KEYNOTE-224: Pembrolizumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib

Andrew X. Zhu, MD, PhD, Massachusetts General Hospital Cancer Center, Boston, Massachusetts

In patients with advanced hepatocellular carcinoma (HCC) previously treated with sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals), treatment with pembrolizumab (Keytruda, Merck) led to favorable durable responses, progression-free survival (PFS), and overall survival (OS), according to a poster and oral presentation by Dr. Zhu.

He noted that immunotherapy approaches, including immune checkpoint blockade, have demonstrated promising results in advanced HCC. Pembrolizumab, an anti-programmed death-1 monoclonal antibody, has shown antitumor activity with manageable safety in multiple tumor types. The open-label phase 2 KEYNOTE-224 trial (NCT02702414) assessed the efficacy and safety of pembrolizumab 200 mg every three weeks given until progressive disease (PD) or intolerable toxicity in 104 patients (median age, 68 years; 83% male) with HCC previously treated with sorafenib. The primary endpoint was objective response rate (ORR) as determined by RECIST 1.1 criteria, assessed every nine weeks.

Dr. Zhu reported one complete response (CR) (1.0%) and 16 partial responses (PR) (15.4%). The ORR (CR + PR) was 16.3%, with a disease control rate (CR + PR plus stable disease) of 61.5%. The PD rate was 32.7%. In responders, median time to response was 2.1 months (range, 1.8–4.8 months), with responses lasting six months or longer in 94% and with a median duration of 8.2 months (range, 2.3–8.3 months). PFS was 4.8 months (95% confidence interval, 3.4–6.6), and median OS was not yet reached (9.4–not estimable).

Grade 3 or higher adverse events occurred in 25.0% of patients, leading to discontinuation in 6.7% and one death (ulcerative esophagitis). “The safety profile was generally comparable to that established for pembrolizumab mono- therapy in other indications,” Dr. Zhu said. No viral flares were observed.

Dr. Zhu concluded, “Pembrolizumab treatment demonstrated efficacy in patients with advanced HCC previously treated with sorafenib.” He also noted that a phase 3 randomized trial (KEYNOTE-240) evaluating pembrolizumab versus placebo as second-line therapy in this population is under way.

Cabozantinib Versus Placebo in Patients With Advanced Hepatocellular Carcinoma Who Have Received Prior Sorafenib: Results From the Randomized Phase 3 CELESTIAL Trial

Ghassan K. Abou-Alfa, MD, Memorial Sloan Kettering Cancer Center, New York, New York

In patients with advanced hepatocellular carcinoma (HCC) who have had prior systemic therapy with sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals), cabozantinib (Cabometyx, Exelixis, Inc.) significantly improved progression-free survival (PFS) and overall survival (OS), according to results from the randomized phase 3 CELESTIAL trial. Dr. Abou-Alfa underscored that, following systemic therapy, prognosis is often poor for patients with advanced HCC, and treatment options are limited.

Cabozantinib inhibits tyrosine kinases, including vascular endothelial growth factor (VEGF) receptors, MET, and AXL, all of which are implicated in carcinogenesis and in promoting tumor progression and angiogenesis. MET and AXL are associated with resistance to VEGF-receptor–targeted therapy, Dr. Abou-Alfa said. Furthermore, elevated expression of VEGF, MET, or AXL is associated with poor prognosis in HCC. In a phase 2 trial of cabozantinib in patients with advanced HCC, the agent demonstrated preliminary clinical activity with a median PFS of 5.2 months and median OS of 11.5 months.

CELESTIAL investigators randomized 707 patients 2:1 to cabozantinib 60 mg once daily (n = 470) or matched placebo (n = 237). Participants had confirmed HCC with Child–Pugh A and had been previously treated with sorafenib (up to two lines of prior systemic therapy for HCC, with progression on at least one). Most (71%) had received one prior regimen. Median age was 64 years. About 78% of the patients had extrahepatic disease spread, and 85% had extrahepatic spread and/or macrovascular invasion. The primary endpoint was OS, with secondary endpoints of investigator-assessed PFS and objective response rate (ORR) per RECIST 1.1 criteria.

The primary endpoint was not met at the first interim analysis (52% of required events), but was met at the second interim analysis (78% of required events; 317/470 deaths with cabozantinib, 167/237 deaths with placebo; hazard ratio [HR],
0.76; \ P = 0.0049\). Median OS was 10.2 months with cabozantinib and 8.0 months with placebo. PFS was 5.2 months with cabozantinib and 1.9 months with placebo (HR, 0.44; 95% confidence interval, 0.36–0.52; \ P < 0.0001\).

For the secondary endpoints, ORR was 4.0% with cabozantinib and 0.4% with placebo (\ P = 0.0086\). Median time to first subsequent systemic anticancer therapy was 6.6 months for cabozantinib and 3.3 months for placebo. Disease control (partial response or stable disease) was achieved by 64% of the cabozantinib group compared with 33% of the placebo group.

Dose reductions were reported in 62% of patients receiving cabozantinib and in 13% of those receiving placebo. Treatment-related adverse events led to discontinuation in 16% of cabozantinib patients and in 3% of placebo patients. Grade 3–4 adverse event rates were 68% and 36% for cabozantinib and placebo, respectively, with hand–foot syndrome (17%) and hypertension (16%) most common in the cabozantinib group. Treatment-related grade 5 adverse events occurred in six patients in the cabozantinib group (hepatic failure, esophagobronchial fistula, portal vein thrombosis, upper gastrointestinal hemorrhage, pulmonary embolism, and hepatorenal syndrome) and in one patient in the placebo group (hepatic failure). Dr. Abou-Alfa noted that adverse events were consistent with the known safety profile of cabozantinib.

