It is time to develop more active treatments in the early-disease setting that actually eradicate ER-positive breast cancer before new mutations and secondary resistance have a chance to develop. In this regard, standard chemotherapy is not the answer.

We commend Elgene Lim and colleagues for providing a comprehensive review on the natural history of hormone receptor–positive breast cancer, highlighting the molecular and clinical heterogeneity of this disease, gaps in our understanding of its underlying biology, and challenges in research and clinical practice. We echo the sentiment that progress in treatment of hormone receptor–positive breast cancer has been slow and the impact of newer endocrine therapy approaches, such as the introduction of aromatase inhibitors (AIs) in the adjuvant setting and extended adjuvant therapy, on relapse and survival has been modest. Additionally, despite progress in the molecular profiling of breast cancer and subclassification of ER-positive disease into luminal A and luminal B subtypes, existing molecular assays have not raised new therapeutic hypotheses. This was the hope with results from the large-scale genome-sequencing studies. However, the tremendous amount of somatic derangement/mutations occurring in ER-positive breast cancer at the genome-wide level and the relative rarity of incidence for most of the significantly mutated genes underscore the need for genetic profiling of thousands of carefully annotated specimens to make sense of the patterns of somatic derangement/mutations that are emerging.

FIGURE

Study Schema for the Phase III ALTERNATE Trial

The model of tumor relapse in relation to anti-estrogen therapy presented by Lim et al (see the Figure in their article) provides a useful framework for categorizing tumors into subgroups based on clinical phenotypes. Rightfully, the authors state that there is no clear demarcation between primary and secondary resistance. We would like to emphasize the utility of the neoadjuvant endocrine therapy Ki67 biomarker strategy in this regard. Since endocrine therapy functions by inhibiting tumor cell proliferation, a viable strategy to quickly tease out at least some “de novo” resistant tumors after diagnosis is to assess tumor Ki67 labeling index, a marker of tumor cell proliferation, 2 to 4 weeks after neoadjuvant endocrine therapy. Reassessment of Ki67 and the calculation of the Preoperative Endocrine Prognostic Index (PEPI) on the surgical specimen following 3 to 4 months of endocrine therapy provide further information about the endocrine responsiveness of the tumor.

As shown in the two neoadjuvant endocrine trials in postmenopausal women with early-stage breast cancer—IMPACT (Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen) and the POL (Preoperative Letrozole) trial—the tumor Ki67 2 to 4 weeks after initiating endocrine therapy, rather than at baseline, correlated with individual patient outcome. We have therefore hypothesized that a 10% Ki67 early-in-treatment cut point can be used as an initial threshold for labeling a tumor endocrine-resistant. At least 20% of ER-rich tumors are in this category and thus need more active systemic therapy than AI monotherapy. The Cohort B of American College of Surgeons Oncology Group (ACOSOG) trial Z1031, a randomized phase II neoadjuvant comparison of the three AIs in postmenopausal women with ER-rich (defined by an ER Allred score of 6 to 8) clinical stage II or III breast cancer, triaged patients with high Ki67 (> 10%) at 2 to 4 weeks on therapy to neoadjuvant chemotherapy, to assess pathologic complete response.
rate as a surrogate marker for chemotherapy sensitivity. The study has completed patient accrual; its results are eagerly awaited. Analyses of these resistant tumors are of great interest, and we urgently need to design trials based on therapeutic targets identified, among which the PI3 kinase pathway presents a rich source of options.[1,8]

The PEPI was developed through retrospective analysis of the P024 trial, correlating post neoadjuvant endocrine therapy tumor characteristics with long-term outcomes, and was subsequently validated in an independent data set from the IMPACT trial.[5] A PEPI score of 0 (T1/2, N0, Ki67 2.7% or less and ER positive), representing approximately 20% to 30% of ER-rich tumors, predicted the best outcome in the absence of chemotherapy, while the relapse rate was significantly higher in the PEPI non-0 group. The PEPI non-0 group provides another opportunity for early identification of endocrine resistance. Again, we come back to ACOSOG Z1031 to look for more answers in the tumor analyses, and a correlation with long-term outcome. As a successor trial to the ACOSOG Z1031, ACTION (the Alliance for Clinical Trials in Oncology) is launching a large neoadjuvant/adjuvant phase III study entitled “ALTERNate approaches for clinical stage II or III Estrogen Receptor positive breast cancer NeoAdjuvant TrEatment in postmenopausal women (ALTERNATE)” to validate the use of PEPI 0 as a surrogate endpoint of endocrine therapy success (Figure). Tumor tissues are collected at baseline, at week 4 on therapy, and at the time of surgery. Biopsies at recurrence as well as sub-studies of novel therapeutic agents in the endocrine-resistant groups (high Ki67 at 4 weeks or PEPI non-0 at surgery) are being planned. At the conclusion of this study, we hope to be in a better position to address ER-positive breast cancer based on a combination of assessment of neoadjuvant response to identify responders who only need endocrine monotherapy and targeted/personalized approaches to the patients with resistant disease. In light of variations in Ki67 analytical practice, the International Ki67 in Breast Cancer Working Group published comprehensive recommendations on the preanalytical and analytical assessment, interpretation, and scoring of Ki67 to facilitate the use of this important marker in clinical research and eventually clinical practice.[9]

How can we prevent the occurrence of secondary resistance? We have been content with the cytostatic effect of endocrine agents, but this treatment is clearly inadequate in many patients. It is time to develop more active treatments in the early-disease setting that actually eradicate ER-positive breast cancer before new mutations and secondary resistance have a chance to develop. In this regard, standard chemotherapy is not the answer.

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