Advances in precision medicine help refine – and redefine – cancer care

Among the groundbreaking findings presented at this year's annual meeting of the American Society of Clinical Oncology were those showing that most women with HR-positive, HER2-negative, early-stage breast cancer who have an intermediate recurrence score can safely skip adjuvant chemotherapy, and that upfront pembrolizumab for patients with NSCLC expressing PD-L1 on at least 1% of tumor cells can not only significantly improve overall survival, but do so with less toxicity than standard chemotherapy.

TAILORx marks major advance for precision medicine in breast cancer

Key clinical point The majority of women with HR-positive, HER2-negative, node-negative early-stage breast cancer who have an intermediate recurrence score can safely skip adjuvant chemotherapy. **Major finding** In women with an Oncotype DX Recurrence Score in the midrange (11-25), invasive DFS with endocrine therapy alone was not inferior to that with chemotherapy plus endocrine therapy (HR, 1.08; $P = .26$). **Study details** A phase 3 trial in 10,273 women with HR-positive, HER2-negative, node-negative, early-stage breast cancer, with a noninferiority randomized component in the 6,711 women with a midrange recurrence score (TAILORx trial). **Funding** This study received funding primarily from the National Cancer Institute, National Institutes of Health. Additional support was provided by the Breast Cancer Research Foundation, Komen Foundation, and US Postal Service Breast Cancer Stamp. **Disclosures** Dr Sparano disclosed that he has a consulting or advisory role with Genentech/Roche, Novartis, AstraZeneca, Celgene, Lilly, Celldex, Pfizer, Prescient Therapeutics, Juno Therapeutics, and Merrimack; has stock or other ownership interests with MetaStat; and receives research funding (institutional) from Prescient Therapeutics, Deciphera, Genentech/Roche, Merck, Novartis, and Merrimack. **Source** Sparano et al. ASCO 2018 Abstract LBA1: https://meetinglibrary.asco.org/record/161490/abstract

Use of the 21-tumor gene expression assay (Oncotype DX Recurrence Score) allows nearly 70% of women with hormone receptor-positive, HER2-negative, node-negative, early-stage breast cancer to safely forgo adjuvant chemotherapy, sparing them adverse effects and preventing overtreatment, TAILORx trial results show.

The findings, which were reported in the plenary session at the meeting and simultaneously published in the New England Journal of Medicine (N Engl J Med. 2018; 379:111-121; [behind paywall]), mark a major advance in precision medicine.

"The rationale for the TAILORx precision medicine trial is that we are really trying to 'thread the needle,'" lead study author Joseph A Sparano, MD, commented in a press briefing. Oncologists typically recommend adjuvant chemotherapy for the half of all breast cancers that are hormone receptor positive, HER2 negative, and node negative, even though its absolute benefit in reducing recurrences in this population is small. "This results in most patients being overtreated because endocrine therapy alone is adequate. But some are undertreated: They do not receive chemotherapy although they could have benefited from it," he noted.

DR SPARANO

The recurrence score is known to be prognostic and predictive of benefit from adding chemotherapy to endocrine therapy, Dr Sparano said. "But there was a major gap: There was uncertain benefit for patients who had a midrange score, which is about two-thirds of all patients who are treated," said Dr Sparano, the associate director for clinical research at Albert Einstein Cancer Center and Montefiore Health System in New York, and vice-chair of the ECOG-ACRIN Cancer Research Group.

The phase 3 TAILORx trial registered 10,273 women with hormone receptor-positive, HER2-negative, node-negative, early-stage breast cancer, making it the largest adjuvant breast cancer trial to date. Analyses focused on the 6,711 evaluable women with a midrange recurrence score (defined as 11 through 25 in the trial), who were randomized to receive endocrine therapy alone or adjuvant chemotherapy plus endocrine therapy, with a noninferiority design. Of note is that contemporary drugs and regimens were used.

Results at a median follow-up of 7.5 years showed that the trial met its primary endpoint: the risk of

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invasive disease-free survival (DFS) events (invasive disease recurrence, second primary cancer, or death) was not inferior for women given endocrine therapy alone compared with counterparts given chemotherapy plus endocrine therapy (hazard ratio [HR], 1.08; *P* = .26), Dr Sparano reported.