“If approved, cabozantinib represents a new treatment option for advanced HCC patients after prior systemic anticancer therapy,” he concluded.

**Prospective Clinical Study of Circulating Tumor Cells for Colorectal Cancer Screening**

- Wen-Sy Tsai, MD, PhD, Chang Gung Memorial Hospital, Taoyuan, Taiwan

A novel circulating tumor cell (CTC) assay (CMx, CellMax Life) based on a simple blood draw has demonstrated high accuracy for detecting colorectal cancer (CRC). The accuracy, which extends to detection of precancerous CRC lesions, is a first for “liquid biopsy” trials, Dr. Tsai said in an oral presentation.

“Colorectal cancer can be preventable because it is a slow-growing disease and can take five to 15 years to develop from polyp to cancer,” he said. Most CRCs, however, are diagnosed late, with 61% of diagnoses taking place when the disease is already regional or distant. While five-year survival rates are 91% when the disease is localized at diagnosis, the rates are 71% with regional disease and 14% with distant disease. Because colonoscopy is invasive, uncomfortable, and inconvenient for people, about one-third of individuals are never screened.

Prior research had shown that the assay was able to detect minute numbers of CTCs (one per one billion blood cells) found in polyps. Detachment of CTCs from the primary tumor and their subsequent circulation through the bloodstream is the fundamental mechanism of metastasis, Dr. Tsai said. His analysis focused particularly on the assay’s specificity because low specificity (which entails a high rate of false-positives) would discourage its routine use.

Participants in the study (\ N = 620\) were older than 20 years of age and had presented for routine colonoscopy or had been diagnosed already with CRC. Colonoscopy and biopsy showed 438 patients had adenomatous polyps or early- to late-stage CRC. The remaining participants were free of precancerous growths or CRC. Investigators then took 2-mL blood samples from all enrollees, processing them with the CMx platform, which includes a lipid-coated chip that captures CTCs.

Dr. Tsai reported that the assay’s sensitivity ranged from 77% for detecting precancerous lesions to 87% for cancer at stages I–IV. Specificity ranged from 84% to 88% for precancerous and cancerous samples. The false-positive rate in the healthy control group was 3.3%, and the false-negative rate in the group with disease was 15.8%. He emphasized that the accuracy was superior to that of the fecal occult blood testing recommended by guidelines. Dr. Tsai also noted that noncompliant individuals prefer blood testing to both stool-based testing and colonoscopy by wide margins. Greater compliance, he suggested, can lead to better outcomes.

Estimates place the likely cost of the assay at about $100, he said. Ongoing studies are evaluating the assay’s utility for other solid tumors (e.g., prostate, breast, lung).

**Nivolumab/Ipilimumab Combination In Patients With DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer: First Report Of the Full Cohort From CheckMate-142**

- Thierry André, MD, Saint-Antoine Hospital, Paris, France

In previously treated patients with DNA mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC), the combination of nivolumab (Opdivo, Bristol-Myers Squibb) and ipilimumab (Yervoy, Bristol-Myers Squibb) provided durable clinical benefit with meaningful quality-of-life improvements, according to results of the Checkmate-142 trial. Earlier findings from this trial had shown a one-year overall survival rate of 85% in patients receiving the combination.

Approximately 4% of patients with mCRC have a deficiency in the DNA mismatch repair system that leads to high microsatellite instability and a concomitant predisposition to mutation. Metastatic DNA dMMR/MSI-H CRC exhibits high levels of tumor neoantigens, tumor-infiltrating lymphocytes, and checkpoint regulators. It has a poor prognosis after treatment with conventional chemotherapy, Dr. André said. In the nivolumab monotherapy cohort of Checkmate-142, nivolumab demonstrated durable responses, sustained disease control, and encouraging survival. Because nivolumab and ipilimumab act synergistically to promote T cell antitumor activity, it was hypothesized that combination therapy could further improve results. Checkmate-142, a nonrandomized, phase 2 investigation, is the largest single study of the combination in this population.

Investigators enrolled 119 patients (median age, 58 years [range, 21–88 years]; 59% male), assigning them to either nivolumab as a single agent (3 mg/kg every two weeks) or nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) every three weeks for four doses, followed by nivolumab (3 mg/kg) every two weeks. Forty percent of the patients had three or more prior lines of therapy, and 76% had two or more.
After a median follow-up of 13.4 months, the objective response rate (ORR) for the combination was 55%. The complete response rate was 3.4%, and the disease control rate (DCR) (complete response plus partial response plus stable disease) was 80%. The DCR for nivolumab alone was 69%. Seventy-eight percent of patients had some degree of tumor reduction. In addition, responses were observed regardless of tumor programmed death ligand-1 expression, BRAF or KRAS mutation status, or clinical history of Lynch syndrome. The median time to response was 2.8 months. Median duration of response has not been reached, Dr. André said.

At the time of the presentation, 94% of responders had ongoing responses, and 63% of patients were continuing treatment (37% have discontinued, 19% for disease progression and 13% for study drug-related adverse events). Progression-free survival among patients receiving the nivolumab/ipilimumab combination was 76% and 71% at nine and 12 months, respectively. Overall survival rates for the same periods were 87% and 85%, respectively.

Dr. André noted that quality-of-life measures (European Organization for Research and Treatment of Cancer’s QLQ-C30 and EuroQol’s EQ-5D VAS) showed significant and sustained improvements. No new safety signals or deaths attributable to treatment were reported. The grade 3–4 treatment-related adverse event rate of 32% (versus 20% for monotherapy) was deemed “acceptable.”

Dr. André concluded, “Nivolumab plus ipilimumab represents a promising new treatment for patients with previously treated dMMR/MSI-H metastatic colorectal cancer.”

