# Progress in Breast Cancer: Overview

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## Abstract

This edition of *CCR Focus* titled *Research in Breast Cancer: Frontiers in Genomics, Biology, and Clinical Investigation* reviews six topics that cover areas of translational research of high impact in breast cancer. These topics represent areas of breast cancer research where significant progress has occurred but also where very important challenges remain. The papers in this *CCR Focus* section are contributed by experts in the respective areas of investigation. Herein, key aspects of these contributions and the research directions they propose are reviewed. *Clin Cancer Res; 19(23); 6353–9. ©2013 AACR.*

## Neoadjuvant Trials and Early Drug Approvals

Achievement of a pathologic complete response (path CR) in the breast and axillary lymph nodes after neoadjuvant chemotherapy has been associated with improved long-term outcome (1). Several neoadjuvant trials with HER2 inhibitors (NOAH, Neo-ALTTO, NeoSphere, TRYPHENA) also suggest that similar conclusions apply to patients with HER2-overexpressing breast cancers. With the increased ability to identify actionable somatic alterations in breast cancer and the concurrent large expansion of targeted therapies and their combinations with standard treatments, it is impossible to test all these regimens in the adjuvant setting and determine their efficacy against micrometastases using survival as an endpoint. However, the preoperative therapy setting offers a clinical research platform where novel combinations can be compared and triaged using path CR as a clinical endpoint predictive of long-term outcome. These examples led to a position taken by the U.S. Food and Drug Administration (FDA) through which the regulatory agency proposed to consider randomized neoadjuvant trials for accelerated drug approval using path CR as a surrogate that is "reasonably likely to predict longer term benefit" at least for some subtypes of breast cancer. After accelerated approval, demonstration of an improvement in disease-free or overall survival would be required (2). Because in patients with ER$^+$ tumors, path CR does not necessarily correlate with long-term outcome, the proposal by the FDA will be tested first in HER2$^+$ and triple-negative breast cancer (TNBC). The potential impact of this recommendation is quite transformative as it can significantly shorten the time when patients have access to new drugs.

On September 30, 2013, the FDA approved the HER2 antibody pertuzumab as a neoadjuvant treatment in patients with HER2$^+$ early breast cancer (3). This approval was based on the results of two neoadjuvant studies, Neo-Sphere and TRYPHAENA (4, 5). The background that led to the recent FDA statement (2), trial design, and biomarker considerations that would use this opportunity, and the clinical implications of this decision, are examined by Bardia and Baselga (6) in this edition of *CCR Focus*.

The predictive value of path CR following neoadjuvant therapy in estrogen receptor–positive (ER$^+$) breast cancer is less clear. However, antiestrogen-induced inhibition of cell proliferation, as measured by Ki67 immunohistochemistry (IHC), in a tumor biopsy obtained after 2 weeks of treatment, is associated with good long-term outcome following adjuvant endocrine therapy (7). These data suggest that an early assessment of cellular response following brief antiestrogen treatment may be used to identify patients with early ER$^+$ breast cancer with a good prognosis after adjuvant endocrine therapy alone. Because this pharmacodynamic biomarker incorporates the effect of therapy in the individual tumor, it may be a powerful complement to other clinical biomarkers in the diagnostic pretreatment biopsy such as estrogen receptor/progesterone receptor (ER/PR) levels, histologic grade, Oncotype DX recurrence score, Ki67, and others. The value, endpoints, and other characteristics of presurgical nontherapeutic studies compared with neoadjuvant and adjuvant trials are summarized in Table 1.

The stronger examples in which the results of neoadjuvant trials have correlated with long-term outcome or with results in patients with metastatic disease are in HER2$^+$ breast cancer. In these trials, patients are selected on the basis of HER2 protein overexpression (by IHC) and/or *HER2* gene amplification as measured by FISH followed by HER2-targeted therapy. This background suggests that for the neoadjuvant platform-to-early drug approvals model to work, patients should be selected on the basis of a biomarker predictive of treatment efficacy. At a minimum, trials should be enriched with "biomarker positive" patients and the results appropriately stratified by such a biomarker.

