short review

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ASCO 2019—Personal highlights on adjuvant breast cancer: (neo-)adjuvant therapy of HER2-negative HR-positive BC

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Summary This article intends to summarize personal highlights from the 2019 ASCO (American Society of Clinical Oncology) Annual meeting. The article does not aim to offer a comprehensive summary of the 1642 abstracts presented, but rather aims to highlight the abstracts that are the most relevant for the neo/adjuvant therapy of the HER2-negative, HR-positive breast cancer. By doing so, the article generates discussion on the practical implications, while portraying the rapidly changing landscape of the use of personalized treatment of early breast cancer in patients with HER2-negative, HR-positive disease.

Keywords Hormonal therapy · Predicting factors · Extended therapy duration

Clinical risk category and chemotherapy benefit: TAILORx

At 2018 ASCO (American Society of Clinical Oncology) TAILORx clinical trial [1] showed that patients who received low (0–10) or intermediate (11–25) recurrence score (RS) on the Oncotype DX® (Genomic Health Inc., Redwood City, CA, USA) test could forego chemotherapy and opt for anti-estrogen therapy only. However, patients with high RS > 25 were benefiting from chemotherapy as well as endocrine therapy.

This year, at the ASCO 2019, researchers shared updates from the TAILORx trial, bringing clarity to predicting risk of breast cancer recurrence in women under 50 [2, 3]. In a secondary analysis, the investigators sought to determine whether integration of RS and clinical risk stratification (tumor size and histologic grade) could more effectively determine prognosis and potential chemotherapy benefit, helping with identification of premenopausal women who might benefit from more aggressive anti-estrogen therapy, such as ovarian suppression.

For the overall population, clinical risk alone was not predictive of chemotherapy benefit. This was also true for the two-thirds of women who were over the age of 50. For the remaining aged 50 or younger, there was a trend favoring chemotherapy, irrespective of clinical risk, although this was not significant. Additionally, they found that there was no benefit from chemotherapy for younger women (age 50 or less) with a recurrence score of 16–25 and at low risk clinically.

The authors concluded that clinical risk stratification provides additional prognostic information to the 21-gene recurrence score, but not prediction of chemotherapy benefit in the overall TAILORx population or those >50 years, and facilitates more refined estimates of absolute chemotherapy benefit for women ≤50 years with a recurrence score of 16–25.

Taken together these findings highlight that the integration of clinical risk and RS in the node-negative population provides both greater prognostic precision and better understanding of the chemotherapy-induced disease-free survival (DFS) improvement. While not being predictive of chemotherapy benefit, the clinical risk did inform us about the distant recurrence risk.

Overall, the study argues that rather than being given chemotherapy, women younger than 50 with an intermediate RS 16–25 who have low clinical risk should be preferentially treated through endocrine therapy optimization (LHRH agonist or oophorectomy). By contrast, younger women with RS 16–25 and high clinical risk showed an absolute benefit with chemotherapy of 6–9%, so both endocrine therapy

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and chemotherapy should be considered for these patients.

Benefit from letrozole after sequential endocrine therapy: GIM

Early hormone receptor-positive breast cancer has a high rate of late recurrence, with most occurring more than 5 years from diagnosis [4]. Based on the data from randomized clinical trials showing that adjuvant endocrine therapy (ET) reduces recurrence of breast and contralateral breast cancer, improving disease-free survival rate (DFS) [5–8] current guidelines recommend up to 10 years of adjuvant ET for patients with node-positive and higher-risk node-negative disease and suggest considering 5 years of adjuvant ET for patients with lower-risk, node-negative disease.

The GIM4 (GIM: Gruppo Italiano Mammella) conducted a prospective, randomized clinical trial to assess the effectiveness of different durations of ET of letrozole after tamoxifen [9]. A total of 2056 postmenopausal patients (I–III stage, HR-positive early breast cancer (EBC)) free of recurrence after 2–3 years of adjuvant tamoxifen were randomized in a 1:1 ratio to receive 2–3 years (short arm, S) or 5 years (long arm, L) of letrozole; with tamoxifen being started within 3 months of completing chemotherapy. The primary endpoint was invasive DFS; secondary endpoints were overall survival (OS) and safety.

The main patient characteristics in both arms were well balanced and the median follow-up was 10 years (IQR range: 8.6–11.4 years). Women in shorter-duration arm had higher treatment completion rates (76% vs 57%). The median duration was as planned 5.0 years in the extended and 2.4 in the shorter-duration arm. Due to toxicity, 13% of patients in the extended and 8% in the shorter-duration arm discontinued the treatment.

The 8-year DFS was 80% (95% CI: 77.3–82.7) and 85% (95% CI: 82.9–87.6) in the S and L arm, respectively (HR 0.82; 95% CI: 0.68–0.98; $p=0.031$). The HR is close to statistical significance demonstrating a small benefit in favor of extended adjuvant therapy. This effect did not change in a multivariate analysis that included nodal status, grading and age.

