


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