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To interview Martine Piccart, contact Julia Gunther at julia.gunther@aacr.org or 215-446-6896. For a photo of Piccart, click [here](#).

Updated APHINITY Trial Data Show Addition of Pertuzumab to Trastuzumab Plus Chemotherapy Continues to Yield Clinical Benefit in Patients With Operable HER2-positive Early Breast Cancer

SAN ANTONIO — Data from six-year analysis of the [APHINITY trial](#) showed that adding pertuzumab to the previous standard of trastuzumab plus chemotherapy after surgery continued to reduce the risk of recurrence and death in patients with HER2-positive early breast cancer, according to data presented at the [2019 San Antonio Breast Cancer Symposium](#), held Dec. 10–14.

Fewer deaths were seen in patients treated with pertuzumab, although the survival benefit was not statistically significant at this time.

“The addition of trastuzumab to chemotherapy after surgery has revolutionized treatment outcomes for patients with HER2-positive early breast cancer, yet roughly 30 percent of patients will still experience recurrence of their disease, a condition for which effective treatments are now available but cure is no longer possible,” said [Martine Piccart, MD, PhD](#), cofounder of Breast International Group and Scientific Director at the Institut Jules Bordet in Brussels. “By adding a different yet complementary HER2 inhibitor, pertuzumab, to this treatment regimen, we hope to further reduce the risk of recurrence and advanced disease in this patient population.”

Earlier results from the phase III APHINITY trial comparing pertuzumab or placebo added to the standard adjuvant chemotherapy plus trastuzumab in patients with operable HER2-positive early breast cancer have been previously [reported](#). They showed that patients treated with pertuzumab had improved rates of estimated three-year invasive disease-free survival (IDFS; time from randomization up to recurrence or death) compared with those in the placebo arm (94.1 percent versus 93.2 percent, respectively). The addition of pertuzumab reduced the relative risk of recurrence by 19 percent, which was statistically significant. The overall survival (OS) did not significantly differ between the two arms in the earlier analysis. The current study reports on the six-year interim analysis of OS and an updated descriptive analysis of IDFS and cardiac safety.

Between November 2011 and August 2013, the APHINITY trial randomly assigned 2,400 patients to the pertuzumab arm and 2,405 patients to the placebo arm. The data cutoff for this updated OS analysis was June 19, 2019, corresponding to a median follow-up time of 74.1 months.

After six years of follow-up, Piccart and colleagues found in this descriptive analysis of IDFS that among the overall population, those in the pertuzumab arm had a reduced relative risk of breast cancer recurrence or death by 24 percent compared with the placebo arm.

Similar to their previous findings, Piccart and colleagues found that patients whose cancer had spread to their lymph nodes continued to derive greatest clinical benefit with the addition of pertuzumab to standard treatments. In the six-year updated analysis, the researchers found that, among patients with node-positive disease, the IDFS in the pertuzumab arm was 87.9 percent, while the IDFS in the placebo arm was 83.4 percent, representing a 4.5 percent improvement. The addition of pertuzumab to trastuzumab and chemotherapy after surgery translated to a reduced relative risk of recurrence by 28 percent in this cohort.

In this updated analysis, one additional primary cardiac event was reported in the pertuzumab arm, and one additional secondary cardiac event was reported in each arm; no new cardiac safety concerns emerged, noted Piccart. “Incidence of primary cardiac events remains less than 1 percent in both arms (0.8 percent in the pertuzumab arm versus 0.3 percent in the placebo arm), providing further evidence that adding pertuzumab to trastuzumab and chemotherapy is safe in the long term,” she said.

“Following this interim analysis, the evidence is now even stronger that adding pertuzumab to the previous standard of care reduces the risk of disease recurrence for patients with HER2-positive breast cancer,” said Piccart. “Altogether, the clinical benefit of pertuzumab, which is exemplified by its treatment effect against breast cancer and its lack of additional significant side effects, is enhanced for women at high risk of breast cancer recurrence in this curative setting.

“A main limitation of APHINITY is that although we have seen fewer deaths among the patients who received treatment with pertuzumab, our data is still immature and have not shown definitive improvement in overall survival. A longer follow-up is needed to see any significant survival benefit,” Piccart said. The next interim analysis is scheduled to take place in 2022.

“Ongoing research using the biological specimens and clinical data collected from this very large study would help in refining the characteristics of the patients who will most benefit from pertuzumab, particularly among those considered to be at lower risk of recurrence only on the basis of absence of lymph node disease,” she added.

This study was supported by Roche.

