Immunotherapy moves into the breast cancer landscape

At this year's San Antonio Breast Cancer Symposium, investigators presented some encouraging findings for difficult-to-treat patient populations, but issues such as therapy side effects and fertility concerns in younger patients also highlighted the importance of looking closely at the risk-benefit relationship in delivering quality, personalized care to patients with breast cancer.

Pembrolizumab shows efficacy in advanced triple-negative breast cancer patients

Key clinical point Immunotherapy with pembrolizumab benefits a subset of patients with advanced, heavily pretreated triple-negative breast cancer. **Major finding** 5 of 27 patients had a durable partial or complete response to pembrolizumab monotherapy. **Data source** A phase 1b study of 32 women with advanced, heavily pretreated triple-negative breast cancer who were placed on pembrolizumab at 10 mg/kg IV every 2 weeks. **Disclosures** Sponsored by Merck. The presenter reported having no conflicts of interest.

Roughly 1 in 5 women with heavily pretreated, advanced triple-negative breast cancer experienced a durable response to monotherapy using the novel immune checkpoint inhibitor pembrolizumab in a small proof-of-concept study. "The acceptable safety and tolerability profile coupled with the promising antitumor activity seen in this very early trial support the further development of pembrolizumab in patients with advanced triple-negative breast cancer," Dr Rita Nanda said in presenting the findings of the KEYNOTE-012 study.

The phase 1b study comprised 32 women with advanced triple-negative breast cancer, all with PD-L1-positive tumors. They were placed on pembrolizumab at a dose of 10 mg/kg IV every 2 weeks. Pembrolizumab is a humanized IgG4 monoclonal antibody that binds to the PD-1 receptor with high affinity, thereby switching off PD-1-mediated inhibition of the antitumor immune response.

This was a group of patients with disease progression despite extensive earlier treatments. Median survival is about 1 year from the time of diagnosis of metastatic triple-negative breast cancer, and since receiving that diagnosis nearly half of the study participants had received 3 or more lines of chemotherapy for metastatic disease. So their median life expectancy at enrollment in KEYNOTE-012 was just a few months, making the durability of the responses seen in the handful of pembrolizumab responders all the more impressive, said Dr Nanda, a medical oncologist at the University of Chicago.

The overall response rate in the 27 evaluable patients was 18.5% using RECIST version 1.1 criteria with central review. One patient had a complete response, and 4 had a partial response. Another 7 had stable disease. One-third of patients showed tumor shrinkage upon imaging.

The median time to response was 18 weeks. At a median 9.9 months of follow-up, the median duration of response had not yet been reached. Three of 5 responders remained on treatment for 48 weeks or longer, whereas the 2 who discontinued pembrolizumab did so at 40 weeks. Median PFS (PFS) was 1.9 months, with a PFS at 6 months of 23%.

Although 56% of patients experienced 1 or more treatment-related adverse events, most of the events were mild and easily managed without treatment discontinuation. However, 4 patients experienced grade 3 anemia, aseptic meningitis, headache, or pyrexia, and a fifth who had rapidly progressive disease developed fatal disseminated intravascular coagulation.

A proprietary Merck assay for PD-L1 showed that 58% of patients with advanced triple-negative breast cancer screened as a prelude to the study were deemed to have PD-L1-positive tumors. But investigators saw no correlation between the degree of PD-L1 positivity and response to treatment, so it remains unclear how to identify beforehand the patient subgroup likely to respond to pembrolizumab.

A phase 2 study is planned for early 2015. Tumor biopsies will routinely be obtained in this and other future trials so investigators can search fresh tissue for useful biomarkers; this was not done in KEYNOTE-012.

— Bruce Jancin

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SOFT trial endorses selective ovarian suppression in early breast cancer

Major finding There was an absolute 7.7% difference in the rate of freedom from recurrent breast cancer at 5 years between women managed in this way and those on standard therapy with tamoxifen only. **Data source** The SOFT study, a randomized, prospective trial involving 3,047 premenopausal women with hormone receptor-positive early-stage breast cancer in 25 countries. **Disclosures** Funded by the National Cancer Institute and Pfizer. The presenter reported having no financial conflicts.

Adding ovarian suppression to 5 years of tamoxifen in women with hormone receptor-positive early breast cancer who remain premenopausal following chemotherapy provides a markedly greater reduction in breast cancer recurrence, compared with standard adjuvant therapy with tamoxifen alone, and combining ovarian suppression with an aromatase inhibitor instead of tamoxifen further improves outcomes, Dr Prudence Francis reported at the symposium.