The groups were also on par, with absolute differences of no more than 1% between rates, with respect to a variety of other efficacy outcomes: freedom from distant recurrence and any recurrence, and overall survival (OS).

Findings were similar across most subgroups. But analyses suggested that women aged 50 years and younger and who had a recurrence score of 16-25 fared better when they received chemotherapy. "Though exploratory from a statistical perspective, this is a highly clinically relevant observation," Dr Sparano said. "It suggests ... that chemotherapy should be spared with caution in this subgroup, after a careful discussion of potential benefits and risks in a shared decision process."

In other findings, analyses of the trial's nonrandomized groups confirmed excellent outcomes in women with a low recurrence score (0-10) who were given endocrine therapy alone, and at the other end of the spectrum, there was need for a more aggressive approach, including chemotherapy, in women with a high recurrence score (26-100).

Ultimately, application of the recurrence score allowed 69% of the trial population to skip chemotherapy: all of the women with a score of 0-10 (16% of the trial population), those older than 50 years with a score of 11-25 (45%), and those aged 50 years or younger with a score of 11-15 (8%).

An ongoing companion phase 3 trial, RxPONDER, is assessing the benefit of applying the recurrence score in women who are similar but ihave node-positive disease.

Study details

All of the women with hormone receptor-positive, HER2-negative, node-negative, early-stage breast cancer enrolled in TAILORx met National Comprehensive Cancer Network guidelines for receiving adjuvant chemotherapy. About 69% had an intermediate recurrence score (11-25) and were randomized. All of the 17% with a low recurrence score (0-10) were given only endocrine therapy, and all of the 14% with a high recurrence score (26-100) were given both adjuvant chemotherapy and endocrine therapy.

Of note, the recurrence scores used to define midrange were adjusted downward from those conventionally used to account for exclusion of patients with higher-risk HER2-positive disease and to minimize potential for undertreatment, Dr Sparano explained.

In the women with midrange scores who were randomized, the hazard ratio of 1.08 for invasive DFS with endocrine therapy alone compared with chemotherapy plus endocrine therapy fell well within the predefined hazard ratio for noninferiority (1.322). The 9-year rate of invasive DFS was 83.3% with endocrine therapy and 84.3% with chemotherapy plus endocrine therapy.

The groups had similar rates of freedom from distant recurrence (94.5% vs 95.0%; HR, 1.10; *P* = .48) and distant or locoregional recurrence (92.2% vs 92.9%; HR, 1.11; *P* = .33), and similar OSs (93.9% vs 93.8%; HR for death, 0.99; *P* = .89).

In exploratory analyses, there was an interaction of age and recurrence score (*P* = .004) whereby women aged 50 years or younger derived some benefit from chemotherapy if they had a recurrence score of 16-20 (9% fewer invasive DFS events, including 2% fewer distant recurrences) or a recurrence score 21-25 (6% fewer invasive DFS events, mainly distant recurrences). "This is information that could drive some younger women who have a recurrence score in this range to accept chemotherapy," Dr Sparano said.

The 9-year rate of distant recurrence averaged 5% in women with midrange scores overall. It was 3% in those with a low recurrence score given endocrine therapy alone, but it was still 13% in those with a high recurrence score despite receiving both endocrine therapy and chemotherapy. The latter finding may "indicate the need to explore potentially more effective therapies in this setting," he proposed.

Tailoring treatment: 'not too much and not too little'

"These are important data because this is the most common form of breast cancer in the United States and other developed countries, and the most challenging decision we make with these patients is whether or not to recommend adjuvant chemotherapy with all its side effects and potential benefits," said ASCO expert Harold Burstein, MD, PhD, FASCO. "The data show that the majority of women who have this test performed on their tumor can be told that they don't need chemotherapy, and that can be said with tremendous confidence and reassurance."

DR BURSTEIN

The recurrence score has been used for a decade, but the trial was necessary because the score was originally developed in patients who were receiving older chemotherapy regimens and older endocrine therapies, and because there have been few data to guide decision making in the large group of patients with midrange scores, he said. "Now we can say with confidence ... that the patients got contemporary chemo regimens and still saw no benefit from chemotherapy.

