# Encouraging data on immunotherapy, cardiotoxicity, and DFS

The immunologic checkpoint inhibitors avelumab and pemrolizomab show promise in patients with metastatic breast cancer; a trastuzumab-based, nonanthracycline regimen yields cardiac safety benefits in early HER2-positive disease; and the oral tyrosine kinase inhibitor neratinib delivers consistent disease-free survival at 3 years: Bruce Jancin and Susan London report from the 2015 annual meeting of the San Antonio Breast Cancer Symposium.

## Avelumab shows selective efficacy in metastatic breast cancer

**Key clinical point** The PD-L1 inhibitor avelumab showed clinical efficacy in specific subsets of metastatic breast cancer patients. **Major finding** Clinical response rate with avelumab for locally advanced or metastatic breast cancer was 33% in women with strong expression of PD-L1 by immune cells within their tumor, compared with single-digit response rates in those with lesser or no expression. **Data source** An open-label phase 1b trial (JAVELIN) in which 168 women with locally advanced or metastatic breast cancer received avelumab at 10 mg/kg every 2 weeks until disease progression. **Disclosures** The study was sponsored by a joint Merck-Pfizer commercial alliance. Dr Dirix reported having no financial conflicts.

The immune checkpoint inhibitor avelumab showed only modest single-digit efficacy in an unselected group of metastatic breast cancer patients, but the results were sevenfold better in the subset of JAVELIN trial participants with strong expression of programmed death-ligand 1 (PD-L1) by immune cells within the tumor, Dr Luc Y Dirix reported at the meeting.

Avelumab is an investigational fully human IgG1 monoclonal antibody that selectively binds to PD-L1. In addition, it's believed that avelumab elicits antibody-dependent cellular cytotoxicity, said Dr Dirix of the University of Antwerp, Belgium.

JAVELIN is a multipronged phase 1b clinical trial that has so far enrolled more than 1,000 participants with various types of advanced cancer. Avelumab has shown antitumor activity in patients with lung, gastric, bladder, ovarian, and other cancers. Phase 3 randomized trials are underway to evaluate avelumab in patients with advanced non-small-cell lung cancer or gastric cancer.

Dr Dirix reported on the 168 JAVELIN participants with locally advanced or metastatic breast cancer refractory to standard therapy, including anthracycline and a taxane. Their median time since diagnosis of metastatic disease was 21.6 weeks at the time they went on avelumab at 10 mg/kg every 2 weeks until disease progression occurred. Roughly half of participants had already undergone three or more regimens for their advanced malignancy.

At a median duration of 10 months follow-up, 1 of the 168 patients had shown a complete response and 7 others had a partial response, for an overall response rate of 4.8%. Of note, 5 of the 8 responders were among the 58 women with triple-negative breast cancer (TNBC). Median time to response was 11.4 weeks, with a relatively long 28.7-week median duration of response. The response was ongoing in 5 of 8 patients at the time of Dr Dirix's presentation.

Of the 136 patients for whom data on PD-L1 expression level were available, 4 of the 12 with PD-L1 expression by at least 10% of immune cells within the tumor had a clinical response, for a 33% rate. Nine patients with TNBC had a PD-L1 response which rose to this level, and 4 of these 9 (44%) had a clinical response.

In contrast, patients whose immune cells within the tumor were PD-L1-negative had a clinical response rate of less than 3%. But expression of PD-L1 by tumor cells was not predictive of benefit from avelumab; even when 25% or more of a patient's tumor cells expressed PD-L1, the clinical response rate was in the single digits.

Ten of 58 patients with TNBC (17%) experienced tumor shrinkage by 30% or more during the course of treatment.

Dr Dirix characterized avelumab's safety profile as acceptable for patients with metastatic breast cancer. Eight patients (4.8%) discontinued participation because of treatment-related adverse events. Potentially treatment-related immune toxicity occurred in 8 patients who became hypothyroid, 3 with autoimmune hepatitis, 3 with pneumonia, and 2 with thrombocytopenia. Three-quarters of these complications were grade 1 or 2.

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Far more common treatment-related adverse events included grade 1 or 2 fatigue, which occurred in 19% of patients, nausea in 13%, and diarrhea in 9%.

