

# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: James L. Abbruzzese, MD

## Highlights of the 2008 San Antonio Breast Cancer Symposium

December 10-14, 2008  
San Antonio, Texas

### 13 BIG 1-98: A randomized double-blind phase III study evaluating letrozole and tamoxifen given in sequence as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer

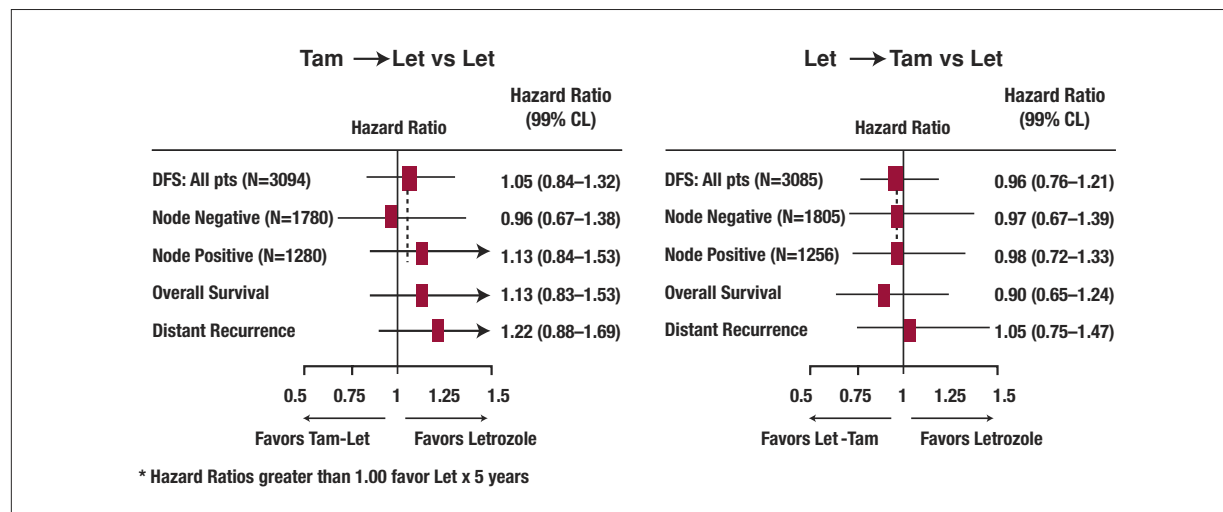
HT Mouridsen, A Giobbie-Hurder, L Mauriac, R Paridaens, M Colleoni, B Thuerlimann, JF Forbes, RD Gelber, A Wardley, I Smith, KN Price, A Coates, A Goldhirsch

A phase III trial comparing letrozole and tamoxifen as adjuvant therapies for postmenopausal women with receptor-positive breast cancer suggested a superior overall survival (OS) with letrozole over tamoxifen. Additionally, sequential treatments of letrozole and tamoxifen did not improve disease-free survival (DFS) compared to letrozole alone (Figure).

Previous studies have shown the superiority of letrozole over tamoxifen in prolonging DFS and reducing the risk of relapse in distant sites. Following these results, the investigators of the BIG 1-98 trial evaluated letrozole and tamoxifen given in sequence and compared it to letrozole alone.

In the 4-arm option of the trial, 6,182 patients were randomized to 5 years of tamoxifen, 5 years of letrozole, 2 years of tamoxifen followed by 3 years of letrozole (TamLet), or 2 years of letrozole followed by 3 years of tamoxifen (LetTam). In the 2-arm option, another 1,828 patients were randomized to receive either tamoxifen or letrozole. The primary endpoint was DFS, defined as the time from randomization to the first recurrence of invasive breast cancer, invasive contralateral breast cancer, second nonbreast malignancy, or death from any cause. Results showed that with a median follow-up of 71 months, adverse events for letrozole and tamoxifen were consistent with the known safety profile of both agents. Monotherapy comparisons in both the 2-arm and 4-arm options (n=4,922) confirmed an improved survival for patients treated with letrozole (Hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.75–1.02;  $P=.08$ ). In this study, approximately one quarter of the patients in the tamoxifen arm crossed over to letrozole after 3–5 years of tamoxifen.

With these findings, investigators supported the initial use of letrozole in patients at higher risk of relapse



**Figure.** Hazard ratios of sequential treatments of letrozole and tamoxifen.

DFS=disease-free survival; Let=letrozole; Tam=tamoxifen.

and suggested that patients who started on letrozole be switched to tamoxifen if required.