"This is not so much about de-escalation ... the goal of this study was not to just use less treatment but to tailor treatment. The investigators chose the title very aptly," said Dr Burstein, a medical oncologist at the Dana-Farber Cancer Institute and associate professor of medicine at the Harvard Medical School, Boston.

"This is extraordinary data for breast cancer doctors and women who have breast cancer. It allows you to individualize treatment based on extraordinary science, which now has tremendous prospective validation," he said. Overall, "women with breast cancer who are getting modern therapy are doing well, and this test shows us how to tailor that management so that they get exactly the right amount of treatment – not too much and not too little."

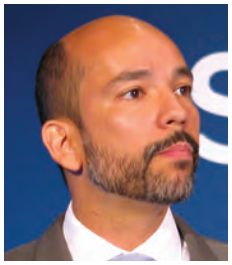
— Susan London

First-line immunotherapy boosts survival in NSCLC patients

Key clinical point Many patients with previously untreated NSCLC could benefit from first-line therapy with the checkpoint inhibitor pembrolizumab. **Major finding** In all patients with expression of PD-L1 on 1% or more of tumor cells, OS was 16.7 months with pembrolizumab, compared with 12.1 months for chemotherapy. **Study details** Randomized phase 3 trial of 1,274 patients with advanced or metastatic NSCLC. **Funding** Merck, the maker of the study drug, funded the study. **Disclosures** Dr Lopes disclosed institutional research funding from Merck Sharp & Dohme, EMD Serono, and AstraZeneca. Dr Heymach disclosed stock/ownership in Bio-Tree and Cardinal Spine, a consulting or advisory role for Abbvie, ARIAD, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Calithera Biosciences, Genentech, Medivation, Novartis, Oncomed, and Synta, and institutional research funding from AstraZeneca. Dr Gandhi reported having no relevant disclosures. **Source** Lopes G et al. ASCO 2018, abstract LBA4. https://meetinglibrary.asco.org/record/165950/abstract

Pembrolizumab as first-line treatment of advanced non–small-cell lung cancer (NSCLC) offered longer OS with better tolerability compared with chemotherapy, results of the Keynote-042 phase 3 randomized trial show.

In 1,274 patients with advanced, previously untreated NSCLC with expression of the PD-L1 on 1% or more of tumor cells, median OS after a median follow-up of 12.8 months was 16.7 months for patients treated with pembrolizumab monotherapy, compared with 12.1 months for patients treated with either paclitaxel or pemetrexed plus carboplatin, reported lead author Gilberto Lopes, MD, of the Sylvester Comprehensive Cancer Center at the University of Miami.



DR LOPES

The survival benefit for immunotherapy was even greater for patients with higher levels of PD-L1 expression: 20 versus 12.2 months for patients with PD-L1 expression of 50% or greater, and 17.7 versus 13 months for patients with PD-L1 expression of 20% or greater, Dr Lopes noted.

For all 3 PD-L1 expression groups, the median duration of response was 20.2 months, compared with 10.8-8.3 months for patients in the chemotherapy arm.

"These are responses that are unlike anything that we have seen with chemotherapy in the past for non–small-cell lung cancer," Dr Lopes said at a briefing before his presentation. "In addition to that, and probably more importantly, patients had fewer adverse events [with pembrolizumab]. Overall, about 60% had any treatment-related adverse event with pembrolizumab, versus 90% with chemotherapy," he added.

'A true milestone'

ASCO expert John Heymach, MD, PhD, of the University of Texas MD Anderson Cancer Center in Houston, said at the briefing that the study was "a true milestone for the field, because now, for the first time, we can say that in non–small-cell lung cancer patients receiving first-line therapy, the vast majority can receive immunotherapy with pembrolizumab instead of chemotherapy."

DR HEYMACH

He noted that an earlier study, Keynote-024, showed that pembrolizumab significantly improved progression-free survival in patients with tumors expressing PD-L1 on at least 50% of cells compared with standard platinum-based chemotherapy (10.3 vs 6 months).

"This more than doubles that population that can start immunotherapy as a first-line treatment, assuming the [Food and Drug Administration] modifies the label in accordance with this study," he added.

