The article by Rouzier and colleagues, published in the August 15, 2005, issue of *Clinical Cancer Research*, demonstrated that different molecular subtypes of breast cancer have different degrees of sensitivity to chemotherapy, but the extent of response to neoadjuvant therapy has a different meaning by subtype. Several molecular subtype–specific clinical trials are under way to maximize pathologic complete response rates in triple-negative breast cancer and HER2-positive cancers, and to provide adjuvant treatment options for patients with residual invasive disease. *Clin Cancer Res*; 21(16): 3575–7. ©2015 AACR. See related article by Rouzier et al., *Clin Cancer Res* 2005;11(16) Aug 15, 2005;5678–85

The most useful disease classification systems are those that not only capture salient biologic features of disease subsets but also guide treatment strategies. Ten years ago, we published an article that demonstrated significantly different chemotherapy sensitivity across different molecular subtypes of breast cancers (1). We found that basal-like and HER2-positive cancers are the most chemotherapy sensitive, followed by the luminal B and luminal A subtypes. Chemotherapy sensitivity was assessed in the context of preoperative therapy of newly diagnosed, stage I–III cancers using a multidrug, third-generation chemotherapy regimen. Pathologic complete response (pCR) rate was used as the study endpoint. Similar observations were subsequently made by many other investigators (2). The realization that luminal B cancers have poorer prognosis compared with luminal A cancers when treated with adjuvant endocrine therapy alone but at the same time have greater chemotherapy sensitivity enabled the development of several molecular diagnostic assays that assist physicians today to select adjuvant chemotherapy for estrogen receptor (ER)–positive breast cancers. The initial success in testing proliferation-related genes that provided an easy basis to select molecular variables to build multivariable prediction models. However, proliferation-related genes carried only modest chemotherapy predictive or prognostic values in triple-negative breast cancer (TNBC), partly due to the almost uniformly high proliferative activity of these cancers (3). Although TNBC showed greater chemotherapy sensitivity than the other molecular subtypes, it has been difficult to identify molecular predictors that could separate the more chemotherapy-sensitive from the less-sensitive cancers within the TNBC subgroup. The only consistent biologic feature that shows a broad association with chemotherapy response in early-stage TNBC resided not in the cancer cells but in the tumor microenvironment. The level of tumor-infiltrating lymphocytes (TIL), and molecular markers that reflect the extent of immune infiltration, are the only currently available (although not yet standardized or routinely reported) predictors of chemotherapy response in TNBC (4). However, although a statistically significant association exists between greater TIL count (and immune gene signatures) and higher probability of pCR, it is difficult to define a TIL threshold below which benefit from treatment could be excluded with certainty.

Efforts to define clinically useful prognostic gene signatures within TNBC also met with limited success. Although it is possible to define better and worse prognostic groups among these cancers, the practical value of these observations is limited because even patients who are in the "good risk" group have 15% to 20% risk of recurrence if treated with surgery alone. Remarkably, the biologic processes that carry the greatest prognostic information in TNBC are also immune and inflammatory parameters in the tumor stroma (5). Considering the clinical decision-making context of TNBC after surgery, which involves choosing between observation or adjuvant chemotherapy, and the lack of data to support that adjuvant chemotherapy could not further improve the outcome of patients assigned to the "good"–prognosis group, which tends to include the most immune-rich tumors, the clinical utility of molecular prognostic predictors for TNBC is modest at best. Not surprisingly, in contrast with the
An Emerging New Treatment Paradigm

