding of tumor biology	NCT02653755
2023	DESCARTES (De-ESCAlating RadioTherapy)[8]	Single-arm radiotherapy omission on the basis of pCR to neoadjuvant therapy	Valuates radiotherapy omission among patients achieving pCR post-neoadjuvant therapy, recognizing that such responders represent a biologically favorable cohort	NCT05416164
2025	ROSALIE[9]	Single-arm radiotherapy omission on the basis of pCR to neoadjuvant therapy	Examines radiotherapy omission among node-negative patients undergoing lumpectomy achieving pCR, using a pragmatic single-arm design, acknowledging difficulties of randomly assigning patients away from established treatment	NCT05866458
2025	NRG-BR008: HERO (HER2 Radiation Optimization)[10]	Single-arm radiotherapy omission on the basis of stage or pCR for HER2-positive breast cancer	Originally designed as a focused, single-arm phase II study of radiotherapy omission in low-risk HER2-positive cancer; redesigned as a phase III randomized noninferiority trial. Exemplifies not only the scientific rationale for treatment de-escalation but also practical challenges imperiling such research	NCT05705401
2015	APT (Adjuvant Paclitaxel and Trastuzumab)[11]	Single-arm landmark trial establishing standard of care for small, node-negative HER2-positive tumors	Demonstrated a 7-year locoregional recurrence-free survival of 99.0% among patients with small, node-negative HER2-positive tumors treated with adjuvant paclitaxel and trastuzumab, who underwent breast-conserving therapy plus radiotherapy	NCT00542451
2019	APT (Adjuvant Paclitaxel and Trastuzumab)[12]	Single-arm landmark trial establishing standard of care for small, node-negative HER2-positive tumors	Confirmatory results showed 5-year invasive disease-free survival of 97%. Illustrates nuances of treatment optimization	NCT00542451
2024	ATEMPT (Adjuvant Trastuzumab Emtansine versus Paclitaxel in Combination with Trastuzumab for stage I HER2-Positive Breast Cancer)[13]	Randomized clinical trial confirmatory of APT paradigm	Adjuvant T-DM1 for 1 year leads to outstanding long-term outcomes for patients with stage I HER2-positive breast cancer. A high HER2DX risk score predicted a higher risk of recurrence	NCT01853748
2025	COMET (Comparing an Operation to Monitoring, with or without Endocrine Therapy for Low-Risk DCIS; AFT-25)[14]	De-escalation	Trial for low-risk DCIS. Despite a randomized design comparing active monitoring with guideline-concordant care (ie, surgical resection), nearly half of patients assigned to standard treatment requested crossover, ultimately affecting accrual dynamics	NCT02926911
2003	NSABP B-06[15]	De-escalation	Established breast conservation	NSABP-B-06
2025	NSABP B-51[16]	De-escalation	Represents a paradigm shift in breast cancer management, showing that patients achieving nodal clearance after neoadjuvant chemotherapy derive no added benefit from regional nodal irradiation	NCT01872975

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TABLE 1. Trials Discussed (continued)

Year	Title of Study/Citation/Link	Type	Results/Description	NCT No.
2022	DAPHNe (De-escalation to Adjuvant antibodies Post-pCR to Neoadjuvant THP)[17]	De-escalation	Reporting a pCR rate of 56.7%, *v* the Compass trial (EA1181) reported 43.8% pCR—a substantial difference despite similar patient populations and treatment approaches	NCT03716180
2025	COMPASS (EA1181) (Cardiovascular Outcomes for People Using Anticoagulation Strategies)[18]	Single arm	Trial of neoadjuvant THP for patients with clinically anatomic stage II/III HER2-positive breast cancer. Reported 43.8% pCR—a substantial difference despite similar patient populations and treatment approaches	NCT04266249

Abbreviations: DCIS, ductal carcinoma in situ; HER2, human epidermal growth factor receptor 2; pCR, pathologic complete response.

reinforce this hesitancy: *A recurrence following treatment omission invites scrutiny in ways that toxicity from administered treatment does not.*