SCOT: Tumor Sidedness and the Influence of Chemotherapy Duration on Disease-Free Survival

- Mark P. Saunders, MD, PhD, Christie Hospital, Christie NHS Foundation Trust, Manchester, United Kingdom

For the first time in a clinical trial, prognosis in unselected patients with cancer of the colon or rectum was shown to be influenced primarily by the higher rates of recurrence in those with right-sided tumors, Dr. Saunders said.

He noted that patients with right-sided tumors who develop metastatic disease have a worse prognosis compared with patients with left-sided tumors. In general, registry studies and meta-analyses have shown that patients with locoregional right-sided tumors have worse overall survival. The PETACC8 study confirmed this, but only in patients who had relapsed. Disease-free survival (DFS) was similar for patients with right- and left-sided tumors.

The SCOT trial included 6,088 patients with high-risk stage II or III cancer of the colon or rectum from 244 centers in six countries. The investigators compared three months and six months of treatment with adjuvant capecitabine and oxaliplatin or leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin (patient/physician choice) and found that DFS for the shorter treatment (76.7%) was noninferior to the longer treatment (77.1%) (noninferiority P = 0.012) in results presented last year.

The present analysis was designed to see if stratification according to tumor sidedness would reveal differences in DFS. Dr. Saunders explained that right-sided tumors included those arising in the caecum and ascending and transverse colon, and left-sided tumors included all cancers distal to and including the splenic flexure.

Patients with right-sided tumors tended to be older (median age, 66 years versus 64 years; P < 0.001), were less likely to be male (53% versus 66%; P < 0.001), were more likely to have T4 tumors (41% versus 24%; P < 0.001), and were less likely to have stage II disease (17% versus 21%; P = 0.001). DFS was significantly worse at three years in patients with right-sided tumors (73% versus 80% for left-sided; hazard ratio, 1.401; 95% confidence interval, 1.216–1.615; P < 0.0001). No correlation was found between chemotherapy duration/sidedness and DFS.

The findings underscore that there must be inherent differences between right- and left-sided tumors, Dr. Saunders said. To identify these differences and find effective treatment strategies for right-sided tumors requires stratification by tumor side of patients in future trials.

BEACON CRC Study Safety Lead-In in Patients With BRAFV600E Metastatic Colorectal Cancer: Efficacy and Tumor Markers

- Eric Van Cutsem, MD, PhD, University of Leuven and University Hospital Gasthuisberg, Leuven, Belgium

Updated results of the BEACON CRC safety lead-in study showed that the triple combination of the BRAF inhibitor encorafenib (investigational, Array BioPharma) 300 mg once daily plus the MEK inhibitor binimetinib (investigational, Array BioPharma) 45 mg twice daily plus standard weekly cetuximab (Erbitux, Lilly) at 400 mg/m² initially and then 250 mg/m² once weekly in 28-day cycles continues to be generally well tolerated with promising antitumor activity.

BRAF mutations are detected in 10% to 15% of metastatic colorectal cancer (mCRC) cases and confer a poor prognosis, according to Dr. Van Cutsem’s poster presentation. Progression-free survival (PFS) is about two months with objective response rates (ORRs) generally below 10%. After failure of first-line therapy, overall survival (OS) is less than six months. In a recent prospective trial of patients with BRAFV600E mCRC who had received one or two prior regimens in the metastatic setting and then standard-of-care irinotecan plus cetuximab, tumor shrinkage was observed in only 21%, and 60% of the patients had 100% or greater increases in tumor volume. Dr. Van Cutsem cited low efficacy in this population in 11 clinical trials with ORRs from 4% to 8.3%, PFS from 1.8–2.8 months, and OS from 4.1–6.2 months.

A phase 2 study of cetuximab and encorafenib in this population led to a median PFS of 4.2 months, an ORR of 22%, and median OS greater than one year. In addition, adding a MEK inhibitor to BRAF inhibition has demonstrated improved efficacy over BRAF inhibition alone. These results led to the BEACON CRC phase 3 study, a three-armed multicenter investigation in patients with BRAFV600E mCRC whose disease has progressed after one or two prior regimens in the metastatic setting. They are to receive either the triplet of encorafenib, binimetinib, and cetuximab compared with investigator’s choice of an irinotecan standard biweekly dose plus cetuximab or leucovorin calcium (folinic acid), fluorouracil, irinotecan plus cetuximab, or the doublet choice of encorafenib plus cetuximab.
Because the triplet combination of binimetinib plus encorafenib plus cetuximab had not been studied previously, a lead-in study to test safety and activity was designed. Among 30 patients enrolled, 29 had the \textit{BRAF}\textsuperscript{V600E} mutation (median age, 59 years; 43% male). Median time on treatment was 7.9 months, with one-third of the patients remaining on study treatment at the time of data cut-off.

The confirmed ORR (complete responses [CRs] plus partial responses [PRs]) was 48% with CRs in three patients. Among patients with one prior line of therapy, the ORR was 62% (two CRs and eight PRs). Among those with two prior lines of therapy, the ORR was 31% (four of 13 patients), including three PRs and one CR. Responses were ongoing in six of 14 responding patients (43%). The remaining 15 patients all achieved stable disease as their best response, with nine patients (60%) having stable disease for six months or longer. The preliminary estimate of median PFS is 8.0 months, with seven of 29 patients still progression free. Dr. Van Cutsem noted that evidence of tumor regression was observed in all but one evaluable patient. The number of prior regimens did not affect outcome.

Common adverse events were consistent with those previously reported for \textit{BRAF}, MEK, and EGFR inhibitors, and included gastrointestinal and skin toxicities.

“Safety and preliminary efficacy data support the initiation of the phase 3 portion of the BEACON CRC trial,” he concluded. Enrollment is currently ongoing.

