JOURNAL WATCH

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Our panel of experts highlight the most important research articles across the spectrum of topics relevant to the field of breast cancer management

Expert panel: Hitoshi Tsuda, National Defense Medical College, Tokorozawa, Japan; Stefan Glück, University of Miami, FL, USA

Muenst S, Soysal SD, Gao F *et al.*
The presence of programmed death 1 (PD-1)-positive tumor-infiltrating lymphocytes is associated with poor prognosis in human breast cancer.
Breast Cancer Res. Treat. 139, 667–676 (2013).

Breast cancer tissue is composed of cancer cells and stroma, and in a subset of cases, the stromal tissue is accompanied by significant tumor-infiltrating lymphocytes (TILs). TILs may be predominantly of a cytotoxic or helper T nature, but it remains unclear whether or not the presence of TILs suggests strong antitumor immunity. The present study focused on the PD-1, a T-cell costimulatory receptor of the CD28/CTLA-4 family. From basic and early clinical studies, cancer cells were suggested to escape or attenuate antitumor immunity using PD-1/PD-L1 signaling pathway. The authors examined the clinical significance of PD-1 expression in TILs using immunohistochemistry and flow cytometry. They detected PD-1-positive TILs in 15.8% of breast cancer cases, and found that the patients with breast cancer with PD-1⁺ TILs showed significantly worse clinical outcomes. By subset analyses, the presence of PD-1⁺ TILs was of prognostic significance in luminal B and basal-like subtypes, but not in luminal A and HER2-enriched subtypes. These results may support the idea that not only the information from TILs, but also that from PD-1 status, is necessary in evaluating the clinicopathological significance of TILs, and may explain, in part, the molecular mechanism of the maintenance of

the microenvironment composed of cancer cells and TILs. Because antibody therapies targeting the PD-1/PD-L1 pathway are already being applied clinically, an assay of PD-1 expression might be of clinical use.

– Written by Hitoshi Tsuda

Dowsett M, Sestak I, Lopez-Knowles E *et al.*
Comparison of PAM50 risk of recurrence score with Oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy.
J. Clin. Oncol. doi:10.1200/JCO.2012.46.1558 (2013) (Epub ahead of print).

In this study, 1017 patients with ER-positive primary breast cancer treated with anastrozole or tamoxifen in the ATAC trial were assessed for risk of recurrence using the PAM50 test by nCounter® (NanoString, WA, USA). This was compared with Oncotype DX recurrence score (RS) and the four traditional markers (ER, PR, HER2 and Ki-67) as tested by immunohistochemistry (IHC) or FISH when appropriate (IHC4). Overall, 940 samples were fully available for comparing the three prognostic approaches: PAM50 versus RS versus IHC4. The authors were able to show that risk of recurrence provided more prognostic information in this patients cohort (ER-positive, axillary lymph node-negative endocrine-treated early breast cancer) than RS or IHC4. This could be practice changing since most oncologists today in the USA use RS in these patients. As chemotherapy did not lead to a response (PCR) and yet the prognosis was excellent, the predictive power of the test

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is proven. This has not yet been validated in a randomized, prospective controlled trial but it is expected that two molecular studies will report such data within the next 2 or 3 years (MINDACT – using the MammaPrint® test (Agendia, CA, USA) – and TAILORx – using Oncotype DX). Until then, it seems that identifying intrinsic subtypes with PAM50 might be more precise; the test is at present not available in the USA.

– Written by Stefan Glück

Petrelli F, Coinu A, Cabiddu M, Ghilardi M, Lonati V, Barni S. Five or more years of adjuvant endocrine therapy in breast cancer: a meta-analysis of published randomised trials. *Breast Cancer Res. Treat.* doi:10.1007/s10549-013-2629-4 (2013) (Epub ahead of print).

Eight randomized trials including 29,138 patients comparing 5 years versus more than 5 years of hormonal therapy in breast cancer were assessed and analyzed. Overall, in ER-positive breast cancers, extended endocrine therapy beyond 5 years of tamoxifen significantly improved overall survival with a relative risk reduction

(RRR) of 11% ($p = 0.03$). It also improved breast cancer-specific survival with a RRR of 22% ($p = 0.0003$), and relapse-free survival showed a RRR of 28% ($p = 0.01$) compared with 5 years of hormonal therapy alone. This meta-analysis is practice changing and certainly confirms the initial trials of extending 5 years of tamoxifen with an additional 5 years of letrozole or exemestane, as well as the more recently reported ATTOM and ATLAS studies.

– Written by Stefan Glück

Pivot X, Romieu G, Debled M *et al.*; PHARE Trial Investigators. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised Phase 3 trial. *Lancet Oncol.* 14(8), 741–748 (2013).

This large, randomized, prospective trial compared the duration of 6 versus 12 months of trastuzumab in early HER2-positive breast cancer: it was a noninferiority randomized trial including patients who received chemotherapy with concurrent or sequential trastuzumab; 3384 patients were randomized. Eligibility criteria included LN⁻ and LN⁺ patients and tumor size >1 cm and

they needed to have received at least four cycles of chemotherapy. The study failed to show that 6 months of trastuzumab is non-inferior to 12 months. The subgroup analysis suggested that the sequential modality for ER-negative tumors impacted the overall results; the subset of patients with concomitant therapy (chemotherapy and trastuzumab at the same time) and ER-positive tumors has indeed shown noninferiority of 6 versus 12 months.

Overall, 12 months of adjuvant trastuzumab remains standard. In patients who receive concurrent chemotherapy with trastuzumab and have ER-positive tumors, the duration of 6 months of treatment does not seem to be inferior.

– Written by Stefan Glück

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