In response to a question about why PD-L1 expression by tumor cells predicted benefit with avelumab in lung cancer and other malignancies in the study but not in metastatic breast cancer, Dr Dirix replied that he and his coinvestigators do not have an answer yet, but are looking into that question.

— Bruce Jancin

## Pembrolizumab shows promise in PD-L1-positive breast cancer

**Key clinical point** Pembrolizumab seems safe and modestly active for treatment of ER-positive, HER2-negative advanced breast cancer that expresses PD-L1. **Major finding** Overall response rate was 12%, and the rate of grade 3 or 4 adverse events was 16%. **Data source** An analysis of 25 women with PD-L1-positive, ER-positive, HER2-negative advanced breast cancer enrolled in a phase 1b trial of pembrolizumab monotherapy in solid tumors (KEYNOTE-028). **Disclosures** Merck & Co sponsored the trial. Dr Rugo disclosed that her institution receives research funding from Merck and Genentech.

The immune checkpoint inhibitor pembrolizumab seems to be safe and modestly active in women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer that expresses programmed death-ligand 1 (PD-L1), based on preliminary results of a phase 1b trial reported at the meeting by Dr Hope S Rugo.

Nineteen percent of women screened for the trial, KEYNOTE-028, had archival or fresh tumors from nonirradiated sites that tested positive for this ligand by immunohistochemistry, said Dr Rugo, the lead investigator of the trial.

A total of 25 of these women received at least 1 dose of pembrolizumab, an antibody to the PD-1 [programmed death-1] cell surface receptor that blocks interaction of the receptor with its ligands, thereby preventing the inactivation of T cells. (The antibody is currently approved by the US Food and Drug Administration for the treatment of melanoma and non-small-cell lung cancer.)

With a median duration of follow-up of 7.3 months, the overall response rate as assessed by investigators using RECIST criteria was 12%, and the clinical benefit rate was 20%, reported Dr Rugo, who is clinical professor in the department of medicine (hematology/oncology) and director of the breast oncology clinical trials program at the University of California, San Francisco reported. Responses were durable, lasting anywhere from about 9 weeks to more than 44 weeks.

The rate of grade 3 or 4 adverse events was 16%. One patient had to have interruption of pembrolizumab because of she developed an immune adverse event.

"Based on these data, we believe that further investigation of immune therapies in ER-positive, HER2-negative breast cancer, particularly using combination therapies that can expand the T-cell compartment, are warranted," said Dr Rugo.

She noted that the trial's findings differ somewhat from those of the JAVELIN study, a similar trial testing avelumab, an investigational antibody against the PD-L1 ligand itself (p. 85) The JAVELIN trial found a much higher PD-L1 positivity rate in screened women – 55% – and a much lower overall response rate of 3%.

These differences may have been due to use of different immunohistochemical assays for PD-L1 in the 2 trials, a lack of data for some patients in the JAVELIN trial, and/or differences in the target of the agent used (PD-1 vs PD-L1 in the JAVELIN trial), Dr Rugo speculated. "It's clear that as we move forward in this field of immunotherapy, which we are all very excited about, that standardization of assays assessing PD-L1 positivity are going to be critical," she concluded.

Giving some background to the research, she noted that PD-L1 expression has been inversely correlated with ER expression. A previous trial found an overall response rate of about 19% in triple-negative breast cancer. For KEYNOTE-028, patients were screened for PD-L1 positivity, even though pembrolizumab targets PD-1, because there is much greater variability in ligand levels than in receptor levels when it comes to determining T cell inactivation, Dr Rugo explained. Of the 25 women treated, 80% had received 3 or more prior lines of therapy for their advanced disease. They were given pembrolizumab every 2 weeks with assessments every 8 weeks initially.

The grade 3 or 4 adverse events observed were cases of autoimmune hepatitis, increased gamma-glutamyl transferase levels, muscle weakness, nausea, and septic shock. However, there were no treatment-related deaths. In patients who developed any-grade immune-related adverse events of interest, 1 patient with autoimmune hepatitis had to have treatment interruption.

All of the responses observed were partial responses. The median time to response was 8 weeks, and the median duration of response was not reached (range, 9-44 weeks). The 3 patients with a response had been in the study for at least 26 weeks as of the data cut-off for analysis.

