of the procarbazine in infertility in this population will be difficult to determine. While the study was randomized and some children did not receive procarbazine, the majority of these patients, when they progressed, went on to receive other potentially toxic chemotherapy regimens, including alkylators and/or cranial irradiation. Unlike the Hodgkin lymphoma survivors, these children often receive multiple successive treatments. The young age of the patients also limits the number who will be over 20 years of age when Children's Oncology Group ends the follow-up. Finally, endocrine deficits were only one aspect of the multiple late effects of brain tumors and treatment that can lead to childlessness.[5] The standard consent form included infertility as one of the risks of therapy, so parents were informed. However, it would be misleading for parents to be told that treatment with one regimen would be more likely to cause inability to have children, since so many other factors also contribute to this problem in this population. For example, the regimen that may be most preserving of fertility may to be the one that prevents progression and the need for these subsequent treatments or delays radiation beyond a critical age. It is clear with all these issues, further study of fertility in brain tumor survivors is needed.

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Adaptive Trials in the Neoadjuvant Setting: A Model to Safely Tailor Care While Accelerating Drug Development

To the Editor: It is clear from the Schott and Hayes[1] critique of the I-SPY 2 (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis 2) trial that they and your readers would benefit from a more-detailed understanding of the study.

Patients in I-SPY 2 have breast cancers $\geq$ 2.5 cm. A core biopsy sent for molecular characterization with the US Food and Drug Administration–approved 70-gene test (MammaPrint)[2] must be 70-gene high risk, hormone receptor–negative or human epidermal growth factor receptor 2–positive for a patient to be eligible for random assignment to weekly paclitaxel $\times$12 weeks with our without an investigational agent followed by four cycles of doxorubicin and cyclophosphamide. Biomarkers are used to identify signatures for experimental regimens that predict an improved pathologic complete response (pCR), which is defined as no invasive tumor present in breast or axillary lymph nodes.[3] Adaptive random assignment hastens this process. Regimens are dropped if they do not improve pCR rates for any biomarker signature.[4] The I-SPY 2 design was created to rapidly evaluate the interaction between the investigational agent and paclitaxel and to drop agents if problems are observed, whereas drugs that improve pCR can follow a regulatory pathway for accelerated approval.[5] Schott and Hayes[1] raise three important issues that we considered carefully when designing the I-SPY 2 trial.

First, they are concerned that novel agents when added to standard therapy for 12 weeks might not enhance the pCR rate. These are the hypotheses being tested. For an investigational agent to be eligible for I-SPY 2, there must be preclinical evidence that shows a lack of interference with taxanes and a strong scientific rationale for additivity or synergy. As a consequence of the adaptive design, if the pCR rate is not increased by paclitaxel plus an investigational agent versus paclitaxel alone for any biomarker signature, as few as 20 patients will be exposed to the combination. Moreover, an agent can be dropped completely or dropped for specific subsets of patients who have no evidence of an enhanced response. This compares with many thousands of women exposed to new agents in the postsurgical adjuvant model favored by the authors. We agree with the authors that neoadjuvant endocrine therapy does not induce pCR in 12 weeks, but we are not considering endocrine therapy in the trial. Moreover, patients with hormone receptor–positive tumors and MammaPrint low-risk scores are not eligible to proceed to chemotherapy in I-SPY 2 because they may benefit from endocrine therapy alone. We are not exposing these patients to chemotherapy plus investigational agents.

The second concern of Schott and Hayes[1] relates to the potential toxicity of investigational agents when given in combination with paclitaxel. Experimental drugs included in I-SPY 2 must demonstrate safety data for the combination and receive approval by an independent advisory committee and the US Food and Drug Administration. Moreover, weekly patient visits allow close toxicity evaluation. Finally, an external independent data safety and monitoring board (DSMB) meets monthly to review toxicity. Patient safety has been at the heart of the trial design. Real-time monitoring helps ensure patient safety.