The Keynote-042 investigators enrolled 1,274 patients with locally advanced or metastatic NSCLC, and randomly assigned them to receive either a maximum of 35 cycles of pembrolizumab 200 mg every 3 weeks, or the investigators' choice of not more than 6 cycles of either paclitaxel–carboplatin or pemetrexed–carboplatin, with optional pemetrexed maintenance for patients with nonsquamous histologies only.

The randomization was stratified by region (Asia vs non-East Asia), Eastern Cooperative Oncology Group performance status 0 or 1, squamous versus nonsquamous histology, and PD-L1 expression, or TPS (tumor proportion score) greater than 50% versus 1%-49%.

As noted before, the primary endpoint of OS in all patients with a TPS of 1% or greater was met, with respective median OS in the pembrolizumab versus chemotherapy groups of 16.7 and 12.1 months, translating into an HR favoring pembrolizumab of 0.81 (P = .0018). Respective hazard ratios for the TPS 20% or greater and TPS 50% or greater groups were 0.77 (P = .0020) and 0.69 (P = .0003).

At 12.8 months of median follow-up, 13% of patients assigned to pembrolizumab were still on the drug, and

4.3% of patients were receiving maintenance pemetrexed.

Treatment-related adverse events of any grade occurred in 399 of 636 patients assigned to pembrolizumab (62.7%), compared with 553 of 615 patients assigned to chemotherapy (89.9%). Grade 3 or greater events occurred in 17.8% and 41% of patients, respectively. There were 13 deaths related to therapy in the pembrolizumab arm (2.0%), and 14 in the chemotherapy arm (2.3%). Adverse events leading to discontinuation were similar between the groups, at 9% and 9.4%, respectively.

There were more immune-mediated adverse events in the pembrolizumab arm than in the chemotherapy arm (27.8% vs 7.2%, respectively), and of those, grade 3 or higher events occurred in 8% and 1.5% of patients. There was 1 immune-mediated death, from pneumonitis, in the immunotherapy arm; there were no deaths related to immune-mediated side effects in the chemotherapy arm.

"I really view this as a 'double whammy' for patients," Dr Heymach said at the briefing. "Often advances in survival for our lung cancer patients come at the cost of significant toxicities. Here, by contrast, not only are patients living longer and having a much higher likelihood of prolonged survival in years, often instead of months, but they're also receiving a treatment that has substantially less toxicity across virtually all measures, and this really impacts the day-to-day life of these patients."

Leena Gandhi, MD, PhD, of the Perlmutter Cancer Center at New York University, the invited discussant at the plenary, agreed that pembrolizumab improves survival, compared with chemotherapy patients with PD-L1 expression levels greater than 1%, but noted that most of the benefit – as also seen in Keynote-024 – was in those patients whose tumors had high levels of PD-L1 expression.

She emphasized that although PD-L1 is an imperfect biomarker, it should still be used to help select patients for therapy and it may be complementary with tumor mutational burden for more precise treatment selection.

"What we know, and what this study adds to, is that PD-L1 really does define a patient population that could receive benefit from pembrolizumab over chemotherapy. Patients with low or no PD-L1 expression likely should get some type of combination therapy," she said. "This study extends what we've seen from other recent studies, which is that chemotherapy alone is no longer a first-line standard of care in non–small-cell lung cancer."

— Neil Osterweil

Better survival with maintenance chemo in youth with rhabdomyosarcoma

Key clinical point 6 months of maintenance chemotherapy improves survival in youth with high-risk rhabdomyosarcoma. **Major finding** Patients given maintenance low-dose vinorelbine and cyclophosphamide had better 5-year OS compared with those not receiving any additional treatment (86.5% vs 73.7%; HR, 0.52). **Study details** A phase 3 randomized controlled trial in 371 patients aged 0-21 years with high-risk rhabdomyosarcoma who had had a complete response to standard intensive therapy. **Funding** The study received funding from Fondazione Città della Speranza, Italy. **Disclosures** Dr Bisogno disclosed that he has a consulting or advisory role with Clinigen Group, and receives travel, accommodations, and/or expenses from Jazz Pharmaceuticals. **Source** Bisogno et al. ASCO 2018, Abstract LBA2. https://meetinglibrary.asco.org/record/161695/abstract

Six months of maintenance chemotherapy prolongs OS in youth with high-risk rhabdomyosarcoma, finds a phase 3 randomized controlled trial of the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG).