"Cost is an issue with these drugs," said attendee Dr Mark Graham II, an oncologist with Waverly Hematology Oncology, Cary, North Carolina. "I'm particularly interested in your nonresponders and the fact that we can see pseudoprogression with these drugs. So for the eventual nonresponders, what is the likely number of cycles that will be necessary to conclude that a patient is not an initial responder?"

Dr Rugo replied that it is difficult to accurately pin down

that number because patients in the trial were taken off the agent as early as 8 weeks along if they had any evidence of progression. "I don't think we know the answer yet, but if you went out to 16 weeks, all the patients that we saw who were going to respond had responded by 16 weeks."

An accurate answer will likely require future studies, she added. "I think it's most complicated in triple-negative disease, where a small phase 1b trial showed a very long median time to response. So this is a good question and it remains to be answered."

— Susan London

## 10-year follow-up shows important cardiac safety benefits with trastuzumab

**Key clinical point** An adjuvant trastuzumab-based, nonanthracycline regimen for early HER2-positive breast cancer offers important cardiac safety benefits over the alternatives. **Major finding** Women with early HER2-positive breast cancer experienced less risk of long-term cardiac toxicity and acute leukemia if their adjuvant therapy consisted of 6 cycles of docetaxel plus carboplatin and 1 year of trastuzumab than if they received trastuzumab plus an anthracycline. **Data source** A phase 3, three-armed clinical trial, with 3,222 patients and a median 10.3 years of follow-up. **Disclosures** Sanofi, with additional support from Genentech, sponsored the trial. Dr Dlamon reported serving on advisory boards for Genentech/Roche, BioMarin, Pfizer, and Novartis.

Final 10-year analysis of the landmark BCIRG-006 trial underscores the safety advantages of a nonanthracycline, trastuzumab-based adjunctive treatment regimen in early-stage HER2-positive breast cancer, Dr Dennis J Slamon reported at the meeting.

At a median 10.3 years of follow-up in the phase 3 randomized trial of 3,222 patients, a substantial reduction in the risk of cardiac toxicity was evident in the women assigned to 6 cycles of docetaxel and carboplatin plus 1 year of trastuzumab (the TCH arm), compared with the 2 anthracycline-containing study arms, he reported.

At baseline, the 3 treatment groups were well balanced in terms of cardiovascular risk factors. Yet over the course of the study, only 4 women in the TCH arm developed clinical heart failure, compared with 21 patients who received 4 cycles of doxorubicin and cyclophosphamide followed by 4 cycles of docetaxel and 1 year of trastuzumab (AC-TH), and 8 patients in the control arm who got 4 cycles of doxorubicin and cyclophosphamide followed by 4 cycles of docetaxel (AC-T).

Thus, adding docetaxel to 1 year of trastuzumab conferred a fivefold increase in this major cardiac complication, compared with trastuzumab alone, noted Dr Slamon, professor of medicine and chief of the division of hematology-oncology at the University of California, Los Angeles.

His presentation of the final analysis also provided important new information on the issue of treatment-related subclinical reductions in cardiac reserve as manifest by decreased left ventricular ejection fraction (LVEF). A greater than 10% reduction in LVEF occurred in 9.4% of the TCH group, 19.2% of the AC-TH group, and 11.8% of the AC-T control group. In 2009 when Dr Slamon presented the 5-year follow-up of BCIRG-006 at the San Antonio meeting, he was able to report that during the first year after treatment the no-anthracycline TCH group showed a recovery of LVEF to near baseline, whereas the LVEF in the AC-TH and AC-T groups did not bounce back through the 5-year mark. The question raised at that point was how long the patient's LVEF would remain diminished.

"With the 10-year data, with LVEFs measured annually after the end of treatment, this loss is real and is maintained. The question now is what will become of these patients when they acquire their long-term, age-related cardiac risk factors after we've already compromised their LVEF to some degree?" he said.

The primary endpoint in BCIRG-006 was disease-free survival (DFS). At final follow-up, with a total of 876 such events, the DFS rate was 74.6% in the AC-TH group and statistically similar at 73% in the TCH group, both of which were superior to the 67.9% figure in the AC-T control arm. Only 10 DFS events separated the TCH and AC-TH groups at 10 years. Overall survival rates in the two trastuzumab arms weren't significantly different either.