**Phase 2 LAPACT Trial of Nab-Paclitaxel Plus Gemcitabine for Patients With Locally Advanced Pancreatic Cancer**

- Pascal Hammel, MD, PhD, Beaujon Hospital, Clichy, France

Thirty percent of patients with pancreatic cancer have unresectable locally advanced tumors (LAPC) for which induction chemotherapy is recommended. The phase 3 MPACT trial in metastatic pancreatic cancer showed that nab-paclitaxel (nab-P) plus gemcitabine reduced primary pancreatic cancer burden threefold compared with gemcitabine alone, suggesting the potential for activity against LAPC, Dr. Hammel said.

The international, multicenter, phase 2 LAPACT trial prospectively evaluated the safety and efficacy of six cycles of nab-P plus gemcitabine induction (125 mg/m\textsuperscript{2} nab-P plus 1,000 mg/m\textsuperscript{2} gemcitabine on days 1, 8, and 15 of each 28-day cycle) in newly diagnosed, untreated patients. After induction, patients without progressive disease or unacceptable adverse events were eligible for continued treatment with nab-P plus gemcitabine, chemoradiation, or surgery per investigator’s choice (IC). If tumor response was deemed adequate, surgery could occur before completion of the induction cycles. Time to treatment failure (TTF) was the primary endpoint.

Of 107 enrolled patients, 61 completed induction, with 20 discontinuations attributed to adverse events. Mean patient age was 65 years, and 55% were women. Forty-six patients (43%) received IC treatment after induction; 13 (12%) continued nab-P plus gemcitabine, 17 (16%) received chemoradiation, and 16 (15%) underwent surgical resection. Median duration of treatment exposure was 20.7 weeks. Approximately 63% of patients had one or more dose reductions and about half had one or more dose delays.

Grade 3 or higher adverse events were reported in 80% of patients. Nonhematologic adverse events included fatigue, anemia, hyperglycemia, and alanine aminotransferase increases, with events of grade 3 or higher occurring in 5.7% to 10.4% of patients. Grade 3 or higher neutropenia occurred in 41.5% of patients, but febrile neutropenia of grade 3 or higher was low at 3.8%. Induction therapy with nab-P plus gemcitabine was tolerable and consistent with known safety profiles, Dr. Hammel commented. He noted that, overall, patients’ global health status was maintained through day 1 of cycle 6.

Reporting on efficacy during induction, Dr. Hammel said there were partial responses in 32.7% and stable disease in 57.9% of patients, with the latter persisting at 16 weeks or longer and at 24 weeks or longer in 44.9% and 32.7%, respectively. Disease control rates at 16 weeks or longer and at 24 weeks or longer were 77.6% and 65.4%, respectively. Progressive disease occurred in 4.7%.

TTF, the primary endpoint, was 8.8 months (90% confidence interval, 6.67–9.82), meeting the protocol-specified target of 6.6 months. Median progression-free survival was 10.8 months, and estimated overall survival was 72% at 12 months.

Dr. Hammel concluded that “Nab-P plus gemcitabine has promising antitumor activity.” He also noted that quality of life was maintained in most patients and that nab-P plus gemcitabine induction allowed for conversion to tumor resection in 15% of patients.

**San Antonio Breast Cancer Symposium**

The San Antonio Breast Cancer Symposium (SABCS), held December 5–9, 2017, drew an attendance of approximately 7,500 medical professionals. We review key sessions on dose intensification, cyclin-dependent kinase 4/6 inhibition, new trial data of combination and adjuvant therapies, acupuncture for aromatase inhibitor arthralgia, and ovarian suppression to potentially preserve fertility in young women undergoing cancer treatment.

**Increasing the Dose Intensity of Adjuvant Chemotherapy: An EBCTCG Meta-Analysis**

- Richard Gray, PhD, MPhil, University of Oxford, Oxford, United Kingdom

Breast cancer recurrence and death are reduced by increasing dose intensity of adjuvant chemotherapy, according to a meta-analysis of 25 early breast cancer trials. Dr. Gray presented the findings of the study during an SABCS press briefing.

Speaking for the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG), he noted that much of contemporary adjuvant chemotherapy is given on conventional schedules every three weeks and is associated with a mortality reduction of about one-third. Cytokinetic modeling, however, suggests that greater chemotherapy dose density, achieved by shortening the intervals between courses or by using sequential as opposed to concurrent treatment schedules, may enhance efficacy. Dose density can be increased in three ways: higher drug doses in each cycle; reduced intervals between treatment cycles; and sequential dosing (e.g., an anthracycline alone followed by a taxane alone).
MEETING HIGHLIGHTS: San Antonio Breast Cancer Symposium

The difficulty associated with the first strategy, Dr. Gray said, is that doubling a dose does not double the benefit and will likely increase toxicities. “The cleaner way of intensifying the dose is simply to give the drugs in a shorter interval,” he said. While eight courses of treatment given every three weeks is typical, giving them every two weeks is feasible. In addition, restarting drug therapy sooner can potentially “knock the tumor cells before they can grow back.”

The EBCTCG meta-analysis included seven trials (n = 10,004) evaluating the dosing of the same drugs every two weeks versus every three weeks and five trials (n = 5,508) evaluating treatment with some differences in chemotherapy every two weeks versus every three weeks. The analysis also evaluated sequential therapy every three weeks in five trials of the same drugs (n = 9,644) and in one trial with some differences in drugs (n = 1,384). Finally, the EBCTCG meta-analysis included six trials of sequential (every two weeks) versus concurrent (every three weeks) treatment with some differences in the drugs used (n = 6,532). The primary outcomes were recurrence and breast cancer mortality.