Rhabdomyosarcoma is a rare but highly aggressive tumor, lead study author Gianni Bisogno, MD, PhD, a professor at the University Hospital of Padova, Italy, and chair of the EpSSG, noted in a press briefing at the meeting, where the findings were reported. In pediatric patients who achieve complete response to standard therapy, "we know that after 1 or 2 years, one-third of these children relapse, and most of them die," he said.

The EpSSG trial, which took about 10 years to conduct, enrolled 371 patients aged 0-21 years with high-risk rhabdomyosarcoma who had had a complete response to standard intensive therapy. They were randomized evenly to stop treatment or to receive 6 months of maintenance treatment consisting of low-dose vinorelbine and cyclophosphamide.

DR BISOGNO

Results reported in the meeting's plenary session showed that giving maintenance chemotherapy improved the 5-year OS rate by an absolute 12.8%, which translated to a near halving of the risk of death. And the maintenance regimen used was generally well tolerated.

"At the end of this long, not-easy study, we concluded that maintenance chemotherapy is an effective and well tolerated treatment for children with high-risk rhabdomyosarcoma," Dr Bisogno said.

There are three possibilities for its efficacy, he speculated. "It may be the duration, the type of drugs used, or the metronomic approach. Maybe altogether, these three different actions have a benefit to increase survival.

"Our group has decided this is the new standard treatment for patients. At least in Europe, we give standard intensive therapy and then we continue with 6 more months of low-dose chemotherapy," Dr Bisogno concluded. "We think that this approach – a new way of using old drugs – can be of interest also for other pediatric tumors."

The trial is noteworthy in that it shows "how to successfully conduct large and important trials in rare diseases," said ASCO expert Warren Chow, MD.

The standard therapy for rhabdomyosarcomas is somewhat different in the United States, typically a regimen containing vincristine, actinomycin D, cyclophosphamide, and (more recently) irinotecan, he noted. "We have not been traditionally using maintenance chemo for any of the pediatric sarcomas, so this is a paradigm shift. These results will need to be tested with US-based protocols before becoming standard of care in the United States. Also, we will need to determine if these results are applicable to patients older than 21 years of age who are considered high risk based solely on their age.

DR CHOW

"Even with these caveats, this is the first significant treatment advance in this rare cancer in more than 30 years," concluded Dr Chow, a medical oncologist and clinical professor at City of Hope, Duarte, Calif. "No doubt, this trial was a home run."

Study details

Patients enrolled in the EpSSG trial had had a complete response to the standard intensive therapy used in Europe: high-dose chemotherapy (ifosfamide, vincristine, and actinomycin D, with or without doxorubicin), radiation therapy, and surgery.

The maintenance chemotherapy consisted of a combination of low-dose intravenous vinorelbine given weekly and oral cyclophosphamide given daily. The 6-month duration was somewhat arbitrary, according to Dr Bisogno. "We had to start somewhere. So when we started, we decided to use 6 months because there was some evidence in the past for regimens that long. In our next European trial, we are going to test different kinds and durations of maintenance because this is very important."

The maintenance regimen was well tolerated compared with the regimen given during standard intensive therapy, with, for example, lower rates of grade 3 and 4 anemia (8.9% vs 48.9%), neutropenia (80.6% vs 91.6%), and thrombocytopenia (0.6% vs 26.0%), which translated to less of a need for transfusions, and a lower rate of grade 3 or 4 infection (29.4% vs 56.4%), Dr Bisogno reported. There were no cases of grade 3 or 4 cardiac, hepatobiliary/pancreatic, or renal toxicity.

Relative to peers who stopped treatment after standard intensive therapy, patients who received maintenance treatment tended to have better DFS (77.6% vs 69.8%; HR, 0.68; $P = .0613$) and had significantly better OS (86.5% vs 73.7%; HR, 0.52; $P = .0111$).

— Susan London