#### 46 Lapatinib combined with letrozole vs. letrozole alone for front line postmenopausal hormone receptor-positive metastatic breast cancer: first results from the EGF30008 Trial

S Johnston, M Pegram, M Press, J Pippen, X Pivot, H Gomez, A Florance, L O'Rourke, J Maltzman, Royal Marsden NHS

In a double-blind, placebo-controlled, phase III trial that investigated the benefit of letrozole with or without lapatinib in patients with hormone receptor-positive postmenopausal metastatic breast cancer, the addition of lapatinib was found to significantly improve the clinical efficacy of the aromatase inhibitor. A subset of hormone receptor-positive HER2-negative patients who may gain benefit from this therapy was also identified.

Combining EGFR/HER2-targeted therapy with aromatase inhibitors for hormone receptor-positive postmenopausal breast cancer was suggested in previous studies to enhance endocrine responsiveness and delay the onset of resistance. To investigate further, researchers recruited 1,286 postmenopausal women with hormone receptor-positive untreated metastatic breast cancer, all of whom were randomized to a once-daily treatment of letrozole (2.5 mg) and lapatinib (1,500 mg) or letrozole and placebo. Patients were stratified according to their visceral or bone-only disease and the time from completion of prior adjuvant endocrine tamoxifen therapy. In the hormone receptor-positive HER2-positive population, the primary endpoint of the study was investigator-assessed progression free survival (PFS). In the overall intent-to-treat (ITT) population, investigator-assessed PFS was a secondary endpoint. Additional secondary endpoints included OS, overall response rate (ORR), clinical benefit rate (CBR), time to and duration of response, and safety.

In the HER2-positive population, the median PFS significantly increased from 3.0 months in the letrozole group to 8.2 months in the lapatinib plus letrozole group (HR, .71; 95% CI, 0.53–0.96; stratified log rank  $P=.019$ ). In the ITT population, the median PFS increased from 10.9 months in the letrozole group to 11.9 months in the lapatinib plus letrozole group (HR, .86; 95% CI, 0.76–0.98; stratified log rank  $P=.026$ ). A significant benefit was confirmed in the HER2-positive population after using a Cox regression analysis of stratification and baseline prognostic factor (HR, .65; 95% CI, 0.47–0.89;  $P=.008$ ). In the ITT population (in which 952 tumor samples were HER2-negative), the Cox regression model concluded that ECOG status, prior adjuvant tamoxifen therapy stratification, the number of metastatic sites, and

baseline serum HER2 ECD have a significant impact on PFS (HR, 0.77; 95% CI, 0.64–0.94;  $P=.010$ ).

In the lapatinib plus letrozole group, ORR in the HER2-positive population was significantly increased from 14.8% to 27.9% (Odds Ratio, 0.4;  $P=.021$ ), with a CBR improvement from 28.7% to 47.7% (Odds Ratio, 0.4;  $P=.003$ ). There was no difference in ORR or CBR in the HER2-negative population. The combination of letrozole and lapatinib was well tolerated.

#### 33 A phase II study of trastuzumab-DM1, a first-in-class HER2 antibody-drug conjugate, in patients with HER2-positive metastatic breast cancer

S Vukelja, H Rugo, C Vogel, R Borson, E Tan-Chiu, M Birkner, SN Holden, B Klencke, J O'Shaughnessy, HA Burris

In a multi-institutional, open-label, single-arm, phase II study that investigated the benefits of the antibody drug conjugate trastuzumab-DM1 (T-DM1), researchers found that T-DM1 as a single agent has clinical activity in patients who have progressed on prior HER2-directed therapy.

In this study, which plans to enroll 100 patients who progressed on prior trastuzumab and chemotherapy, 92 patients have been enrolled. T-DM1 (3.6 mg/kg) was administered by IV infusion every 3 weeks to patients with HER2-positive metastatic breast cancer. The primary objective was to assess objective response rate, safety, and tolerability. Researchers also measured the duration of objective response and PFS, characterized the pharmacokinetics of the regimen, and assessed the formation of antibodies to T-DM1. After the first 30 patients had completed 4 cycles (12 weeks) of treatment, a preplanned protocol-specified interim analysis of efficacy data was performed; a final analysis will be conducted 26 weeks after the last patient has been enrolled.

As of June 2008, a total of 30 patients were evaluable for efficacy per protocol. Results showed that the median duration of prior trastuzumab was 76.1 weeks (range, 12–379); 13 patients (42%) received prior lapatinib. Based on investigator assessments, 12 patients (40%) had a partial or complete response. The independent review facility (IRF) has reported a partial response in 9 of 30 patients (30%). Grade 2 adverse events (AEs) include thrombocytopenia (10%), fatigue (13%), nausea/vomiting (10%), and infusion reaction/fever/chills (10%). Grade 3 thrombocytopenia occurred in 10% of the patients, and grade 4 AEs (thrombocytopenia and transaminase elevation) occurred in 2 patients (6%). Sixteen patients (52%) discontinued therapy, progressive disease being the reason for 11 of the discontinuations.