Dr. Gray reported that increasing the dose intensity of chemotherapy reduced the recurrence and death from breast cancer by about 15%. Pooled analysis (n = 34,122) showed an overall relative risk reduction in recurrence of 15% (32.0% versus 28.4%; P < 0.00001) and a mortality reduction of 13% (22.2% versus 19.5%; P < 0.00001).

Reductions in recurrence with dose-intense chemotherapy were similar in estrogen receptor-positive (ER+) and ER– disease and did not differ significantly by any other tumor or patient characteristic. There were no increases in death without recurrence when the dose-intense and standard arms were compared (overall or during chemotherapy).

“So whichever way the trials achieved dose intensification, they seem to be finding benefits and fewer recurrences. This is quite remarkable how consistent all these different approaches were,” Dr. Gray said. He recommended more trials like this addressing “bread-and-butter” questions, such as whether eight courses are better than six courses.

MONALEESA-7: Ribociclib Improved Progression-Free Survival for Pre- and Perimenopausal Women With Hormone Receptor-Positive Advanced Breast Cancer

- Debu Tripathy, MD, The University of Texas MD Anderson Cancer Center, Houston, Texas

In postmenopausal women with de novo and/or recurrent hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer, adding ribociclib (Kisqali, Novartis) to letrozole significantly prolonged progression-free survival (PFS) compared with letrozole alone, according to MONALEESA-7 findings.

Younger women with advanced breast cancer have a distinct tumor biology, experience more aggressive disease, and are more likely to die from their cancer than older women, Dr. Tripathy noted in an SABCS press conference. It was estimated, he said, that in 2017 in the U.S. about 19% of invasive breast cancers would be diagnosed in women 49 years of age or younger, with higher rates (42%) in the Asia-Pacific region. While endocrine therapy with ovarian suppression is the recommended first-line treatment for premenopausal women with HR+, HER2– advanced breast cancer, resistance and disease progression ultimately occur.

Investigators enrolled 672 patients in MONALEESA-7, the first phase 3 trial investigating cyclin-dependent kinase (CDK) 4/6 inhibitor-based regimens as a front-line treatment specifically for premenopausal women with advanced breast cancer. The patients were randomized to ribociclib in combination with either tamoxifen or a nonsteroidal aromatase inhibitor (NSAI) (letrozole or anastrozole) and goserelin (n = 335) or to placebo in combination with the same oral hormonal therapy options and goserelin (n = 337). Ribociclib is an orally available CDK inhibitor targeting the cyclin D1/CDK4 and cyclin D3/CDK6 cell cycle pathway. The primary endpoint was investigator-assessed PFS.

The median age of patients in MONALEESA-7 was about 44 years; approximately 58% of the women were Caucasian and about 30% were Asian. Dr. Tripathy reported that the MONALEESA-7 primary endpoint was met, with median PFS significantly improved in the ribociclib arm at 23.8 months compared with 13.0 months in the placebo arm (hazard ratio [HR], 0.553; P = 0.0000000000093). Among women receiving tamoxifen as the partner drug to ribociclib, median PFS was 22.1 months in the ribociclib arm and 11.0 months in the placebo arm (HR, 0.585). In those receiving an NSAI with ribociclib, median PFS was 27.5 months versus 13.8 months for placebo (HR, 0.509). Subgroup analysis revealed PFS benefits for ribociclib across all subgroups.

Among the secondary endpoints, overall response rate was 40.9% in the ribociclib plus tamoxifen/NSAI arm and 29.7% in the placebo plus tamoxifen/NSAI arm (P = 0.00098). Among those women with measurable disease, the respective rates were 50.9% and 36.4% (P = 0.000317). The clinical benefit rate in this latter group was 79.9% for those receiving ribociclib and 67.3% for those receiving placebo (P = 0.00034).

While neutropenia was higher in the ribociclib arm (76.0% versus 8.0% in the placebo arm), it was associated with fewer infection and in only 2.0% of ribociclib patients and in 1.0% of placebo patients.

SABCS Co-Director and press conference moderator Virginia Kaklamani, MD, leader of the breast cancer program at The University of Texas Health Science Center at San Antonio, asked Dr. Tripathy if he felt that oncologists are replacing chemotherapy with CDK4/6 inhibitors in the metastatic setting. He responded, “I think so. There has been a trend to use hormonal therapy even before these drugs came on the scene. But we have very few trials. Most patients who are watched carefully can do just as well with hormonal therapy in the front line. The new biological agents, especially this class of drugs, do represent, for an even greater population of patients, the ideal first-line treatment.” He commented further that he tends to use aromatase inhibitors among possible endocrine partners because “they are associated with slightly improved outcomes, and their toxicity profiles may be a little more favorable. They can cause more symptoms than tamoxifen, so it’s good to have it available as an option.”
The PANACEA study met its primary endpoint among women with metastatic, human epidermal growth factor receptor-2-positive (HER2+) breast cancer resistant to trastuzumab (Herceptin, Genentech) who received pembrolizumab (Keytruda, Merck) with trastuzumab. No responses were observed in patients who were programmed death ligand-1 (PD-L1) negative.

Dr. Loi noted at an SABC press briefing that HER2+ breast cancer has high levels of T-cell infiltration. Tumor-infiltrating lymphocytes (TILs) are associated with improved prognosis and response to trastuzumab and chemotherapy. In addition, trastuzumab has been shown to have immune-mediated mechanisms of action. Preclinical studies have suggested immune-mediated mechanisms of trastuzumab resistance that can be overcome with checkpoint inhibition combinations.