This was a key finding of SOFT, a randomized comparison of adjuvant tamoxifen or exemestane plus ovarian suppression versus tamoxifen alone in 3,047 patients in 25 countries.

The other key finding in SOFT was that not all premenopausal patients benefited from ovarian suppression. Those who didn't receive chemotherapy based on a decision made with their physician had excellent outcomes with 5 years of tamoxifen alone, with a 95.8% disease-free survival at 5 years. In those patients, who were typically closer to the age of natural menopause onset and had cancers with a more favorable pathology than women who underwent chemotherapy, adding ovarian suppression offered no further advantage over tamoxifen alone, added Dr Francis, head of breast medical oncology at the Peter MacCallum Cancer Center, Melbourne, Australia.

The SOFT trial was unique in that it mandated that only women with documented recovery of ovarian function within 8 months of completing chemotherapy were eligible for enrollment.

At a median follow-up of 5.6 years, the 5-year disease-free survival rate was 84.7% in patients randomized to tamoxifen alone and not significantly different at 86.6% in those assigned to tamoxifen combined with ovarian function suppression. But the study design included 2 distinct populations – 53% of patients received chemotherapy and 47% did not – and their outcomes were distinctly different.

The group that had undergone chemotherapy tended to have a higher baseline recurrence risk. Patients in that group were younger (average age, 40 years) and typically had larger, higher-grade tumors and were more likely to be node positive. Their 5-year rate of freedom from breast cancer recurrence was 78% with tamoxifen alone, 82.5% with tamoxifen and ovarian suppression, and 85.7% with exemestane combined with ovarian suppression. That translates to a 22% decrease in the relative risk of recurrence in women on tamoxifen plus ovarian suppression. The absolute 7.7% difference in freedom from recurrent breast cancer at 5 years between women on exemestane plus ovarian suppression, compared with tamoxifen alone equated to a 35% relative risk reduction.

The advantage of ovarian suppression was most notable in the 350 study participants who were younger than 35 years. Their 5-year rate of freedom from recurrent breast cancer was 67.7% with tamoxifen alone, 78.9% with tamoxifen combined with ovarian suppression, and 83.4% with exemestane and ovarian suppression, for an absolute difference of 15.7%, compared with tamoxifen only.

Findings from previous studies suggested that women diagnosed with hormone receptor-positive breast cancer before age 35 are at particularly high risk of disease recurrence. This was borne out in SOFT. One in 3 women under age 35 who were assigned to tamoxifen alone had further breast cancer within 5 years, compared with just 1 in 6 on exemestane plus ovarian suppression, Dr Francis reported.

Systematic assessment of quality of life and treatment toxicities featured prominently in the SOFT trial. Add-on ovarian suppression was associated with increased rates of menopausal symptoms, insomnia, hypertension, diabetes, osteoporosis, and depression. The endocrine toxicities became less pronounced after 2 years. Patient reports of sexual dysfunction were more prominent and longer lasting in the exemestane group. In all, 15% women stopped ovarian suppression by 2 years, and 22% stopped by 3 years.

— Bruce Jancin

Decreased weight, increased activity improved breast cancer survival for some women

Key clinical point Diet and exercise seem to improve outcomes in some women with breast cancer. **Major finding** A dietary intervention conferred an average 2-year survival advantage upon women with ER+/PR+ breast cancer. **Data source** A randomized trial involving 2,437 women with early-stage, treated breast cancer. **Disclosures** Sponsored by the National Cancer Institute. Dr Chlebowski had no financial disclosures.

Losing weight and exercising may be an important key to good outcomes in some women with breast cancer - especially those with hormone receptor-negative tumors. For women with tumors that are both estrogen and progesterone receptor-negative, losing at least 5 lb or 5% of total body weight decreased the 10-year risk of all-cause mortality by 64%, Dr Rowan Chlebowski said at the symposium.

Although it was a post hoc exploratory analysis, the subgroup findings suggest that a lifestyle intervention pro-

gram could be an effective way to help increase a woman's chances of surviving, said Dr Chlebowski, chief of medical oncology at the UCLA Medical Center, Los Angeles. "From a scientific standpoint, others will have to look at this post hoc analysis and decide whether the data warrant further investigation in a trial to confirm the findings, but on an operational basis, for a woman with breast cancer, there are so many other health benefits associated with this kind of weight loss," he said.