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**Table 1.** Role of neoadjuvant and short presurgical studies in drug development in breast cancer

| Type of study | Endpoint | Number of patients | Length of follow-up | Therapeutic | Use for drug approval | Cost |
|---|---|---|---|---|---|---|
| Adjuvant | Relapse-free and overall survival | 1,000s | Years | Yes | Yes | Very high |
| Neoadjuvant | Clinical and path CR | 100s | Months | Yes | Yes (2013) | High |
| Short presurgical | Change in biomarker (Ki67, TUNEL, P-AKT, etc.) | Under 100 | Weeks | No | No | Not as high |

Abbreviation: TUNEL, terminal deoxynucleotidyl transferase–mediated dUTP nick end labeling.
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Examples include BRCA-mutant tumors and PARP inhibitors, tumors with PI3K pathway mutations and PI3K inhibitors, and TNBC with basal-like gene expression and platinum agents.

This approach may also identify patients at a high risk of recurrence, i.e., those with significant residual disease in the breast after neoadjuvant therapy. Another benefit of a preoperative approach is that, except for patients who experience a complete response, tumor tissue is always available at the time of surgery. These "drug resistant" residual cancers may harbor a similar molecular profile to that of drug-resistant micrometastases and can be interrogated with massive parallel sequencing of DNA extracted from the mastectomy specimen. Confirmation of this concordance between the residual cancer in the breast after neoadjuvant therapy and metastatic recurrence(s) requires additional investigation. If there was concordance, deep profiling of the residual cancer in the breast can be used to identify actionable biomarkers of drug-resistant tumors and novel targetable mechanisms of drug resistance.

The standard of care for patients with TNBC without evidence of metastatic disease after completion of neoadjuvant therapy and surgical excision of the cancer is watchful waiting. This conduct might not be appropriate for patients at a very high risk of early recurrence such as those with a high residual disease burden in the breast (8). However, the appropriate therapy for those patients is unknown. Thus, we propose that the unbiased profiling of targetable alterations in (residual) breast cancers after neoadjuvant therapy will identify pathogenic molecules or networks that can be therapeutically targeted in the immediate postoperative period (Fig. 1). This approach builds on the neoadjuvant platform-to-early drug approvals model elegantly described by Bardia and Baselga (6). Examples of this trial design are in progress. Since patients would be treated at a time of minimal residual disease, i.e., when only clinically silent micrometastases are present, delivery of an appropriate systemic targeted therapy is likely to have a significant impact in the rate of metastatic recurrence and death.

## "Actionable" breast cancer genomics and targeted therapies

Clinical subtypes of breast cancer are differentiated based on the expression of ERα, PR, and the HER2 (ERBB2) oncogene. These clinical markers can predict the response to antiestrogens and anti-HER2 therapies with a reasonable degree of accuracy. Using gene expression profiling, several molecular subtypes (termed the PAM50 intrinsic subtypes) of breast cancer have been characterized (9). These include luminal A (high ER/PR expression, sensitivity to antiestrogens, good prognosis), luminal B [lower ER and negative PR expression, less responsive to antiestrogens, high proliferative rate (Ki67) and histologic grade, poor prognosis], HER2-enriched (containing HER2 gene-amplified tumors and a subset lacking HER2 amplification but harboring a HER2 expression signature), basal-like (mainly tumors not expressing ER, PR, and HER2, high relapse rate, initially responsive to chemotherapy), and claudin-low (tumors with a large cancer stem cell–like component, resistant to chemotherapy, poor prognosis; ref. 10). Although molecular stratification has improved risk prediction and clinical trial design, the genomic alterations and therapeutic targets (in addition to ER, PR, and HER2) underlying these subtypes have not been fully established.