PANACEA, a phase 1b/2 clinical trial, enrolled 58 women with advanced breast cancer that had progressed on prior trastuzumab-based treatment. Tumors were centrally assessed for HER2 positivity, PD-L1 status, and the number of TILs. The phase 1b dose-escalation portion of the trial found no dose-limiting toxicities for the anti-PD-1 agent pembrolizumab. The phase 2 study included 40 PD-L1-positive and 12 PD-L1-negative patients. All received intravenous pembrolizumab 200 mg every three weeks in combination with standard trastuzumab doses for 24 months or until disease progression. The primary objectives were efficacy and safety for the combination among patients with PD-L1-expressing tumors. Rejecting the null hypothesis required six or more objective responses in the phase 2 portion. An exploratory analysis of efficacy according to baseline stromal TIL (sTIL) levels was also planned.

Mean age was 49 years in the PD-L1-positive patients and 56.5 years in the PD-L1-negative patients. Immune-related adverse events led to discontinuations in four patients (6.9%), with thyroid dysfunction and pneumonitis most common. No cardiac events were reported.

In the PD-L1-positive intent-to-treat population, the objective response rate was 15.2% (one complete response and five partial responses), and the disease control rate was 24.0%. The median duration of disease control was 11.1 months, and the median duration of response was 3.5 months. Mean duration of response was 10.0 months. Five patients (10.8%) continue with no progression, Dr. Loi said. Twelve-month progression-free survival was 13.0% in PD-L1-positive patients and 0% in PD-L1-negative patients ($P = 0.07$). She noted that 12-month overall survival was 65.0% in the PD-L1-positive group and 12.0% in the PD-L1-negative group ($P = 0.0006$). “PD-L1 status is prognostic, and also contains all the responders,” Dr. Loi commented.

Regarding the exploratory endpoint, Dr. Loi noted, “We observed that the median level of TIL infiltration in the metastatic lesions was 1.0%, which was 20 times less than what we observed in primary HER2+ breast cancers. However, we did note a significantly higher TIL level in the PD-L1-positive cohort and also significantly higher TIL levels in patients who achieved an objective response or disease control. So higher TIL levels are associated with an increased chance of response.”

Dr. Loi also said that in seeking a potential predictive marker for response, the PANACEA team found that with sTILs of 5% or higher compared with sTILs lower than 5%, the objective response rate was 39% versus 5%. Disease control rates were 47% versus 5% at the same cut-offs.

“For responders, the pembrolizumab and trastuzumab combination offers durable control without chemotherapy,” she concluded. She observed that metastatic HER2+ disease in the heavily pretreated setting is poorly immunogenic (the majority of patients had low TILs in metastatic lesions).

The Synergism or Long Duration (SOLD) Trial: A Randomized Phase 3 Study of Adjuvant Trastuzumab for Nine Weeks Versus One Year Combined With Adjuvant Taxane-Anthracycline Chemotherapy for Early HER2-Positive Breast Cancer

• Heikki Joensuu, MD, PhD, Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland

While noninferiority of nine-week administration of trastuzumab (Herceptin, Genentech) plus docetaxel versus chemotherapy and one-year duration of adjuvant trastuzumab could not be demonstrated for disease-free survival (DFS), docetaxel dosing with trastuzumab warrants further study in early human epidermal growth factor receptor 2-positive (HER2+) breast cancer, according to Dr. Joensuu.

Based on several lines of evidence, concomitant administration of trastuzumab with a taxane improves trastuzumab efficacy and might be synergistic. In addition, continuing trastuzumab after combined trastuzumab and taxane might not markedly add to efficacy, he suggested. While chemotherapy plus trastuzumab for one year is the current standard of care, small trials have shown similar DFS and overall survival in patients receiving either nine weeks or 12 months of trastuzumab. One year of treatment with trastuzumab is lengthy, expensive, and sometimes associated with adverse cardiac events. Congestive heart failure was reported in fewer than 3% of patients in the pivotal trials, but risk is probably greater in elderly patients, Dr. Joensuu said.

The Synergism or Long Duration (SOLD) trial investigators randomly assigned 2,176 patients (median age, 56 years) with early-stage HER2+ breast cancer: 1:1 to a nine-week trastuzumab arm or a 12-month trastuzumab arm. Included patients had histologically confirmed HER2+ disease that was node-positive, or node-negative with a size larger than 5 mm (if 6–10 mm, histological grade 2 or 3), and had left ventricular ejection fractions of 50% or greater.

Patients in both arms received three cycles of docetaxel (80 mg/m² or 100 mg/m²) and trastuzumab three times a week, followed by three cycles of chemotherapy. While patients in the nine-week arm received no further treatment, those in the 12-month arm received trastuzumab every three weeks for 14 cycles. Women with estrogen receptor-positive cancer received guideline-recommended endocrine treatment and radiation therapy as per institutional practice.
The five-year survival estimates placed DFS at 90.5% in the 12-month treatment arm and 88.0% in the nine-week treatment arm (hazard ratio [HR], 1.39; 90% confidence interval [CI], 1.12–1.72). The overall survival five-year estimate was 95.9% in the 12-month arm and 94.7% in the nine-week arm (HR, 1.36; 95% CI, 0.98–1.89), and distant DFS was 94.2% and 93.2%, respectively (HR, 1.24; 90% CI, 0.93–1.65).

A prespecified DFS subgroup analysis showed benefit for the nine-week regimen over the 12-month regimen among patients receiving a docetaxel dose of 100 mg/m² (92.2% for nine weeks versus 87.8% for 12 months; HR, 0.71; 90% CI, 0.44–1.14), but showed advantage for 12-month treatment among those receiving docetaxel at 80 mg/m² (91.3% for 12 months versus 86.8% for nine weeks; HR, 1.66; 90% CI, 1.30–2.11).