Dr Chlebowski reported long-term follow-up data from the Women's Intervention Nutrition Study (WINS). It enrolled 2,437 women from 1994-2001 who had been treated for early-stage breast cancer. The women, aged 48-79 years, were randomly assigned to a lower-fat dietary intervention group or a control group whose patients ate their regular diet. The intervention group met monthly with a registered dietitian and kept food journals. They were also encouraged to increase physical activity.

At the start of the study, both groups consumed similar amounts of calories from fat; about 57 g per day or 30% of daily caloric intake. At the end of the first year of observation, the women in the dietary intervention group had reduced their fat intake by an average of 24 g daily, compared with the daily 5-g drop in the control group. The difference between the 2 groups was maintained throughout the trial. By the fifth year of the trial, the women in the intervention group weighed an average of 6 lb less than the women in the control group.

But at the current follow-up (maximum of 20 years) there was no significant between-group difference in disease-free survival (control group: 17% deaths vs intervention group: 13.6%), either in the entire group or in the subgroup of those with estrogen- and progesterone-receptor-positive tumors.

However, the subanalysis of those who were negative, the difference was significant, with a 2-year survival advantage in the intervention group (14 vs 12 years; HR, 0.64; $P = .045$).

Dr Chlebowski noted that the findings may be particularly important for women with triple-negative tumors because the data suggest that about 73% of women with ER- or PR-negative cancers are anticipated to be triple-negative. He said the protective mechanism is not entirely clear, but it may be related more to total calorie decrease rather than decreasing fat alone, despite fat's proclivity to increase total estrogen levels. "Estrogen does not seem to be the driver here," he said. Instead, the benefit may have more to do with controlling growth factors, inflammation, and glucose levels.

He did point out that the data are a bit old, and that only 6% of women in the study received tamoxifen. But he stressed that further investigation could refine the results and that, in any case, controlling weight confers a multitude of benefits on anyone, regardless of health.

— Michele G Sullivan

Tamoxifen therapy at 20: reduced incidence, but no survival benefit

Key clinical point Prophylactic tamoxifen reduced breast cancers in vulnerable women, compared with placebo, but didn't affect overall mortality. **Major finding** 5 years of tamoxifen treatment translated into a 30% decrease in the incidence of breast cancers in at-risk women, but there was no survival benefit at 20 years of follow-up. **Data source** The IBIS-1 trial, which randomized more than 7,000 women to 5 years of either tamoxifen or placebo. **Disclosures** Supported by Cancer Research UK. Dr Cuzick has received funding for other trials from AstraZeneca and consults for it. The company provided the study drug and placebo.

Five years of tamoxifen provided 20 years of breast cancer prevention to some at-risk women who took it prophylactically. However, their 20-year all-cause mortality was no different from those taking placebo (182 vs 166 deaths), nor was their mortality from breast cancer (31 vs 26, respectively), Jack Cuzick, PhD, said at the symposium.

"Although we saw clear, lasting benefits of tamoxifen in reducing breast cancer incidence, uncertainty with respect to mortality remains," said Dr Cuzick, the John Snow professor of epidemiology at Wolfson Institute of Preventive Medicine at Queen Mary University, London. He suggested that, in light of the small number of deaths, the study was not sufficiently powered to detect any significant survival difference. But women in the IBIS-1 trial will continue to be observed, and future analyses could clarify the issue, he added. "Although 20 years seems like a long follow-up time, it is actually too early to make any clear statement about mortality. However, we are concerned about an excess emergence of ER-negative tumors, which we saw after 10 years."

IBIS-1 randomized 7,154 healthy pre- and postmenopausal women to 5 years of either 20 mg daily tamoxifen or placebo. These women were aged 35-70 years at baseline and presented with an increased breast cancer risk attributable to a family history. IBIS-1 findings were first reported in 2002, when 4-year follow-up found a 32% reduction in breast cancer risk associated with tamoxifen. But it also found a significant increase in deaths in the tamoxifen group compared with the placebo group (25 vs 11, respectively), many of which were attributable to more endometrial cancer (11 vs 5).

In 2007, the investigators published the trial's 8-10 year findings. At that time, tamoxifen was associated with a 27% decreased risk of any breast cancer, and a 34% decreased risk of developing an ER-positive cancer. It found a consistent prophylactic benefit for tamoxifen; most of the risk reduction, however, occurred in the 5-year active treatment phase. The significant increase in death had continued (25 vs 11), although that report indicated that no specific cause, including endometrial cancer, drove that finding.