Recently, high-throughput genomic analyses such as massively parallel sequencing (MPS), expression microarray, and comparative genomic hybridization (CGH) have allowed for the construction of comprehensive catalogs of the genomic architecture of breast cancer in large sample sizes (reviewed in ref. 11). These data combined have provided a catalog of somatic alterations (mutations, deletions, amplifications, rearrangements) in more than 3,500 breast tumors. These results confirm the somatic mutation landscape where few genes are mutated in many tumors (i.e., *TP53*) while many genes are recurrently mutated in few tumors (12). These diverse mutations can often be organized into several frequently mutated pathways. These data provide novel insights into the pathogenesis and further classification(s) of the disease that may or may not always be linked to the clinical subtypes described above. In lung cancer and melanoma, therapies specifically targeted to
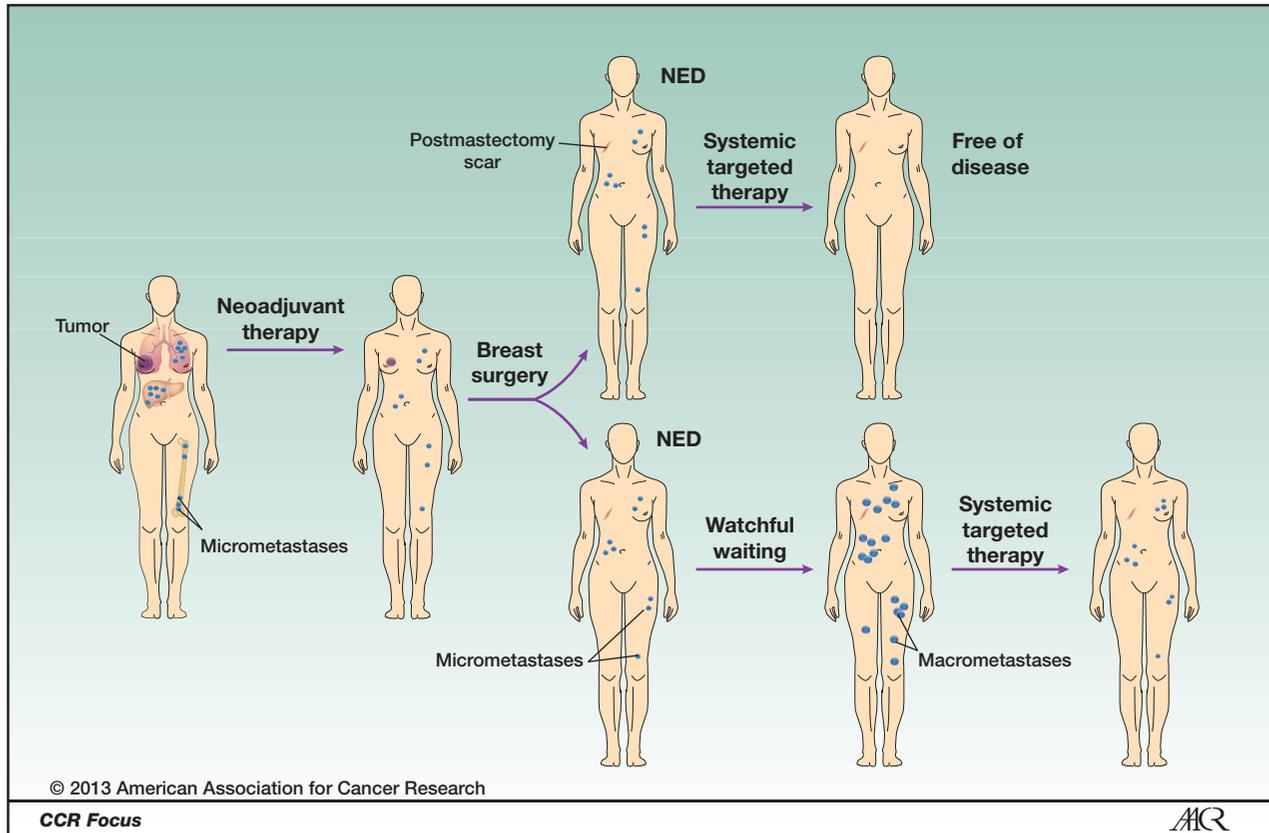
**Figure 1.** Targetable alterations in (residual) breast cancers after neoadjuvant therapy may inform (adjuvant) treatment for the immediate postoperative period. Most patients with breast cancer present with a primary tumor and subclinical micrometastases (left). In a significant fraction of patients, systemic neoadjuvant therapy reduces the primary tumor and eliminates most micrometastases. Immediately after surgery, patients are considered to have no evidence of disease (NED). We propose "drug-resistant" residual cancer in the breast and micrometastases share a molecular identity. Thus, identification of targetable alterations in the mastectomy specimen may provide leads for systemic targeted therapy that, if deployed immediately after surgery, would eliminate micrometastases and potentially improve cure rates (top row). In TNBC, for example, the standard of care for patients with residual cancer in the breast of lymph nodes after neoadjuvant chemotherapy is watchful waiting. Most if not all those patient eventually recur (macrometastases), at which time the cancer can be palliated with more systemic therapy but it is in general no longer curable (bottom row).