Cardiac toxicity was higher in the 12-month treatment group compared with the nine-week group (3.9% versus 2.0%; P = 0.012). Congestive heart failure was reported in 1.9% of the nine-week group and in 3.3% in the 12-month group (P = 0.046).

“Chemotherapy plus one year of anti-HER2 therapy should remain the standard,” Dr. Joensuu concluded. He noted, however, that there was not much difference between groups in distant DFS and overall survival and that further study of docetaxel/trastuzumab dosing is warranted.

### Acupuncture Reduced Joint Pain Caused By Aromatase Inhibitor Treatment in a Randomized, Phase 3 Clinical Trial

- Dawn L. Hershman, MD, Herbert Irving Comprehensive Cancer Center, Columbia University, New York, New York

Among postmenopausal women with early-stage breast cancer receiving treatment with an aromatase inhibitor, acupuncture treatment significantly reduced joint pain, according to results of the randomized, phase 3 SWOG S1200 trial.

“Aromatase inhibitors are among the most common and most effective treatments for postmenopausal women diagnosed with hormone receptor-positive [HR+] breast cancer; however, many patients suffer from side effects that cause them to miss treatments or stop treatment altogether,” Dr. Hershman said. “We need to identify strategies to control these side effects, the most common of which is debilitating joint pain and stiffness.” She noted that several small studies have suggested that acupuncture may be beneficial for aromatase inhibitor-associated arthralgia.

The trial, conducted at 11 centers, included 226 early-stage HR-breast cancer patients (median age, 60.7 years), all of whom had pain starting or increasing after initiation of aromatase inhibitor therapy. Investigators randomized 59 patients to sham acupuncture with needles inserted into nonacupoints and 110 patients to true acupuncture (Chinese medicine point prescriptions). Fifty-seven patients were assigned to wait-list control (no treatment).

Patients receiving true acupuncture or sham acupuncture had twice-weekly sessions for six weeks followed by one session per week for six more weeks. Pain measures included the Brief Pain Inventory–Short Form (BPI), a self-administered 14-item questionnaire with a 0-to-10 scale with higher scores indicating more pain and pain impact on functioning. The primary outcome was mean worst BPI pain score at six weeks.

The mean BPI worst pain for the true acupuncture arm was 0.92 points lower than the mean BPI worst pain for the sham acupuncture arm (P = 0.01) and 0.96 points lower than the mean BPI worst pain for the wait-list control arm (P = 0.01). In addition, the proportion of patients who had a reduction of two or more points in worst pain was significantly greater in the true acupuncture arm than in the sham acupuncture and wait-list control arms (58%, 33%, and 31%, respectively; P < 0.009; P < 0.004). The same pattern of significant benefit for the true acupuncture group versus sham and wait-list groups persisted in BPI stiffness evaluated with the Western Ontario and McMaster Universities Osteoarthritis Index for hips/knees and the Modified Score for the Assessment and Quantification of Chronic Rheumatic Affections of the Hands.

Dr. Hershman noted that while the acupuncture intervention was completed by 12 weeks, the pain score improvements remained statistically significant at the 24-week assessment.

Grade 1 bruising was more common with true acupuncture than with sham acupuncture (47% versus 2%; P = 0.01). Otherwise adverse events were generally absent or minimal for both.

“We have shown consistently, with multiple measures assessing pain and stiffness, that true acupuncture generated better outcomes than either control group in a large multicenter randomized controlled trial,” Dr. Hershman said.

### Phase 3 EMBRACA Trial: Talazoparib Prolonged Progression-Free Survival in Patients With Advanced, BRCA-Mutated Breast Cancer

- Jennifer Litton, MD, The University of Texas MD Anderson Cancer Center, Houston, Texas

“In EMBRACA, talazoparib [investigational, Pfizer] demonstrated superior clinical benefit in all subsets of patients, regardless of receptor subtype (HR [hormone receptor]-positive or triple-negative breast cancer), number of prior lines of chemotherapy, BRCA mutation type, and central nervous system metastasis,” Dr. Litton said in an SABCS press briefing. She noted that talazoparib is a dual mechanism inhibitor of the poly (ADP-ribose) polymerase (PARP) enzyme that also traps PARP on DNA, preventing DNA damage repair and leading to the death of BRCA1/2-mutated cells. Promising results with talazoparib have been reported in early phase trials.

EMBRACA is an open-label, randomized, phase 3 trial comparing the efficacy and safety of 1 mg talazoparib daily with standard, single-agent, physician’s choice of therapy (PCT) in patients with advanced breast cancer and a germline BRCA1/2 mutation. PCT generally consisted of capcitabine, eribulin (Halaven, Eisai, Inc.), gemcitabine, or vinorelbine. Investigators randomly assigned patients (2:1) to talazoparib (n = 287) or PCT (n = 144).

Progression-free survival (PFS), assessed by blinded independent central review, was the primary outcome measure, with secondary objectives of overall survival (OS), overall response rate (ORR), clinical benefit rate at 24 weeks (CBR24), and safety.

Median PFS was 8.6 months for patients in the talazoparib arm versus 5.6 months for those in the PCT arm (P < 0.0001). Patients in the talazoparib arm were 45.8% less likely to have disease progression compared with those in the PCT arm. Improvements in ORR and CBR24 also favored talazoparib.
significantly. Complete responses were observed in 12 patients receiving talazoparib and none in the PCT group. Time to clinical deterioration was 24.3 months for talazoparib patients and 6.3 months for those receiving PCT. While overall survival data are not yet mature (51% of projected events), the hazard ratio is currently 0.76 (95% confidence interval, 0.54–1.06; *P* = 0.105), a trend favoring talazoparib.