At the meeting, Dr Cuzick discussed the latest findings of IBIS-1, which has now followed the cohort for up to 20 years (median, 16 years). "We have seen a continued separation of the cancer incidence curves, with a 20-year incidence of 7.8% vs 12.3% [for tamoxifen and placebo, respectively]," he said. "We saw that the 30% overall reduction was maintained; the number needed to treat to prevent 1 breast cancer was 22, which is very favorable when compared to prevention strategies for other diseases."

The incidence of ER-positive tumors was reduced, compared with placebo, he added (4.9% vs 8.3%, respectively), with a number needed to treat of 29. However, Dr Cuzick said, there was a slight increase in the incidence of ER-negative tumors after 10 years. "This is likely because these are tumors that would have appeared earlier as ER-positive tumors, but under tamoxifen, they were held back for some time and eventually broke out as ER-negative tumors."

Hormone therapy was allowed in IBIS-1, and about 50% of women were taking hormones during at least part of the study. They did not experience the same level of benefit form tamoxifen as those who were not taking hormone therapy (12% vs. 38%, respectively). "This is very clear evidence that the benefits are substantially greater in those who are not using concurrent [hormone therapy] when on tamoxifen," he said.

However, tamoxifen was associated with side effects and risks, including an increased risk of developing other cancers. Of most concern was the 45% increase in the risk of endometrial cancer, which accounted for 5 deaths in the treatment group; there were no deaths from endometrial cancer in the placebo group. "We had hoped that endometrial cancer might not translate into such a large morality increase as there were no deaths due to this in the 8-year follow-up. We do need to be aware of this."

Recurrent breast cancer was the single largest cause of death, but the between-group difference was not significant. Cardiovascular deaths were similar between the groups, and all that did occur, did so during the treatment period. Nonmelanoma skin cancers were 39% more likely in the tamoxifen group, although they caused no deaths. "This was a very large increase and a surprise; we really don't understand it," Dr Cuzick said. There were 12 fewer colorectal cancers in the tamoxifen group.

— Michele G Sullivan

Fulvestrant outperforms anastrozole in advanced breast cancer

Key clinical point The selective estrogen receptor down-regulator fulvestrant proved superior to anastrozole in disease progression and overall survival in women with hormone receptor-positive advanced breast cancer. **Major finding** At a median follow-up of 48.8 months, overall survival was 54.1 months in patients on fulvestrant, compared with 48.4 months with anastrozole. **Data source** The FIRST trial, a phase 2, open-label study of 205 women randomized to fulvestrant or anastrozole. **Disclosures** Sponsored by AstraZeneca. The presenter has received research funds from and served as a consultant to the company.

Fulvestrant resulted in a 30% improvement in overall survival, compared with anastrozole as first-line therapy for postmenopausal women with hormone receptor-positive advanced or metastatic breast cancer in the randomized FIRST trial. This new finding follows a previously reported 34% reduction in the risk of disease progression in an earlier FIRST analysis. Plus, significant improvements in both disease progression and overall survival were seen with fulvestrant at 500 mg as second-line endocrine therapy in the phase 3 CONFIRM trial.

The clinical performance of fulvestrant in these 2 studies outpaces that of any other endocrine therapy for advanced breast cancer, Dr John Robertson said at the symposium. "I don't know of any other endocrine therapy where you can see both a time-to-progression and overall survival benefit in both the second- and first-line settings. This is a new and exciting development in endocrine therapy for women with advanced breast cancer."

FIRST was a phase 2, open-label study involving 205 women randomized to intramuscular fulvestrant at 500 mg once monthly or the aromatase inhibitor anastrozole at 1 mg/day orally. Aromatase inhibitors have been considered the standard therapy in this setting.

At a median follow-up of 48.8 months, the median overall survival was 54.1 months in the fulvestrant arm, compared with 48.4 months with anastrozole, for a 5.7-month advantage in favor of fulvestrant. This translated to a 30% reduction in the risk of death in the fulvestrant group ($P = .041$), which Dr Robertson believes patients and their families will consider highly clinically meaningful.

"When I first started taking care of breast cancer patients like these 30 years ago, the average survival was 24 months. In this study, with fulvestrant it's 54 months. We're seeing step-by-step improvements," said Dr Robertson, professor of surgery at the University of Nottingham, England.

The advantage in overall survival seen with fulvestrant was consistent across all predefined subgroups based on age, previous chemotherapy or endocrine therapy, visceral involvement status, and progesterone receptor status. Both treatments were generally well tolerated, with no new safety concerns observed.

— Bruce Jancin