some of these mutations or gene rearrangements are already approved. That is not yet the case in breast cancer, despite the overwhelming amount of molecular information in large breast cancer cohorts. The process and barriers for the incorporation of tumor genomics into clinical research and care in breast cancer are comprehensively discussed by Tabchy and colleagues (13) in this edition of *CCR Focus*.

A challenge to developing new therapeutics against cancer with these commonly altered genes lies in understanding the biologic functionality of these mutations. Is the alteration a driver of an oncogenic phenotype? The presence of an alteration does not imply oncogene dependence and, as such, a therapeutic vulnerability. Does the mutation confer a gain-of-function, a loss-of-function, or a new functionality altogether? Support for clinical targeting of these alterations will require *in vitro* and *in vivo* experimentation to understand if and how the mutation functions biologically and whether it is therapeutically "actionable."

As discussed by Tabchy and colleagues (13), the use of these somatic alterations as selectable biomarkers in investigational clinical trials must be approached cautiously.

However, the increased availability of Clinical Laboratory Improvement Amendments–certified MPS at academic centers and commercial sources is already presenting patients and oncologists with new treatment options and dilemmas in the clinical care setting. Known functional mutations in "targetable" genes are being identified in patients seeking cancer care, but drugs directed against these lesions may not yet be approved for use in breast cancer. Furthermore, some mutations will be variants of unknown significance (i.e., mutations not previously observed in genes of interest). Tumor heterogeneity will lead to identification of mutations that are clearly not in all tumor cells. Cancers will present with multiple "actionable" targets, but the key driver(s) of cancer progression may not be apparent. The use of a tumor registry where presence of these lesions in the tumor can be correlated with patient outcome would be a helpful initiative. With such a registry, a group of consistent anecdotal responses may provide a lead for formal studies addressing drug efficacy. Finally, the pace of discovery of genomics in breast cancer might be ahead of a regulatory process less used to drug approvals limited to small subsets

of patients with a particular tumor genotype. Despite these many unanswered questions, we anticipate that in the coming years, translational and clinical investigators, cancer care providers, basic scientists, drug makers, assay developers, funding agencies, and patients and advocates should be able to perfect the catalog of molecular lesions in cancers associated with sensitivity of resistance to treatment and, as such, increase cure rates in breast cancer.

### Triple-negative breast cancer: many diseases and even more therapies to test

TNBC lacks detectable expression of ER, PR, and HER2, is often associated with basal-like gene expression, and represents a heterogeneous group of tumors at clinical, histopathologic, and molecular levels (12). Although as a group TNBCs are initially sensitive to conventional chemotherapy, they also demonstrate higher relapse rates and an overall shorter survival compared with other breast cancer subtypes. Clinical studies have shown good responses with PARP inhibitors in TNBC with *BRCA* gene deficiency (14). The DNA cross-linker cisplatin has also shown clinical activity in patients with *BRCA1*-mutant TNBC (15), but its role in TNBC with wild-type BRCA1 is less clear.

