Alan Ho, MD, PhD, presents results of a trial testing tipifarnib. The agent targets HRAS, long considered undruggable.

for these patients are 13% to 15% for immune checkpoint inhibitors and less than 10% for chemotherapy or cetuximab, Ho said.

All patients experienced adverse events, and more than 10% experienced hematologic side effects, namely anemia, neutropenia, and leukopenia. These were also the most common adverse events of grade 3 or higher.

"We have very compelling antitumor activity in a heavily pretreated cohort of these recurrent metastatic head and neck cancer patients with *HRAS* mutations," Ho said. Next, researchers will test tipifarnib in the pivotal phase II AIM-HN/SEQ-HN trial of *HRAS*-mutant HNSCC. They also plan to explore tipifarnib in combination with other agents, including chemotherapy, immune checkpoint inhibitors, and targeted therapies—particularly in patients with *HRAS* mutations at a VAF of less than 20%.

Targeting the RAS–RAF–MAPK pathway "has been one of the holy grails of cancer, given the high frequency of *RAS* mutations in tumors such as colorectal, pancreas, and melanoma," said William Sellers, MD, of the Broad Institute of Harvard and MIT in Cambridge, MA, who was not involved in the trial. Sellers added that the tipifarnib trial, along with others testing agents that act on the same pathway, "emphasizes the excitement … of what's happening in the cancer field in general, and in particular in the RAS pathway." *–Catherine Caruso* ■

Early Pembrolizumab Ups TNBC Responses

Adding the PD-1 inhibitor pembrolizumab (Keytruda; Merck) to neoadjuvant chemotherapy may improve outcomes in early-stage triple-negative breast cancer (TNBC), researchers reported at the ESMO Congress 2019, September 27–October 1, in Barcelona, Spain. In the phase III KEYNOTE-522 trial, patients treated with the combination had a significantly higher pathologic complete response (pCR) rate and trended toward better event-free survival than those who received chemotherapy alone.

Patients with early-stage TNBC typically receive neoadjuvant chemotherapy, followed by surgery to remove the tumor. However, given the aggressiveness of TNBC, and patients' poor prognosis once it metastasizes, researchers have pushed to develop treatment regimens that might stem the disease at an early stage. "It is well established that patients who achieve a pathological complete response after neoadjuvant chemotherapy have a long-term clinical benefit," said Peter Schmid, MD, PhD, of Barts Cancer Institute at Queen Mary University of London, UK, who presented the results.

When combined with chemotherapy in phase I and II trials, pembrolizumab had promising neoadjuvant activity in early-stage TNBC. In KEYNOTE-522, researchers assigned 1,174 patients with newly diagnosed, early-stage TNBC in a 2:1 ratio to receive neoadjuvant pembrolizumab plus chemotherapy or a placebo plus chemotherapy. After surgery, patients assigned to the combination arm received pembrolizumab, whereas patients assigned to the chemotherapy arm received a placebo.

In an analysis of the first 602 patients, performed after a median follow-up of 15.5 months, 64.8% of those in the pembrolizumab arm experienced a pCR compared with 51.2% of those in the chemotherapy-only group—a statistically significant difference that was seen regardless of nodal stage, tumor size, patient age, chemotherapy regimen, or PD-L1 expression. Among all 1,174 patients, just 7.4% of those treated with pembrolizumab experienced disease recurrence, compared with 11.8% of those who received chemotherapy alone, a trend that has not yet reached statistical significance.

"The safety profile in general is consistent with what we know for single-agent therapy with pembrolizumab and other checkpoint inhibitors, as well as the combination of chemotherapy and checkpoint inhibitors," Schmid said. During neoadjuvant treatment, 76.8% of patients in the combination arm experienced grade 3 or higher adverse events, compared with 72.2% of those in the chemotherapy arm; throughout adjuvant treatment, 5.7% of patients receiving pembrolizumab experienced grade 3 or higher adverse events, compared with 1.9% of patients receiving a placebo. Overall, 42.3% of patients treated with pembrolizumab experienced immune-related side effects—most commonly hypothyroidism or rashes—or infusion reactions, compared with 21.3% of patients in the control arm.

"This is the first phase III neoadjuvant immunotherapy study to report [results in TNBC], so this is very exciting," said Sherene Loi, MD, PhD, of the Peter MacCallum Cancer Centre at the University of Melbourne in Australia, who provided commentary on the trial.

Loi was particularly intrigued by data suggesting that PD-L1 status does not predict whether patients with early-stage TNBC will respond to immunotherapy. "This is somewhat surprising because in the advanced setting, it is only the PD-L1–positive patients that benefit," she said, a result that should be investigated further.

Loi noted that it isn't entirely clear how pCR translates into event-free survival—or how patients who experience immune-related side effects will fare over time. "There is no doubt in my mind that checkpoint blockade will help us treat early-stage triple-negative breast cancer patients better," she said. "However, we need to wait for longer and more mature event-free survival data … to understand the benefit." *–Catherine Caruso* ■

Olaparib to Change Practice in mCRPC

For the first time, a phase III trial has shown that a PARP inhibitor can be effective in patients with metastatic

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Olaparib can prolong survival in patients with metastatic castration-resistant prostate cancer, says Maha Hussain, MD.

castration-resistant prostate cancer (mCRPC) who have faulty DNA-repair genes. In the PROfound trial, the drug extended median radiographic progression-free survival (rPFS) and increased the objective response rate (ORR) in patients with *BRCA1/2* and *ATM* mutations, compared with newer hormonal agents.