Piccart has served as a consultant on the scientific advisory board at Roche, for which she has received honoraria. Additionally, Piccart is a consult for the advisory boards of AstraZeneca, Camel-IDS, Crescendo Biologics, Debiopharm, G1 Therapeutics, Huya Bioscience International, Immunomedics, Eli Lilly, The Menarini Group, Merck, Novartis, Odonate Therapeutics, PeriphaGen, Pfizer, and Seattle Genetics. She is a scientific board member for Oncolytics and Radius.

Piccart’s institution receives funding from Eli Lilly, Merck, Pfizer, Radius Health, Roche/Genentech, AstraZeneca, Novartis, Servier Pharmaceuticals, and Synthon Pharmaceuticals.

ABSTRACT

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Interim overall survival analysis of APHINITY (BIG 4-11): A randomized multicenter, double-blind, placebo-controlled trial comparing chemotherapy plus trastuzumab plus pertuzumab versus chemotherapy plus trastuzumab plus placebo as adjuvant therapy in patients with operable HER2-positive early breast cancer

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The APHINITY trial demonstrated that pertuzumab, when added to adjuvant trastuzumab and chemotherapy, modestly but statistically significantly improved invasive disease-free survival (IDFS) among patients with HER2-positive, operable breast cancer. From November 2011 until August 2013, 2400 patients were randomly assigned to receive pertuzumab and 2405 to receive placebo. The clinical cut off-date for the primary analysis was 19 Dec 2016 after a median follow-up of 45.4 months. In the intent-to-treat (ITT) population, the estimates of the 3-year rates of IDFS were 94.1% in the pertuzumab group and 93.2% in the placebo group (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.66 to 1.00; P=0.045). The benefit appeared more pronounced in patients with node-positive disease, with a HR of 0.77 (95% CI 0.62-0.96), and in those with hormone receptor-negative disease, where the HR was 0.76 (95% CI 0.56-1.04). Based on these results, pertuzumab in combination with trastuzumab was approved for high risk early HER2-positive breast cancer patients. The first interim analysis of OS took place at that same time. A total of 169 patients had died, with no significant treatment effect with regards to mortality found at that time. Diarrhea, grade 3 or higher, was more frequent within the pertuzumab group (9.8%) compared with the placebo group (3.7%). Heart failure, cardiac death, and cardiac dysfunction were infrequent in both treatment groups. Results: At 74.1 months of median follow-up (clinical cut-off date June 19, 2019), we now report results of the pre-planned, calendar-driven second interim OS analysis which requires a p-value of 0.0012 to reach statistical significance. Updated descriptive analyses of IDFS and cardiac safety were also performed. Fewer deaths were observed in the pertuzumab (P) arm [125 (5.2%) vs 147 (6.1%)], however statistical significance was not reached at this interim analysis. The hazard ratio for OS is 0.85 [95% CI 0.67-1.07 (p=0.17)]; 6-year OS percents are 94.8% vs 93.9% (0.9% difference). Updated IDFS results based on 508 events in the ITT population are: hazard ratio 0.76 [95% CI 0.64-0.91]; 6-year IDFS percents are 90.6% vs 87.8% (2.8% difference). Of note, the difference was due mainly to the reduction in distant (5.9% vs 7.7%) and loco-regional (1.2% vs 2.0%) BC relapses. The node-positive cohort continues to derive clear benefit from the addition of P: hazard ratio 0.72 (95% CI 0.59-0.87). The benefit in terms of 6-year IDFS percent is 4.5% [87.9% vs 83.4%]. In the node-negative cohort, the IDFS hazard ratio is 1.02 (95% CI; 0.69-1.53) with 95% of patients being event-free in both arms at 6 years. With longer follow up, a treatment benefit of P is also seen in the hormone receptor (HR) positive cohort: IDFS hazard ratio for HR positive is 0.73 (95% CI 0.59-0.92). IDFS hazard ratio for HR negative is 0.83 (95% CI 0.63-1.10). No new cardiac safety concerns emerged. One additional primary cardiac event (heart failure) was reported in the P arm and 1 additional patient in each arm had a secondary cardiac event resulting to 18 and 8 for primary cardiac events and 65 and 68 for secondary cardiac events in the P and placebo arms, respectively. The benefit of P in HER2+ early BC is maintained, with the greatest benefit continuing to be observed in the node positive population. With longer follow-up, the benefit of P no longer appears to depend on HR status. Continued follow

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up of patients is very important to determine possible benefit for OS. A calendar-driven third interim OS analysis is planned in 2.5 years, and the event-driven final OS analysis is planned when 640 deaths have occurred.

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