New data show pembrolizumab improves breast cancer outcomes regardless of age or menopausal status

March 19 2024

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New data from the KEYNOTE-756 phase 3 clinical trial show that adding the immunotherapy drug pembrolizumab to chemotherapy before and after surgery for breast cancer leads to better outcomes for patients regardless of their age or menopausal status.

The findings, presented at the 14th European Breast Cancer Conference (EBCC 14), add to information available on the effect of pembrolizumab in patients with early-stage breast cancer that is at high risk of recurring or spreading further, and that is estrogen receptor positive (ER positive) and HER2 negative.

KEYNOTE-756 is an international trial that has been running for eight years. It randomized 1,278 patients to receive pembrolizumab or placebo in addition to neoadjuvant chemotherapy (given before surgery) followed by adjuvant (given after surgery) pembrolizumab or placebo in combination with an endocrine therapy. The patients had invasive ductal carcinoma (IDC), meaning the cancer had started to spread out of the milk ducts into the surrounding breast tissues.

Professor Javier Cortés, Director of the International Breast Cancer Centre in Barcelona, Spain, said, "We have already reported that there was a statistically significant increase in the pathological complete response rate in patients receiving pembrolizumab compared to those receiving the placebo. The pathological complete response rate, meaning that no cancer cells remained in the breast or lymph nodes, was 24.3% in patients treated with pembrolizumab compared to 15.6% in patients treated with the placebo.

"Now we can show that these pCR rates occurred regardless of the patients' age or menopausal status. In patients younger than 50 years old, the pCR rate was 23.8% in those on pembrolizumab (76 out of 319 patients) compared to 16.9% (55 out of 326) for those receiving placebo, and was 24.7% (78 of 316 patients) versus 14.2% (45 of 317)

respectively in those aged 50 or older. In pre-menopausal women, the pCR rate was 23.4% (83 out of 354 patients) versus 16.1% (57 out of 353) respectively, and in post-menopausal women, it was 24.8% (69 out of 278 patients) versus 14.6% (42 out of 287), respectively.

"We also found that adding pembrolizumab to neoadjuvant chemotherapy did not delay the time to surgery. The average time to surgery in both groups of patients was about a month. The average time after surgery to the start of adjuvant treatment was 1.2 months in both groups."

The study found that there were similar rates of breast-conserving surgery and mastectomy in both groups. Among the patients who had breast-conserving surgery, 41.3% (262 patients) received pembrolizumab and 43.7% (281 patients) received placebo. Among those who had a mastectomy, 55.3% (351 patients) were treated with pembrolizumab and 54.4% (350 patients) had the placebo.

Tissue collected at the time of surgery was analyzed to see if any cancer cells remained after the neoadjuvant treatment, known as residual cancer burden (RCB). Neoadjuvant pembrolizumab resulted in a lower RCB for more patients, regardless of how well the immunotherapy had blocked a protein called PD-L1, which also drives some breast cancers.

Pathology reports found that 35% of patients (222 patients) treated with pembrolizumab had no or very small amounts of cancer cells remaining (RCB 0-1) versus 23.6% of patients (152) receiving placebo. A moderate amount of RCB (RCB-2) was found in 40.8% of patients treated with pembrolizumab versus 45.3% (259 versus 291 patients), and extensive RCB (RCB-3) was found in 20.5% versus 28.9% of patients respectively (130 versus 186 patients).

When the researchers looked at the effect of pembrolizumab according

to whether patients had cancer that was ER positive in less than 10% of cells or in 10% or more, they found that 64.7% of patients (22 out of 34) with less than 10%, who were treated with pembrolizumab, had an RCB status of 0-1, compared to 37.2% of patients treated with placebo (16 out of 43). In patients with 10% or more ER positive cells, 33.3% compared to 22.7% had an RCB 0-1 status (200 out of 601 patients versus 136 out of 600 patients respectively).

Dr. Fatima Cardoso, Director of the Breast Unit of the Champalimaud Clinical Centre, Lisbon, Portugal, is the principal investigator for the trial. Speaking before EBCC 14, she said, "KEYNOTE 756 trial showed that the addition of pembrolizumab to neoadjuvant chemotherapy significantly increased pathological response at the time of surgery, and this was true regardless of PD-L1 levels and estrogen receptor positivity. However, we saw a bigger benefit with higher PD-L1 levels and in ER-low tumors.

"KEYNOTE-756 is also the only trial that is powered to analyze the impact of immunotherapy in long-term outcomes for this subtype of breast cancer."

Adverse events from the treatments were unchanged from previous reports from the trial and were consistent with what is known already about each regimen.

The trial continues to follow the patients, and information is being collected on survival rates and whether there are any recurrences of cancer or other related symptoms.

Professor Michail Ignatiadis from the Institut Jules Bordet in Brussels, Belgium, is Chair of the 14th European Breast Cancer Conference and was not involved in the research. He said, "We have heard more data from the KEYNOTE-756 trial about which ER positive / HER2 negative

patient subgroups benefit most from pembrolizumab in terms of pathological complete response. Longer follow-up is needed in order to see whether the improvement in pCR rates will result in more patients living for longer without their disease recurring, and we look forward to these data in due course."

More information: Abstract no: 4, "Neoadjuvant pembrolizumab or placebo + chemotherapy, followed by adjuvant pembrolizumab or placebo plus endocrine therapy for early-stage high-risk ER+/HER2− breast cancer: Results from the phase 3 KEYNOTE-756 study", Wednesday 20 March, Young Investigator Innovation Award and oral abstract session.

Provided by European Organisation for Research and Treatment of Cancer