The large genomic studies discussed above did not identify many somatic alterations potentially associated with a therapeutic sensitivity in TNBC or basal-like breast cancer. However, the high degree of genomic rearrangement identified in this subtype (16) supports the further examination of agents targeting the DNA damage response and repair mechanisms, which are defective in a subgroup of TNBCs. Nonetheless, many unanswered questions remain as to how future clinical trials should incorporate targeted therapies in TNBC. The recent studies addressing the molecular diversity of TNBC and its biologic and clinical implications are discussed by Turner and Reis-Filho (17) in this edition of *CCR Focus*.

A recent study identified biologically diverse TNBC clusters using transcriptome datasets from 21 independent studies (18). These clusters were defined by DNA damage response genes, mesenchymal features, immune-related genes, and androgen receptor (AR) signaling. The "mesenchymal" cluster overlaps with a previously reported claudin-low breast cancer subtype also characterized by loss of epithelial differentiation, an intense immune infiltrate, and cancer stem-like characteristics. Using TNBC cell lines and xenografts, Lehmann and colleagues associated these clusters with particular therapeutic vulnerabilities, i.e., antiandrogens in the AR luminal cluster, cisplatin, and other DNA damaging agents in the DNA damage response subgroup, and PI3K/TOR inhibitors in the mesenchymal genes cluster (18). The value of these expression signatures for treatment selection and prediction of response remains to be determined.

Compared with ER$^+$ and HER2$^+$ breast cancers, TNBC appears to harbor fewer actionable mutations that can be targeted with a therapeutic intent. In addition, this clinical subtype encompasses a molecularly heterogeneous group of tumors. Circumstantial evidence in line with this heterogeneity is the initial low response to chemotherapy among luminal AR$^+$ and metaplastic TNBCs. Furthermore, recent studies suggest that many TNBCs exhibit a continuous distribution of copy number alterations and point mutations per tumor, which are not associated with one another (16). Presence of these heterogeneous multiclonal pools of transformed cells presents an additional hurdle for targeted therapies. For instance, therapeutic targeting of lesions present in only one of five theoretical clonal populations may not be sufficient to induce a clinical response.

There is general acceptance that clinical trials in TNBC should focus in defined subsets identified by a molecular biomarker for patient selection and/or stratification. Despite the overwhelming scientific evidence in support of this heterogeneity, clinical studies in TNBC have continued to enroll patients based on clinical markers, potentially explaining the plethora of negative trials in this breast cancer subtype. In addition, for trials in which there is a group of patients who clearly benefits from a novel therapy, tumor material should be collected for retrospective massive parallel sequencing aimed at identifying unsuspected molecular targets or biomarkers predictive of such clinical benefit or drug resistance.

### Tumor dormancy: a major challenge in ER$^+$ breast cancer

In this edition of *CCR Focus*, Zhang and colleagues (19) contribute their perspective on mechanisms of cancer dormancy and potential approaches to address late metastatic recurrences of these dormant cancers. Late recurrences predominantly affect patients with ER$^+$/HER2$^-$ tumors and are defined as those occurring over 5 years after diagnosis. Over half of the recurrences of ER$^+$ cancers occur 5 years or longer after diagnosis and surgical excision of the primary tumors. Furthermore, at least a quarter of the recurrences occur in the second decade after original diagnosis (20). This slow natural history, even at a time when adjuvant endocrine therapy has been prolonged to 10 years, has been used to infer a subclinical state in which cancer cells remain quiescent but viable or are dividing slowly but also dying at such a rate that the tumor does not grow. Not inconsistent with this notion, late recurrences beyond 5 years are not associated with markers of high proliferation in the primary breast tumors (21).

Experimental evidence suggests the existence of various mechanisms of cancer dormancy, including angiogenesis, cellular dormancy (G$_0$–G$_1$ arrest), and immune surveillance by the host (22). Mouse and human breast cancer cell lines and xenografts and transgenic mouse mammary tumors have been used to discover and study these mechanisms. However, evidence that any of these is operative in patients with breast cancer is almost nil, thus challenging the usefulness of these experimental models for the study of cancer dormancy.