The authors' third concern is the potential interference of new agents with paclitaxel. They drew an analogy of inferior results with concurrent versus sequential chemotherapy and tamoxifen. In this example, the preclinical data that predicted this outcome

were published years[6] before the 1,500-patient adjuvant clinical trial, which showed inferior results with concurrent tamoxifen.[7] Meanwhile, before trial completion, thousands of women were treated inappropriately.

Just as Schott and Hayes[1] are concerned about the I-SPY 2 design, we are concerned about the pace and price of testing one drug every 5 to 10 years in thousands of women. Innovation can and should exist while guaranteeing patient safety. I-SPY 2 has teamed with 50+ patient advocates, 100+ academics and community physicians, 22 clinical centers, the Foundation for the National Institutes of Health Cancer Biomarkers Consortium, the US Food and Drug Administration, the National Cancer Institute Cancer Therapy Evaluation Program, an independent advisory group composed of senior cancer leaders who are not involved in the trial, an independent DSMB, and 10+ pharmaceutical and biomarker companies. To date, we have randomly assigned more than 200 patients without limitations imposed by the DSMB.

The concerns expressed by Schott and Hayes[1] were prime considerations in our trial design, but we arrived at a different conclusion regarding the way forward. The conducting of an intensive study of patients receiving neoadjuvant therapy is a model for the treatment of all cancers. By testing new agents on a standard-of-care platform, performing molecular profiling, incorporating imaging, applying strict criteria for drug inclusion, using adaptive random assignment, and providing real-time safety monitoring, we are fulfilling the demands of our patients to bring the promise of personalized therapies to the clinic.[8]

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Advocates' Perspective: Neoadjuvant Chemotherapy for Breast Cancer

To the Editor: Although it is clear that Schott and Hayes[1] are motivated to improve treatment for breast cancer, they appear overly cautious about moving beyond the traditional drug-development paradigm that focuses on incremental improvements by adding new drugs to traditional chemotherapy. Because we have been personally affected by cancer, we are not satisfied by this approach and believe we must seek innovative strategies to accelerate progress. Like Schott and Hayes,[1] we are committed to evidence-based medicine, although we often come to different conclusions about the best path forward. As advocates, many of whom have been involved in the I-SPY 2 (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis 2), we have written this letter to urge innovation, including the use of neoadjuvant trials and to address the criticism of I-SPY 2 of Schott and Hayes.[1]

First, we take issue with their claim that there are "limited clinical advantages of neoadjuvant chemotherapy" because only a fraction of patients who are not eligible for breast-conserving surgery become eligible with neoadjuvant therapy. For those women, the advantage is significant. We recommend that for women without the initial option of breast-conserving surgery, the standard of care should include the offer of neoadjuvant systemic therapy.

Second, neoadjuvant trials provide more rapid indication of the potential value of investigational agents and the appropriate subgroup of patients. Such trials lead to the refinement of imaging and biomarker assessments of which Schott and Hayes[1] are concerned.

Third, Schott and Hayes[1] express concerns about the potential antagonism of targeted and cytotoxic therapy in neoadjuvant trials. Preclinical data have suggested that additive or synergistic effects are more likely. Combinations need to be tested in clinical trials. A potential innovative trial design might administer a targeted therapy neoadjuvantly and a cytotoxic therapy postsurgically, perhaps sparing patients who achieve a pathologic complete response (pCR) the toxicity of chemotherapy altogether.

Fourth, Schott and Hayes[1] worry about false negatives. Many false negatives, particularly for targeted agents, may be a consequence of testing them in patients with an extensive tumor burden that is highly mutated. Patients with early-stage breast cancer may be more likely to benefit from these agents, and thus, our concern about false negatives decreases for neoadjuvant trials of early-stage breast cancer.

As concerns the three clinical scenarios that Schott and Hayes[1] describe, we again offer alternative reactions. Their first scenario is a patient who is estrogen receptor–positive, progesterone receptor–positive, and human epidermal growth factor receptor 2–negative who does not achieve a pCR after neoadjuvant chemotherapy. Although the pCR rate is lower in women with estrogen receptor–positive disease, it is not insignificant. The administration of endocrine therapy neoadjuvantly and deferring a decision about chemotherapy until after surgery could reduce the number of women subjected to the toxicity of