Complete imaging and pathologic resolution of metastatic breast cancer in response to therapy is rare (although it is becoming more common with multimodality HER2-targeted therapies in HER2-positive cancers) and, therefore, in clinical trials, tumor shrinkage ≥ 30% is often considered as a meaningful signal for drug activity. We, and others, have proposed that in the neoadjuvant treatment setting of early-stage breast cancer, pCR defined as complete eradication of invasive cancer from the breast and lymph nodes (ypT0/is, ypN0) represents a more meaningful endpoint than clinical or imaging response because of its strong association with survival. Patients with breast cancer who achieve pCR, or have minimal residual cancer burden, have excellent survival regardless of molecular subtype, whereas those with residual invasive disease (RD) have variable prognosis that is influenced by disease subtype and extent of RD (10). Patients with TNBC and residual cancer after neoadjuvant chemotherapy have a poor prognosis that is proportionate to the extent of residual cancer, whereas many patients with ER-positive cancer have excellent survival in spite of RD. This strong association between pCR and survival at the individual patient level in TNBC, and also in HER2-positive cancers, motivates the efforts to develop regimens that maximize pCR rates. In 2013, the FDA granted its first accelerated approval for a drug, pertuzumab, based on its success at improving the pCR rate in HER2-positive breast cancer. However, the relationship between improvements in pCR rate and clinical trial-arm level survival remains controversial because several, admittedly underpowered, trials failed to demonstrate significant survival improvement in trial arms with a higher pCR rate. There are many reasons (e.g., good baseline prognosis, effective post-neoadjuvant therapies, and pCR preferentially occurring in patients with good prognosis) why a regimen with substantially increased cytotoxic activity demonstrated by increased pCR rate could produce only small improvement in survival (11). Only substantially larger trials, or trials restricted to high-risk patient populations with high event rates, will have the adequate power to prospectively test the relationship between higher pCR rate and improved survival. It is important to remember that absence of evidence (from underpowered trials) is not evidence of absence for an effect.

An important corollary of these observations is that pCR itself can be used as the elusive predictive marker that defines the patient population among TNBC and HER2-positive cancers that benefitted the most from a given neoadjuvant chemotherapy regimen, and RD defines the patients who need further novel therapies to improve their outcome. Several neoadjuvant clinical trials have been designed to increase pCR rates for TNBC that capitalize on the improved molecular understanding of the disease and its microenvironment. A number of trials are being planned to combine neoadjuvant chemotherapy with immune checkpoint inhibitors based on preclinical results that indicate that chemotherapy-induced cytotoxicity is partly mediated by an antitumor immune response in the tumor microenvironment, which is also consistent with the higher pCR rates seen in immune-rich tumors. Until very recently, no adjuvant treatment options existed for TNBC and HER2-positive patients with RD; however, today at least four randomized clinical trials are ongoing or planned to test the efficacy of different novel adjuvant treatment strategies in this clinical setting. TDM1 is being tested as adjuvant treatment in HER2-positive breast cancers that have RD after trastuzumab/pertuzumab-containing neoadjuvant chemotherapy (NCT01196052). Olaparib is being tested in germline BRCA-mutated TNBC patients, including those with residual cancer after neoadjuvant chemotherapy (NCT02032823). Two other adjuvant trials are planned or will soon be activated for TNBC with RD that will test carboplatin (EA 1131A) and the anti-PD-1 antibody pembrolizumab, respectively (SWOG S1418). If these trials show positive results, the treatment paradigm for these molecular subtypes will fundamentally change. Positive results would establish neoadjuvant chemotherapy as the most logical and cost-effective initial therapy using pCR (and minimal residual cancer burden) as an important biologic early surrogate marker to determine who will need subsequent adjuvant therapy.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: L. Pusztai, R. Rouzier, W.F. Symmans
Writing, review, and/or revision of the manuscript: L. Pusztai, R. Rouzier, W.F. Symmans

Grant Support
This work was supported in part by grants from the Breast Cancer Research Foundation (L. Pusztai and W.F. Symmans) and Susan G. Komen (W.F. Symmans).

Received April 28, 2015; revised May 13, 2015; accepted May 13, 2015; published online August 14, 2015.
References

Clinical Cancer Research

CCR 20th Anniversary Commentary: Divide and Conquer — Breast Cancer Subtypes and Response to Therapy

Lajos Pusztai, Roman Rouzier and W. Fraser Symmans


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/21/16/3575

Cited articles
This article cites 11 articles, 6 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/21/16/3575.full#ref-list-1

Citing articles
This article has been cited by 1 HighWire-hosted articles. Access the articles at:
http://clincancerres.aacrjournals.org/content/21/16/3575.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.