It is proposed that genetically fit tumor cells, as a result of the accumulation of oncogenic alterations, are the ones that metastasize. Recent studies suggest that systemic dissemination of breast cancers occurs early (23). The fact that those

disseminated tumor cells (DTC) pause and do not give clinical manifestations immediately is further indirect evidence of a dormant state. This pause in the progression of DTCs also implies that they need to accumulate additional genetic alterations to relieve dormancy, thus leading to metastatic clinical progressions later on. For all these reasons, it is my opinion that the vast genomic information obtained from ER+ tumors at the time of diagnosis is unlikely to shed significant light about the mechanisms permitting or inducing a viable dormant state and its subversion years later.

This background also suggests that to fully understand dormancy, cancer cells must be characterized during their dormant state. Zhang and colleagues (19) propose this characterization may include circulating DNA, RNA, and protein markers of these dormant cells. However, not all (dormant) DTCs are destined to progress and recur clinically, adding another challenge to the ability of this characterization to predict late recurrences. These studies may also be limited in their ability to identify therapeutically actionable alterations that upon a targeted intervention will maintain dormancy of tumor cells or eliminate them by interfering with their mechanisms of survival and drug resistance.

Therefore, we propose that to fully understand dormant breast cancer and envision rational approaches to eliminate it, a "TCGA-like" enterprise focused on ER+ late recurrences will be required. We posit these tumors, as a result of evolutionary and treatment pressures, will harbor genomic alterations not present in the primary cancer while retaining many of the original traits. Patient-derived xenografts may be used as a complement to assess this genetic drift over time and identify acquired mechanisms of cancer progres-

sion, as recently shown by Li and colleagues (24). Whether these lesions are causally associated with tumor dormancy can be triaged and studied in experimental systems and subsequent clinical trials with targeted drugs.

## Harnessing the immune system to eradicate breast cancer

The studies highlighted up to now focus mainly on tumor cell–autonomous mechanisms that drive cancer progression and are being targeted therapeutically. In contrast, recent progress in immunotherapies to other tumor types has reinforced a decade of studies suggesting the immune system and the tumor microenvironment play an important role in breast cancer outcome (25–27). A logical question of whether the immune system is a critical component of the response of breast cancer to treatment (28).

Multiple reports have shown that the degree and type of lymphocytic infiltration in breast cancers are related to outcome. Early disagreements regarding the importance of the immune system were likely related to some extent to what was later recognized as the immunosuppressive nature of some lymphocytic infiltrates in tumor samples. For example, Alexe and colleagues (29) identified by gene expression a subset of HER2+ breast cancers with good prognosis. This signature was enriched with genes involved in "immune support" pathways, including T-cell activation, inflammation-mediated chemokine and cytokine signaling, and B-cell activation (Fig. 2). This signature was validated histologically by showing samples with either a dense lymphocytic infiltrate or devoid of lymphocytes (29). In this edition of *CCR Focus*, Disis and Stanton (30) discuss advances in our understanding of the role of the immune system in breast cancer, including the nature



Figure 2. HER2+I breast cancers have a prominent lymphocytic infiltrate. A, Kaplan–Meier curves for the HER2+ subtypes (89% and 42% long-term distant metastasis-free survival for HER2+I and HER2+NI; $P = 0.01$). HER2+I tumors were found to be highly enriched in immune-related genes. B, typical histologic image of a tumor with a prominent lymphocytic infiltrate (top right) and a tumor with no lymphocytic infiltrate (bottom right). T, region with tumor cells; L, region with prominent lymphocytes. Adapted from Alexe and colleagues (29).

