Study identifies highly effective treatment option for patients with HER2-positive breast cancer

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Combining the chemotherapy drugs docetaxel and carboplatin with the HER2-targeted therapy trastuzumab was identified to be an ideal postsurgery treatment option for patients with HER2-positive breast cancer, regardless of tumor size and whether or not disease has spread to the lymph nodes, according to results from the BETH study presented here at the 2013 San Antonio Breast Cancer Symposium, held Dec. 10-14.

"Worldwide, anthracyclines such as doxorubicin [Adriamycin] and epirubicin have dominated breast cancer treatment for decades because of a perceived incremental benefit of 3 to 5 percent in disease-free survival and overall survival that was observed in meta-analysis overview studies that viewed breast cancer as a single disease," said Dennis J. Slamon, M.D., Ph.D., director of clinical/translational research at the University of California, Los Angeles (UCLA) Jonsson Comprehensive Cancer Center, and professor of medicine and chief of the Division of Hematology/Oncology at the UCLA Department of Medicine. "It turns out that anthracyclines were particularly active in the treatment of HER2-positive disease once we applied molecular subtype analyses to breast cancers. These data were derived from treatments used before the development of trastuzumab. In HER2-positive breast cancers, anthracyclines improved outcomes dramatically while adding little or no incremental benefit to the other subtypes that represent 75 to 80 percent of the disease. Unfortunately, the long-term side effects of

anthracyclines in all groups include congestive heart failure and leukemia. We and others have previously shown that adding trastuzumab to anthracycline-based therapy in adjuvant disease increases this cardiac toxicity between three- to fivefold.

"Our new results, which surpassed our expectations, show that it really is not necessary to include an anthracycline as part of the treatment regimen to obtain really ideal results for patients with HER2-positive breast cancer, even if they have a large tumor or have node-positive disease," added Slamon, who is also a leader of a Stand Up To Cancer Dream Team. "The importance of the results lies in the fact that the TCH [docetaxel, carboplatin, and trastuzumab] combination has a much better safety profile than anthracycline and trastuzumab combinations and is now equally effective."

Slamon and colleagues designed a large, randomized, phase III clinical trial to evaluate whether adding a therapy called bevacizumab to postsurgery chemotherapy plus trastuzumab improved outcomes for patients with HER2-positive breast cancer that had spread to the lymph nodes or was highly likely to recur. They called the trial BETH, "bevacizumab and trastuzumab adjuvant therapy in HER2-positive breast cancer."

A total of 3,509 patients were enrolled in the BETH trial. The majority, 3,231, was in cohort 1 and randomly assigned to either TCH or TCH with bevacizumab. Cohort 2 was much smaller, with 278 patients randomly assigned by physicians who elected to use anthracycline-based therapy in addition to trastuzumab, using the anthracycline epirubicin, with or without bevacizumab.

The researchers found that disease-free survival after a median of 38 months follow-up was 92 percent for both arms of the TCH cohort. "These are among the best results we have seen to date in the adjuvant

treatment of HER2-positive breast cancer," said Slamon. Disease-free survival in the control arm of cohort 2, patients randomly assigned to the anthracycline-containing chemotherapy and trastuzumab regimen, was slightly less, at 89 percent. Slamon noted that this was not a statistically significant difference and was based on a very small number of cases for comparison with the nonanthracycline TCH arm.

"In addition, the results of the trial are negative for any benefit from adding bevacizumab to adjuvant therapy for HER2-positive breast cancer. It does not appear to improve outcomes," said Slamon. "But this may be because 92 percent of patients in the TCH control arm remain disease-free after a median follow-up of 38 months. It is going to be difficult to develop treatment regimens that have even better response rates than that. While there is some small room for improvement, we now need to further concentrate on improving the safety of adjuvant treatment regimens."

The researchers are continuing to follow patients to determine whether outcomes remain similar between the two arms of each of the cohorts in the long term. "But my feeling is that the TCH regimen is driving the very positive responses we are seeing and I doubt that bevacizumab will make a significant difference, even after longer follow-up posttreatment," added Slamon.

More information: Publication Number: S1-03

Presenter: Dennis J. Slamon, M.D., Ph.D.

Title: Primary results from BETH, a phase 3 controlled study of adjuvant chemotherapy and trastuzumab ± bevacizumab in patients with HER2-positive, node-positive or high risk node-negative breast cancer

Background The humanized monoclonal antibody (mAb) trastuzumab

(H) + chemotherapy (chemo) prolongs disease-free survival (DFS) in patients (pts) with HER2-positive breast cancer (BC) in the adjuvant setting. Vascular endothelial growth factor (VEGF-A), one central regulator of angiogenesis, is a downstream target of HER2. Tumors overexpressing HER2 also overexpress VEGF-A and exhibit increased angiogenic potential. Combining H with the anti-VEGF-A mAb bevacizumab (B) significantly decreased tumor volume vs B or H alone in HER2-positive xenograft models and demonstrated efficacy in phase 2 studies. In the phase 3 AVEREL study in pts with HER2-positive metastatic BC, adding B to H + docetaxel (T) led to a non-significant increase in a duration of PFS and objective response rates. Chemo plus H±B is now explored in this large phase 3 trial to assess the impact of VEGF-A blockade on residual or micrometastatic disease in the adjuvant setting.

Methods BETH (NCT00625898) is a randomized, phase 3, open-label study evaluating the addition of B to 2 different H-chemo regimens. Pts had centrally-confirmed HER2-positive BC (FISH+ and/or IHC 3+), ECOG PS 0-1, unilateral invasive breast adenocarcinoma, total mastectomy or lumpectomy, and LVEF ≥55%. Prior therapy with anthracyclines, taxanes, carboplatin (C), H or B for any malignancy or radiotherapy, chemo, and/or targeted therapy for the currently diagnosed BC were not permitted. Pts were stratified by center, hormone receptor status (ER and/or PR-positive, ER/PR-negative), and axillary lymph node status (0,1-3, 4+) before inclusion into 1 of 2 chemo cohorts, and then randomized. All pts were recruited by investigators from the Translational Research in Oncology (TRIO/CIRG), the National Surgical Adjuvant Breast and Bowel Project (NSABP) or a group of independent sites. Cohort 1 (3231 pts) included pts receiving 6 cycles of TCH±B followed by H±B for 1 yr after the first dose. Cohort 2 (278 pts) included pts from some independent sites electing to use anthracycline-based therapy and these pts received 3 cycles of TH±B followed by 3 cycles of 5-fluorouracil, epirubicin, cyclophosphamide followed by H±B to complete 1 yr of treatment. T was given at 8 mg/kg IV loading dose, 6

mg/kg IV q3w thereafter; B was given at 15 mg/kg IV q3w. The primary endpoint is invasive DFS (IDFS) for B-containing vs. non-B-containing regimens. Secondary endpoints are IDFS within chemo cohorts, DFS, overall survival, recurrence-free interval (RFI), distant RFI, safety including specific cardiac assessments, and the identification of predictive biomarkers for B. The sample size was determined to test the hypothesis of interest, both in the faster accruing cohort and overall. With 3509 pts enrolled, the trial will have 85% power to detect a HR of 0.70 favoring the addition of B overall, irrespective of chemo regimen. With ~3000 pts in the faster-accruing cohort, the study will have 80% power to detect a hazard ratio (HR) of 0.70 at a 2-sided alpha of 0.05. Median duration of follow-up will be 36 months in Jun 13, cut-off date of the primary analysis. Initial efficacy, safety, and plasma marker analyses will be reported.

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