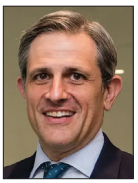
BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

Section Editor: Hope S. Rugo, MD

The Use of Genomic Assays to Guide Chemotherapy in Breast Cancer



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H&O What was the impetus for the OPTIMA trial?

KK The goal of OPTIMA, which was led by investigators in the United Kingdom, was to examine use of the Prosigna (Veracyte) 50-gene assay as an integral marker to determine which patients could avoid chemotherapy for high-risk estrogen receptor–positive (ER+), human epidermal growth factor receptor 2–negative (HER2–) early breast cancer.[1] Previous studies that evaluated genomic assays in breast cancer include TAILORx[2] and RxPONDER,[3] which looked at the Oncotype DX (Exact Sciences) 21-gene assay, and MINDACT,[4] which looked at the MammaPrint (Agendia) 70-gene assay. One big difference between OPTIMA and these trials is that OPTIMA included patients with N2 disease (4-9 positive nodes), whereas the patients in TAILORx had N0 disease (no positive nodes), those in RxPONDER had N1 disease (1-3 positive nodes), and those in MINDACT had N0 or N1 disease. In addition, unlike the premenopausal women in the other studies, those in OPTIMA were required to receive at least 3 years of ovarian function suppression.

H&O Can you describe the design of the OPTIMA trial?

KK The prospective phase 3 OPTIMA trial enrolled 4429 patients who were at least 40 years of age and had undergone surgery for ER+/HER2– early breast cancer. Patients who had N0 disease or nodal micrometastases (N1mic) were required to have a tumor with a diameter of at least 3 cm, whereas those with N1 or N2 disease were not required to have a tumor of that size. Patients were randomly assigned in a 1:1 ratio to receive standard treatment with chemotherapy plus endocrine therapy or undergo genomic testing with Prosigna to determine further treatment. Patients whose risk of recurrence (ROR) score on genomic testing was greater than 60 ("high") received standard treatment, whereas those whose score was 60 or lower ("low") received endocrine therapy alone. Patients were not told whether they were in the control arm or the investigational arm. The primary endpoint was invasive breast cancer–free survival (IBCFS).

Premenopausal patients received at least 3 years of ovarian function suppression along with oral endocrine therapy. Patients were considered postmenopausal if they were older than 45 years and had not menstruated within the last 12 months, had undergone a bilateral salpingo-oophorectomy, or had estradiol and follicle-stimulating hormone levels that were in the postmenopausal range.

H&O Can you describe the results of the OPTIMA study?

KK After a median follow-up of approximately 4 years, the researchers found no difference in IBCFS between the 2 arms in the complete per-protocol population; the adjusted hazard ratio was 1.03. In the up to two-thirds of the participants with a low ROR score, no difference in IBCFS was observed; the adjusted hazard ratio was 1.06. Patients with a low ROR score were postmenopausal in 60% of cases and premenopausal in 40% of cases, and the results did not differ between these patient groups.

The fact that the premenopausal women were required to receive at least 3 years of ovarian function suppression was an importance advance from earlier studies, which had no such requirement. Only approximately 16% of premenopausal patients in the endocrine-therapy

arm of RxPONDER received ovarian function suppression. The OPTIMA trial was the first study in which we were able to compare treatment approaches on the basis of a genomic assay for patients who had received optimal endocrine therapy, although it is worth noting that the trial was designed before the approval of CDK4/6 inhibitors as adjuvant therapy.

H&O Was there any signal that the disease of the highest-risk subgroups behaved differently from that of the low-ROR population?

KK The majority of the patients had a low ROR score, and most of those who had node-positive breast cancer had N1 disease. Just 20% of patients who had node-positive breast cancer and a low ROR score had N2 disease, and there did not seem to be any difference in the results for these patients—although it is worth noting that fewer than 40 events occurred in this population. Because we have few patients with a low ROR score and 4 to 9 nodes, we do not know how generalizable this finding is. For example, what was the median number of positive lymph nodes in the participants with N2 disease, and are the results for patients with 4 positive nodes different from the results for those with 9 positive nodes?

H&O What were some of the other limitations of this trial?

KK The vast majority of patients in this trial were non-Hispanic Whites, which limits the generalizability of the results. In addition, the fact that the median follow-up is only 4 years is a limitation because at least half of the recurrences of this subtype of breast cancer develop after the first 5 years. However, it is worth mentioning that most of the benefit of chemotherapy, when it occurs, is seen within the first 5 years. Follow-up in OPTIMA is ongoing.

H&O What are the roles of various genomic assays at your institution?

KK When we wish to use a genomic assay at my institution to determine whether a patient requires neoadjuvant therapy, we generally use the MammaPrint assay. We have real-world 3-year data from the FLEX Registry demonstrating that patients with ER+/HER2– breast cancer who are categorized as high-risk 2 for distant metastasis on MammaPrint may benefit from an anthracycline, whereas those who are categorized as high-risk 1 do not benefit from an anthracycline.[5] The ongoing SWOG S2206 trial is looking at the role of immunotherapy in stage 2 or 3 breast cancer according to the results of this assay (NCT06058377). In addition, I-SPY uses MammaPrint to determine who may be at high risk and eligible for chemotherapy and/or antibody-drug conjugates vs who may be at low risk and eligible for endocrine optimization if they have an ER+ tumor.

When we have postmenopausal patients who have N0 or N1 disease at my institution, we use the OncoType DX assay because we have longer follow-up from TAILORx and RxPONDER than from OPTIMA. Where we have made a change is in the management of premenopausal women who are older than 40 years and have N1 disease; we are now using the Prosigna assay for these patients. When patients are postmenopausal and have N2 disease, we discuss with them the role of an assay. If it is decided to use an assay, we also favor the Prosigna assay in that context. I will also mention that a phase 3 study from ECOG-ACRIN called RxFINE-Low is looking at the role of the Oncotype DX recurrence score who have high–anatomic risk ER+/HER– breast cancer, including those with N2 and N3 disease (NCT07391774).

H&O Will the results of OPTIMA change the National Comprehensive Cancer Network (NCCN) or American Society of Clinical Oncology (ASCO) guidelines?

KK Given the results of OPTIMA, I think that it is time for the NCCN and ASCO guidelines to be revisited. Fortunately, insurers are already covering Prosigna for patients.

Disclosures

Dr Kalinsky is a consultant for Genentech/Roche, Immunomedics, Seagen, AstraZeneca, Daiichi Sankyo, Puma Biotechnology, Mersana Therapeutics, Menarini Silicon Biosystems, Myovant Sciences, Takeda, and Merck. His spouse is an employee of ADC Therapeutics and a prior employee of EQRx.

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