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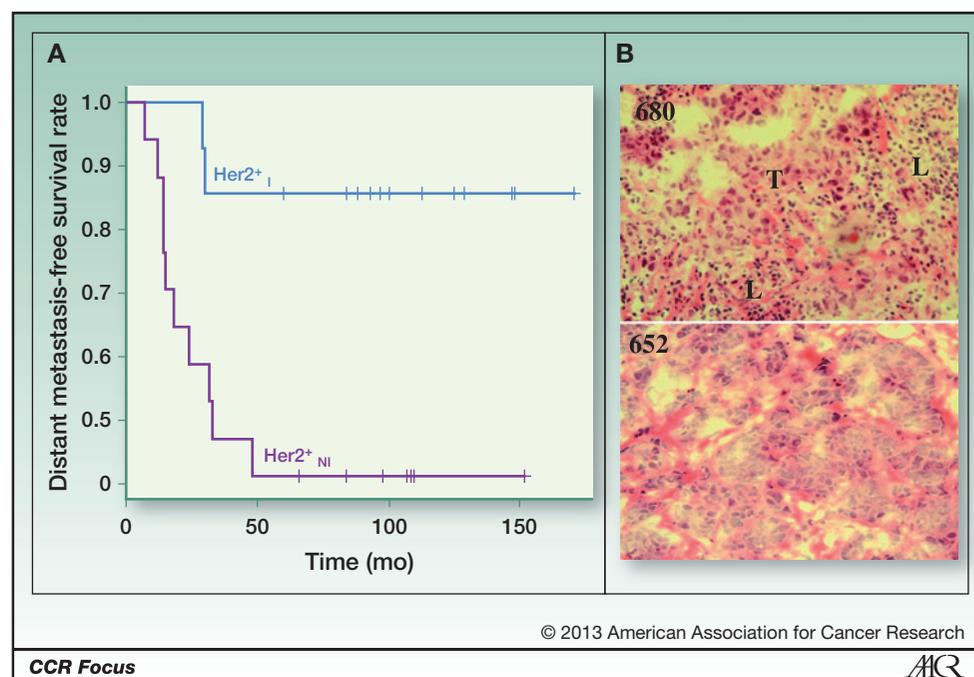
of those lymphocytic infiltrates and approaches to engage and enhance cytotoxic T cells over regulatory T cells with a therapeutic purpose. Given the many available effective treatments for breast cancer, the ability to combine them with immunotherapies offers the potential to make greater inroads in the treatment of breast cancer.

### The problem of sanctuary sites for systemic therapies

Finally, this *CCR Focus* section highlights a problem that has confronted oncologists since the early days of chemotherapy of breast cancer. Systemic and regional therapies were attempted in the 1960s, but there was some lack of urgency due to the typical failure of treatment outside the central nervous system (CNS). Whole-brain radiotherapy and steroids could temporally control CNS metastases until patients succumbed to systemic disease. Progress in systemic therapy has led to observation of patients with disease progression only in the CNS and the prospect of much continued systemic disease control without adequate CNS therapies (31).

The CNS is protected by a complex blood–brain barrier (BBB) composed of endothelial cells, the tight junctions between them, and the surrounding astrocyte foot processes. Influx and efflux drug transporters determine which molecules cross the BBB, and most cancer chemotherapeutics do not cross the BBB in concentrations sufficient to treat cancer. Of note, some small-molecule inhibitors achieve sufficient concentrations and are being increasingly used in

patients with HER2$^+$ brain metastases (32). In this *CCR Focus* series, Lin and colleagues (33) describe efforts to identify effective agents that will cross the BBB. How and when breast cancer cells are seeded to the CNS and how they remain dormant until later relapse adds to the complexity of the problem.

## Conclusions

Breast cancer still remains as the second most common cause of mortality among women. We should recognize, however, that the last decade has witnessed the largest collection of discoveries leading to progress in the understanding of the molecular and cellular biology of breast cancer, the separation of the disease into different subtypes with different pathogenesis and thus therapeutic vulnerabilities, the identification of new therapeutic targets, and significant changes in the natural history of some of the breast cancer subtypes as the result of combinatorial therapies. All these are reasons for optimism and the anticipation that the field is on the threshold of even more meaningful breakthroughs.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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