From the patient perspective, the "more is better" heuristic exerts a powerful influence. Despite substantial treatment burden, patients often prefer maximal therapy over nuanced risk-benefit deliberations. This preference reflects fundamental psychological asymmetries: Patients more readily perceive potential harms from undertreatment than from overtreatment, even when data suggest that the marginal benefits of additional treatment may be minimal. In HERO, patients receiving potentially lifesaving HER2-targeted therapy often declined participation specifically because of concerns about radiotherapy omission. The COMET[14] trial for low-risk ductal carcinoma in situ encountered inverse challenges: Despite a randomized design comparing active monitoring with guideline-concordant care (ie, surgical resection), nearly half of patients assigned to standard treatment requested crossover, ultimately affecting accrual dynamics. This highlights that patients who are interested in de-escalation may not accept randomization once they have understood the study's supporting rationale. COMET was unique in allowing these patients to participate, whereas for studies such as HERO, those same patients likely were lost to follow-up if they were interested in radiotherapy omission but did not want to risk being randomized to radiation.

The regulatory environment compounds these challenges. Increased scrutiny in the current economic climate has shortened evaluation windows for trial performance. Studies are often assessed during early socialization periods when accrual lags, without adequate recognition that practice-changing trials (particularly those challenging established paradigms) require extended lead time for provider and patient acceptance. This creates tension between methodological rigor and practical feasibility.

Historical accrual patterns reveal that many practice-changing breast cancer trials initially struggled with enrollment before gaining momentum, underscoring that paradigm-shifting studies often require extended periods before achieving stable accrual.

Notably, our review of cooperative group accrual data suggests that landmark trials including NSABP B-06,[15] which established breast conservation, and NSABP B-51,[16] recently reported in *The New England Journal of Medicine*, would have been terminated under HERO-like scrutiny on the basis of early accrual patterns. This creates a troubling precedent wherein the very studies most likely to change practice are least likely to receive the patience required for completion.

Pragmatic Approaches to De-escalation Research

The oncology community must recognize that trial design should be context-dependent. Not all questions require randomization, and de-escalation studies face unique challenges warranting design flexibility. Several principles should guide decision-making regarding when single-arm approaches are appropriate: First, single-arm designs are most suitable when historical controls are robust, when baseline event rates are low and well-characterized, and when populations can be precisely defined by reproducibility. Second, rigorous statistical frameworks are crucial, including designs with prespecified stopping rules, Bayesian approaches incorporating prior information, and noninferiority thresholds on the basis of established historical data and clinical judgment. Third, eligibility criteria must be sufficiently stringent to define genuinely low-risk populations while permitting adequate accrual. Fourth, multi-institutional participation ensures generalizability and guards against single-center biases.

However, single-arm approaches should not become the *default* for treatment de-escalation research. The absence of a concurrent control group can render a poorly designed study misleading or uninterpretable, and perhaps the most critical limitation of single-arm studies is the inherent reliance on historical or cross-trial comparisons. A compelling example in HER2-positive breast cancer is the DAPHNe trial,[17] which reported a pCR rate of 56.7%, whereas the COMPASS trial (EA1181)[18] reported a 43.8% pCR rate, a substantial difference despite similar patient populations and treatment approaches. Numerous other studies evaluating taxanes with platinum and HER2-directed therapies have similarly reported discordant pCR rates. These variations reflect factors that single-arm designs cannot control: temporal changes in diagnostic criteria, differences in patient selection even within similar eligibility criteria, heterogeneity in treatment delivery and supportive care, evolution in imaging and pathological assessment, and unrecognized confounders that randomization would balance.

Randomized trials remain essential when historical controls are heterogeneous or affected by temporal trends, when baseline event rates are high, when even small differences could affect survival or quality of life, when biological rationale is uncertain or contested, or when multiple competing interventions exist with unclear comparative effectiveness. Ultimately, if stakeholder consensus mandates definitive randomized evidence to prompt a practice change, single-arm approaches may be suboptimal.

From a regulatory perspective, several adaptations would facilitate de-escalation research: explicit recognition that accrual challenges are inherent to studies randomizing away from standard treatment, longer evaluation periods accounting for necessary trial socialization within provider and patient communities, design requirement flexibility when randomization proves prohibitive, and enhanced international collaboration to avoid redundant competing trials that fragment already-limited patient populations.