Despite recent therapeutic advances, patients with mCRPC have a poor prognosis. However, up to 30% of patients have tumors with mutations in DNA-repair genes, including those involved in homologous recombination repair (HRR). "These gene alterations can confer sensitivity to PARP inhibition," said Maha Hussain, MD, of Northwestern University in Chicago, IL, who presented the findings at the ESMO Congress 2019, September 27–October 1, in Barcelona, Spain. In a previous phase II trial, the PARP inhibitor olaparib (Lynparza; AstraZeneca) demonstrated antitumor activity in patients with mCRPC and HRR mutations—including alterations in *BRCA1/2* and *ATM*, the most well-characterized DNA-repair genes (N Engl J Med 2015;373:1697–708).

The PROfound trial tested olaparib in patients with mCRPC and HRR alterations whose disease had progressed despite receiving either abiraterone (Zytiga; Janssen) or enzalutamide (Xtandi; Astellas/Pfizer). In cohort A, 245 patients with *BRCA1/2* or *ATM* mutations were randomized 2:1 to receive olaparib or the physician's choice of enzalutamide or abiraterone plus prednisone; in cohort B, 142 patients with alterations in other HRR-related genes received olaparib or the physician's choice.

Patients in cohort A who were treated with olaparib had a median rPFS of about 7.4 months and an ORR of 33.3% and had not yet reached median time to pain progression, compared with about 3.6 months, 2.3%, and 9.9 months, respectively, in patients who received a physician's-choice therapy. Patients treated with olaparib in both cohorts had a combined median rPFS of about 5.8 months and an ORR of 21.7%, compared with about 3.5 months and 4.5% in patients receiving the physician's choice.

In an interim analysis, patients in cohort A treated with olaparib had a median overall survival (OS) of 18.5 months, compared with 15.1 months in the control group. When combined, patients treated with olaparib in both cohorts had a median OS of 17.5 months, compared with 14.3 months in the control group. In an exploratory analysis, Hussain and her team found that olaparib had clinical activity in patients with mutations in HRR genes other than *BRCA1/2* and *ATM*, including *CDK12* and *CHEK2*. "This highlights the fact that not all DNA repair–defect genes are the same," Hussain said.

Overall, half of the patients who received olaparib experienced side effects classified as grade 3 or higher, and 16.4% discontinued treatment, compared with 37.7% and 8.5% of patients in the control group.

"This is a truly practice-changing study," said Eleni Efstathiou, MD, PhD, of The University of Texas MD Anderson Cancer Center in Houston, who discussed the findings. "In those patients with [DNA damage–repair] alterations, mainly *BRCA2*, we saw clinically meaningful improvements, and when it comes to prostate cancer therapy strategy … we're entering into the targeted-therapy era."

"Disease outcome variability, we know, is largely driven by underlying molecular heterogeneity. The challenge remains to identify causal pathways of disease progression that can be targeted," Efstathiou added. "Our goal is progress. It's not perfect yet; this trial moves the field forward."
–*Catherine Caruso* ■

NOTED

The FDA approved the PARP inhibitor niraparib (Zejula; Tesaro) for patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with at least three chemotherapies and whose tumors are positive for homologous recombination deficiency. The decision was based on the phase II QUADRA trial in which patients had an overall response rate of 24%.

Bristol-Myers Squibb's **PD-1 inhibitor nivolumab (Opdivo) and its CTLA4 inhibitor ipilimumab (Yervoy) could be a new first-line treatment** for advanced non–small cell lung cancer. In the CheckMate-227 trial, the combination extended median overall survival compared with chemotherapy, regardless of PD-L1 level. Results were presented at the ESMO Congress 2019 in Barcelona, Spain, and concurrently published (N Engl J Med 2019 Sep 28 [Epub ahead of print]).

GRAIL released data validating its multicancer early-detection test that analyzes cell-free DNA in blood samples. The company ran its test on 1,264 participants, including 654 people with cancer. With 99.3% specificity, the test had an overall detection rate of 76% for 12 cancers that generally have a poor prognosis.

Multiple organizations, including the American Cancer Society, published guidelines outlining how **exercise can reduce the risk of developing cancer** and improve the prognosis for people with cancer (CA Cancer J Clin 2019 Oct 16 [Epub ahead of print]). The guidelines suggest that physically active people could reduce their risk of certain cancers by up to 69% compared with those who are sedentary, and exercise during or after cancer treatment is associated with longer life and improved mood and energy levels.

At the Biopharma Congress in Washington, DC, **FDA leaders expressed concern about the agency's ability to recruit and retain experts** in cutting-edge scientific fields such as cell and gene therapies and oncology. "We're dealing with the issue of a very competitive job market," said Peter Marks, MD, PhD, director of the FDA Center for Biologics Evaluation and Review.

For more news on cancer research, visit *Cancer Discovery* online at http://cancerdiscovery.aacrjournals.org/CDNews.