Grade 3–4 hematologic adverse events were reported in 55% of patients receiving talazoparib and 39% receiving PCT. Grade 3–4 gastrointestinal and skin/subcutaneous tissue disorder rates were lower for the talazoparib group. Overall, grade 3–4 serious adverse event rates were similar for the two groups (approximately 25%). Rates of adverse event-attributable deaths were 2.1% and 3.2%, respectively, for the talazoparib and PCT arms. “Talazoparib was generally well tolerated, with minimal nonhematologic toxicity and few adverse events resulting in treatment discontinuation,” Dr. Litton said. Quality-of-life assessments showed that patients receiving talazoparib had a significant delay in the time to deterioration in health compared with patients in the PCT arm.

**Phase 3 Trial of Additional Two Years Versus Additional Five Years of Anastrozole After Initial Adjuvant Endocrine Therapy: The ABCSG-16 Trial**

- Michael Gnant, MD, Medical University of Vienna, Vienna, Austria

In the ABCSG-16 trial, adding five years of anastrozole to standard five-year adjuvant endocrine therapy (tamoxifen, aromatase inhibitor [AI] sequence) did not improve disease-free survival (DFS) compared with an additional two years of anastrozole, Dr. Gnant said at an SABCS press briefing.

Long-term risk of relapse in hormone receptor-positive (HR+) breast cancer is significant, and more than half of disease relapses occur after the first five years of follow-up. While extended adjuvant therapy with AIs after initial tamoxifen has been demonstrated to improve the DFS of postmenopausal patients with HR+ breast cancer, the optimal duration of extended AI therapy is unknown. Moreover, it remains unclear whether patients after AI treatment in the first five years benefit similarly from extended adjuvant AI therapy as patients do after tamoxifen. It is important to establish how long the treatment should be given, Dr. Gnant said, “because this treatment leads to prolonged side effects and impacts quality of life.”

ABCSG-16 investigators enrolled 3,484 postmenopausal women with HR+ early-stage breast cancer in 71 Austrian centers and randomized them to receive either two years or five years of extended adjuvant therapy. All had undergone an initial five years of adjuvant endocrine treatment (either tamoxifen or other regimens containing AIs). Median patient age was 64 years. Eighty percent of women had breast-conserving surgery, and 29% had additional neoadjuvant chemotherapy. Tumor size was smaller than 2 cm in 72% of patients. Treatment in the first five years had been tamoxifen only in 51%.

After a median follow-up of 106.2 months, DFS was 71.1% in the two-year arm and 70.3% in the five-year arm (hazard ratio [HR], 1.007; 95% confidence interval [CI], 0.87–1.16; *P* = 0.925). The secondary endpoint of overall survival (OS) was 85.3% in the two-year arm and 84.9% in the five-year arm (HR, 1.007; 95% CI, 0.82–1.23; *P* = 0.947). Time to contralateral breast cancer and time to second primary cancer were similar for both groups.

The difference in fracture rates in the five-year and two-year groups (6.3% versus 4.7%, respectively) nearly achieved statistical significance (HR, 1.353; 95% CI, 1.00–1.84; *P* = 0.053).

“There is no benefit of continuing/escalating endocrine treatment beyond seven years,” Dr. Gnant concluded. “Extension of anastrozole treatment to five additional years leads to increased side effects including fractures and should be avoided.”

**Temporary Ovarian Suppression With Hormone Analogue May Preserve Fertility During Breast Cancer Chemotherapy**

- Matteo Lambertini, MD, Institut Jules Bordet, Brussels, Belgium

Treatment with a gonadotropin-releasing hormone analogue (GnRHa) could safely and effectively protect ovarian function and potentially preserve fertility in premenopausal women receiving chemotherapy for early-stage breast cancer, according to a meta-analysis of five randomized clinical trials.

“Fertility preservation and pregnancy-related issues are high-priority areas of concern for young women with breast cancer,” Dr. Lambertini noted. Premature ovarian insufficiency (POI) is a common side effect of chemotherapy in premenopausal patients, he added, with substantial negative impacts on their quality of life. Oocyte/embryo cryopreservation are standard strategies for fertility preservation, but they do not prevent the risk of chemotherapy-induced POI. While temporary ovarian suppression with GnRHa during chemotherapy has been studied in randomized controlled trials as a strategy to preserve ovarian function and potential fertility, data are mixed and its role remains controversial.

Dr. Lambertini and colleagues conducted a systematic review and meta-analysis of five clinical trials (PROMISE-GIM6, POEMS/SWOG S0230, Anglo Celtic Group OPTION, GBG-37 ZORO, Moffitt-led trial) with GnRHa use during chemotherapy, with ovarian function and fertility preservation as the efficacy outcome and with survival as the safety outcome. The analysis included 436 women receiving GnRHa and 437 women as controls (median age, approximately 38.5 years).

Dr. Lambertini reported that the rate of POI was 14.1% in the GnRHa group and 30.9% in the control group (odds ratio [OR], 0.38; 95% confidence interval [CI], 0.26–0.57; *P* < 0.001). While the secondary endpoint of one-year amenorrhea was similar for the groups (36.8% for GnRHa versus 40.4% for controls), two-year amenorrhea significantly favored the GnRHa group (18.2% versus 30.0%) (OR, 0.51; 95% CI, 0.31–0.85; *P* = 0.009). Post-treatment pregnancy rates were higher in the GnRHa group (10.3% versus 5.5%; *P* = 0.030). There was also a trend favoring OS for the GnRHa group (hazard ratio, 0.67; 95% CI, 0.42–1.06; *P* = 0.083). “This suggests that administering GnRHa during chemotherapy can be considered safe in breast cancer patients,” he said.

“This strategy should be considered as an option to reduce the likelihood of chemotherapy-induced POI and potentially improve future fertility in premenopausal early breast cancer patients undergoing neoadjuvant chemotherapy,” he said.