To answer the question of whether patients with higher-risk HER2-positive early breast cancer require anthracycline-based adjunctive therapy in order to maximize benefit, the investigators did a subanalysis restricted to the roughly 400 women with four or more positive lymph nodes. The DFS rate was 62.9% with TCH and a near-identical 62.8% with AC-TH, both superior to the 53.6% DFS rate in the AC-T group.

All 8 cases of acute leukemia occurred in the AC-TH and AC-T study arms.

— Bruce Jancin

## Neratinib shows consistent breast cancer benefit at 3 years

**Key clinical point** Delayed adjuvant neratinib after chemotherapy and trastuzumab continues to show significant benefit in women with HER2-positive breast cancer. **Major finding** The invasive DFS rate at the 3-year follow-up in women with HER2-positive breast cancer remained significantly higher with delayed adjuvant neratinib compared with placebo (92% vs 89.1%, respectively). **Data source** A double-blind, randomized clinical trial (ExteNET) of 2,840 women with stage II-IIIc HER2-positive breast cancer with node-positive disease who were randomized to oral neratinib at 240 mg/day or placebo for 1 year following completion of adjuvant chemotherapy and 1 year of trastuzumab. **Disclosures** Puma Biotechnology sponsored the trial. Dr Chan reported serving as a consultant to Pfizer, Amgen, and Eisai.

The investigational oral tyrosine kinase inhibitor neratinib showed continued benefit in terms of reduced invasive disease-free survival (DFS) at 3 years of follow-up in women with early-stage HER2-positive breast cancer in the randomized, double-blind ExteNET trial, Dr Arlene Chan reported at the meeting.

The 3-year analysis was not prespecified. It was performed because Dr Chan and her coinvestigators were concerned that the previously reported benefit seen at 2 years might be lost with longer follow-up, as has occurred with trastuzumab in the landmark HERA trial. However, the absolute 2.3% benefit for neratinib compared with placebo seen at 2 years in ExteNET was maintained at 3 years in the updated analysis, where the absolute difference remained effectively unchanged at 2.1%, said Dr Chan, vice chair of the Breast Cancer Research Center of Western Australia in Perth.

Moreover, most patients have reached the 4-year mark in follow-up, where the invasive DFS benefit has remained significant in favor of neratinib over placebo, at 90.5% versus 88.6%, respectively, she added.

ExteNET was a large international trial of 2,840 women with stage II-IIIc HER2-positive breast cancer with node-positive disease who were randomized to oral neratinib at 240 mg/day or placebo for 1 year beginning an average of 4.4 months after completing adjuvant chemotherapy and 1 year of trastuzumab.

The impetus for ExteNET was the well-established observation that relapse occurs in up to 26% of trastuzumab-treated patients at 8-plus years of follow-up. The study hypothesis is that neratinib, a tyrosine kinase inhibitor of HER1, -2, and -4, will prevent or delay disease recurrence because it attacks the cancer through different a mechanism of action than that from of trastuzumab.

At 2 years of follow-up post neratinib, the invasive DFS rate was 93.9% with active therapy and 91.6% with placebo, as previously reported by Dr Chan. At 3 years in the roughly 85% of patients who remained in the study, which changed sponsors in the interim, the rates were 92% and 89.9%.

The 3-year outcomes were most robust in patients who began neratinib less than 1 year after completing trastuzumab and who were hormone receptor positive. In this subgroup, the 3-year invasive DFS rate was 93.3% with neratinib versus 88.6% with placebo. That, Dr Chan said, is the scenario where delayed adjuvant neratinib might prove beneficial in clinical practice.

Patients with hormone receptor-negative disease didn't benefit from neratinib.

Forty percent of patients on neratinib developed grade 3 diarrhea, the agent's major side effect and one that is a class effect with the tyrosine kinase inhibitors. Most cases occurred within the first 30 days of treatment and lasted for a median of 5 days, with 1.4% of neratinib-treated patients being hospitalized for this complication.

Dr Chan noted that the study protocol precluded prophylaxis with loperamide during the first month of neratinib, which has been shown by other investigators to markedly reduce the frequency and severity of diarrhea.

Another ExteNET follow-up is planned at the 5-year mark.

— Bruce Jancin