The argument for single-arm de-escalation studies is not one of methodological compromise, but rather one of methodological pragmatism. When randomized trials fail because of structural barriers rather than scientific invalidity, and when the unmet clinical need is urgent, rigorously designed single-arm studies represent an imperfect but pragmatic path forward. Perhaps more importantly, the oncology community must accept that optimal care does not equal maximal treatment, and that the perpetual insistence on randomized evidence when such trials prove infeasible creates its own harm in the interim. The goal is not to champion any single methodology, but to ensure that the evidentiary tools available to the field match the complexity of the questions being asked.

In conclusion, the closure of HERO represents more than the termination of a single study; it represents a missed opportunity to address a question of genuine importance to patients and the health care system. It reflects systemic challenges threatening our collective ability to optimize cancer care through evidence-based de-escalation. The confluence of provider hesitancy, patient anxiety, federal funding scrutiny, and methodological rigidity creates an environment inadvertently impeding precisely the studies patients most need. Identifying these barriers creates opportunities for intervention.

Moving forward, the oncology community must embrace pragmatic, context-appropriate trial designs. Regulatory bodies must explicitly recognize the unique challenges of de-escalation research, funding mechanisms must accommodate extended socialization timelines for paradigm-shifting studies, cooperative groups must lobby for these operational reforms, and the clinical community must embrace patient-centered outcomes that value treatment burden reduction alongside disease control.

The question HERO sought to answer (ie, whether selected patients with HER2-positive breast cancer can safely omit radiotherapy) remains unanswered. During this ongoing debate, thousands of women annually receive radiotherapy that may offer minimal benefit following HER2-targeted therapy. The scientific imperative to establish whether this treatment can be safely omitted persists. The challenge before us is to create an environment in which such questions can be addressed through pragmatic, achievable study designs generating actionable evidence rather than demanding methodological perfection that forecloses inquiry altogether.

AFFILIATIONS

[1]Memorial Sloan Kettering Cancer Center, New York, NY
[2]The University of Texas MD Anderson Cancer Center, Houston, TX
[3]Memorial Sloan Kettering Cancer Center Monmouth, Middletown, NJ
[4]Women and Infants Hospital of Rhode Island, Warren Alpert Medical School of Brown University, Providence, RI
[5]AdventHealth Cancer Institute, Orlando, FL
[6]Allegheny Health Network Cancer Institute/Drexel University College of Medicine, Pittsburgh, PA
[7]NSABP/NRG Oncology, UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, PA

CORRESPONDING AUTHOR

Lior Z. Braunstein, MD; e-mail: braunstl@mskcc.org.

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AUTHOR CONTRIBUTIONS

Administrative support: Eleftherios P. Mamounas, Thomas B. Julian
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Lior Z. Braunstein
Employment: Memorial Sloan-Kettering Cancer Center

Melissa P. Mitchell
Employment: MD Anderson Cancer Center
Honoraria: DAVA Oncology, Physicians' Education Resource
Research Funding: ARTIDIS
Travel, Accommodations, Expenses: Vision RT, SABCS

Atif J. Khan
Employment: Memorial Sloan-Kettering Cancer Center
Stock and Other Ownership Interests: Novavax, Xtrava Health, IgniteData
Consulting or Advisory Role: IgniteData
Research Funding: Clovis Oncology, Merck KGaA, Varian Medical Systems
Patents, Royalties, Other Intellectual Property: Use patent for the drug riluzole awarded to Rutgers University with me as inventor
Uncompensated Relationships: AI MindSystems Foundation

Eleftherios P. Mamounas
Honoraria: PrecisCa, Merck, Novartis
Consulting or Advisory Role: bioTheranostics, Merck, PrecisCa, Exact Sciences, Novartis, Delphi Diagnostics, GE Healthcare, AstraZeneca
Speakers' Bureau: Merck

Norman Wolmark
Research Funding: Breast Cancer Research Foundation (Inst)
Travel, Accommodations, Expenses: American Surgical Association

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