There was no difference in OS between treatment arms for both the intent to treat (ITT) (HR: 0.82) and landmark analysis (HR: 0.86).

Among 1960 patients evaluable for toxicity, osteoporosis was diagnosed in 47 (4.8%) in the S arm and 81 (8.3%) patients in the L arm ($p=0.002$). Bone fractures occurred in 5 (0.5%) and 9 (0.9%) patients in the S and L arm, respectively ($p=0.29$).

Authors concluded that after 2–3 years of adjuvant tamoxifen, extended treatment with 5 years of letrozole resulted in significant improvement in DFS compared to the standard duration of 2–3 years of letrozole.

Overall, the results of the GIM4 LEAD study fit with our existing standard of care, where extended adjuvant ET is offered to patients with higher-risk disease (node-positive disease, as well as node-negative disease and higher-risk disease traits—larger and grade 3 tumors), as it confers a small but significant benefit as compared with shorter-duration ET. However, remaining on the Aromatase inhibitors (AI) long term can be challenging for some patients due to the toxicity profile. Regarding the total treatment duration, the results of the current study (significant difference between 7 vs 5 years) combined with the finding of the ABCSG-16 trial [10] which found no difference between 10 vs 7 years of the extended adjuvant ET highlight that the clinicians should have individualized discussions with each patient, considering 7–10 years for higher-risk patients and 5 years for lower-risk node-negative patients.

Trans-aTTom: Breast Cancer Index for prediction of endocrine benefit and late distant recurrence

The aTTom (adjuvant tamoxifen—to offer more?) study was a prospective phase III trial that randomized 6953 HR+ women to stop or continue tamoxifen (TAM) for 5 more years after completing at least 4 years of prior TAM [11]. Results at 9 years of median follow-up demonstrated fewer breast cancer recurrences (21% vs 25%; RR = 0.86 [95% CI 0.77–0.96]; $P=0.006$) and reduced breast cancer mortality (13% vs 15%; HR = 0.91 [95% CI 0.80–1.04]; $P=0.18$) but increased incidence of endometrial cancer with longer TAM use ($P<0.0001$).

A remaining challenge in the context of extended endocrine therapy for hormonal-positive breast cancer is how to identify which patients will gain the most benefit and which patients can stop earlier to avoid toxicity.

To aid the identification of patients who will benefit from 10 years vs 5 years of adjuvant tamoxifen, the Trans-aTTom trial was designed to assess the predictive value of the Breast Cancer Index (H/I) status, whether high or low, within the aTTom trial cohort [14].

The Breast Cancer Index® (BCI; Biotheranostics, Inc., San Diego, CA, USA) is an 11-gene expression test measuring tumor proliferative status and the 2 gene ratio measuring estrogen signaling, which provides a prognostic score for assessing the risk of cumulative (0–10 years) and late (post 5 years) recurrence, with BCI (H/I) having been shown to predict benefit from extended endocrine therapy (ET) after 5 years of tamoxifen [12, 13].

Primary and secondary endpoints were recurrence-free interval (RFI) and disease-free interval (DFI), respectively. A total of 2637 tumors were centrally assessed for ER, PR and HER2 status leading to 1822 HR+ patients analyzed (1018 N0, 583 N+). Initial results from patients with N+ disease at 12 years of

median follow-up showed 287 (49%) were classified as BCI(H/I)-high and 296 (51%) were classified as BCI(H/I)-low.

BCI(H/I)-High patients showed a statistically significant benefit of 9.8% in RFI with 10 years vs 5 years of TAM (HR = 0.35 [95% CI 0.15–0.85]; $P = 0.027$), whereas BCI(H/I)-low patients showed no benefit (–0.2% RFI; HR = 1.07 [95% CI 0.69–1.65]; $P = 0.77$). The authors concluded that data provide further validation and establish level 1B evidence for BCI as a predictive biomarker for preferential benefit from EET in HR+ breast cancer.

The results of this trial align well with the outcomes from earlier trials including the MA.17 trial, which found a significant benefit for extended AI therapy vs placebo among BCI (H/I)-high patients following 5 years of tamoxifen [6, 7].

Taken together, these data highlight the BCI as an effective predictive biomarker, which is logical considering that the BCI (H/I) test is a measure of ER signaling. In BCI (H/I)-high breast cancer with strong ER signaling, endocrine therapy would be expected to be quite effective, and indeed is where we see a benefit with 10 years of adjuvant endocrine therapy. Conversely, for a BCI (H/I)-low cancer with low ER signaling, benefits of endocrine therapy would be expected to be more modest, which they indeed are. The further value of these results lays in their addressal of the necessity for evidence-based tools, like BCI (H/I), to be referenced when discussing with patients about extending endocrine therapy beyond 5 years.

Conflict of interest S. Beslija declares that he has no competing interests.

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