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# Immunotherapy Shows Early Promise for Patients With Trastuzumab-resistant Breast Cancer

SAN ANTONIO —A combination of pembrolizumab (Keytruda) and trastuzumab, tested in patients with trastuzumab-resistant advanced HER2-positive breast cancer, was well tolerated and had clinical benefit in patients whose tumors were positive for a biomarker for pembrolizumab, according to data presented from the phase Ib/II PANACEA trial at the 2017 San Antonio Breast Cancer Symposium, held Dec. 5–9.

"We wanted to investigate if immunotherapy approaches can work in patients with advanced HER2-positive breast cancer that is resistant to trastuzumab," said Sherene Loi, MD, PhD, associate professor at Peter MacCallum Cancer Centre in Melbourne, Australia, working with the International Breast Cancer Study Group (IBCSG).

It is estimated that approximately 20 percent of invasive breast cancers are HER2-positive, and some of these patients develop resistance to trastuzumab, a HER2-specific monoclonal antibody utilized for treatment of the disease. Loi and colleagues hypothesized that immunotherapy may help to overcome trastuzumab resistance in this subset of breast cancers.

"We believe that immune evasion is a part of the biological resistance to trastuzumab in patients with this disease," commented Loi. "Prior studies from our group have shown that antitumor immunity is important for improved outcomes in patients with advanced HER2-positive breast cancer." Loi and colleagues previously demonstrated that patients with trastuzumab-resistant advanced HER2-positive breast cancer had evidence of poor immune responses, and preclinical studies revealed that anti-PD1 immunotherapy improved the therapeutic activity of trastuzumab.

In this phase Ib/II clinical trial, Loi and colleagues enrolled 58 patients with advanced breast cancer that had progressed on prior trastuzumab-based therapies. Tumors were assessed centrally for HER2 positivity and PDL1 status, and for quantity of tumor-infiltrating lymphocytes (TILs).

The Phase Ib portion of the trial was a dose-escalation study of pembrolizumab, an anti-PD1 therapy that targets the T-cell checkpoint protein PD1, in conjunction with the standard dose of trastuzumab. No dose-limiting toxicities (DLTs) were observed.

In phase II, the investigators enrolled 40 patients and 12 patients to the PDL1-positive and PDL1-negative cohorts, respectively. Patients received 200mg of pembrolizumab every three weeks in combination with the standard dose of trastuzumab for 24 months or until disease progression.

In the PDL1-positive intent-to-treat population, the trial met its primary endpoint with an objective response rate (ORR) of 15 percent and disease control rate (DCR) of 25 percent. In a

subgroup of PDL1-positive patients with 5 percent or more TILs present in the metastatic lesion, the ORR was 39 percent and the DCR was 47 percent, suggesting that quantification of TILs may help identify patients who will most benefit from this treatment. No responses were observed in the PD-L1 negative cohort.

Five (10.8 percent) patients in the PDL1-positive cohort continued to have no disease progression at the time of reporting, Loi noted. Pembrolizumab with trastuzumab was well tolerated, with grade 1-2 fatigue as the most commonly reported adverse event (21 percent). The most common immune adverse events reported were hyper and hypo-thyroidism (grade 1-2 at 6.7 percent) and pneumonitis (grade 3-4 at 3.4 percent).

Final safety and efficacy results from this trial will be presented on Wednesday, Dec. 6.

"This proof-of-principle study suggests that immune evasion is a mechanism of resistance to trastuzumab and contributes to disease progression in advanced HER2-positive breast cancer," noted Loi. "Our results suggest that PD1 inhibition is likely to become part of the treatment armamentarium of HER2-positive disease in the future."

This study was sponsored and managed by the International Breast Cancer Study Group, in collaboration with the Breast International Group, and funded by Merck & Co., Inc., Kenilworth, N.J., USA (known as MSD outside the United States and Canada), through a subsidiary.

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