Investigators concluded that the safety profile of T-DM1 appears tolerable at the recommended dose. Preliminary data showed a 40% investigator-determined response rate and a 30% IRF-reported response rate.

### 31 Neoadjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer: primary efficacy analysis of the NOAH trial

L Gianni, W Eiermann, V Semiglazov, GM Manikhas, A Lluch, S Tjulandin, A Feyereislova, P Valagussa, I Baselga

The multicenter, randomized, open-label, phase III NOAH trial evaluated the addition of trastuzumab to an anthracycline- and taxane-based chemotherapy for patients with HER2-positive locally advanced breast cancer (LABC). Researchers concluded that neoadjuvant trastuzumab significantly increased the event-free survival (EFS) rate in this patient population suggesting that neoadjuvant trastuzumab with chemotherapy be used as a standard treatment option.

Women aged 18 years with HER2-positive LABC (IHC 3-positive or FISH-positive, T3N1 or T4, any T + N2 or N3 or + ipsilateral supraclavicular node involvement) were randomized to receive 3 cycles of doxorubicin (60 mg/m) and paclitaxel (150 mg/m q3w), 4 cycles of paclitaxel (175 mg/m q3w), and 3 cycles of CMF (cyclophosphamide 600 mg/m, methotrexate 40 mg/m, 5-fluorouracil 600 mg/m q4w) on days 1 and 8, with or without concomitant trastuzumab (8 mg/kg loading dose then 6 mg/kg q3w for 1 year) before surgery. LABC patients who were HER2-negative (IHC 0/1+) also received the same chemotherapy regimen. The primary endpoint was EFS, defined as the time between randomization and disease recurrence, progression, or death from any cause. Secondary endpoints were pathologic complete response (pCR), ORR, OS, and safety.

Of the 327 patients enrolled, inflammatory breast cancer was present in 27% of HER2-positive tumors, versus 14% of HER2-negative tumors; 35% of HER2-positive tumors versus 64% of HER2-negative tumors were hormone receptor-positive. The EFS rate at 3 years, analyzed after 88 events in the HER2-positive group, was significantly better in the trastuzumab plus chemotherapy arm compared with the chemotherapy alone arm (70.1% vs 53.3%; HR, 0.56;  $P=.007$ ). EFS rate in the HER2-negative arm was 67.4%. Multivariate analysis, which included disease stage and hormonal receptor status, found that trastuzumab treatment was the only variable that was significantly associated with EFS outcome. Both ORR and pCR were significantly higher in the trastuzumab plus chemotherapy arm compared to the chemotherapy alone arm (ORR, 89% vs 77%;  $P=.02$ ; pCR, 39% vs

20%;  $P=.002$ ). Interestingly, the HER2 positive chemotherapy alone arm and the HER2 negative arm showed similar results for ORR and pCR. Overall, trastuzumab plus chemotherapy in the neoadjuvant setting was well tolerated with acceptable cardiac safety.

### 37 Neratinib (HKI-272), an irreversible pan erbB receptor tyrosine kinase inhibitor: phase 2 results in patients with advanced HER2+ breast cancer

HJ Burstein, Y Sun, AR Tan, L Dirix, JJ Vermette, C Powell, C Zacharchuk, RA Badwe

Patients with stage IIIB, IIIC, or IV ErbB2-positive advanced breast cancer were evaluated in an open-label, 2-arm, phase II study to further characterize the safety and efficacy of neratinib. Investigators confirmed that neratinib demonstrates robust antitumor activity in this patient population.

In a previous phase I study, neratinib, which irreversibly inhibits the tyrosine kinase receptors ErbB1 (EGFR) and erbB2 (HER2), showed antitumor activity in patients with solid tumors. In this study, the ErbB2 gene amplification in tumor tissue was a requirement for entry. Patients were assigned to arm A if they had prior treatment with trastuzumab and to arm B if they had no prior treatment with trastuzumab or any other ErbB2-targeted drug. All patients received oral doses of neratinib (240 mg) daily. The primary endpoint was PFS rate at 16 weeks.

With 66 patients enrolled in arm A and 70 patients in arm B (median age, 50 years), common neratinib-related AEs were diarrhea (89%), nausea (29%), vomiting (23%), fatigue (16%), and anorexia (15%). Diarrhea, the only grade 3 AE, occurred in 27% of arm A patients and 11% of arm B patients. Dose reductions were admitted in 27% of all patients—36% in arm A and 19% in arm B—mostly because of diarrhea. The main reasons for patients discontinuing the study were disease progression (arm A, 74%; arm B, 43%) and AEs (arm A, 8%; arm B, 4%).

The objective response rates (complete or partial response) were 26% (95% CI, 16–39%) in arm A and 51% (95% CI, 38–64%) in arm B for independent assessment; the rates were 34% (95% CI, 23–47%) in arm A and 62% (95% CI, 49–74%) in arm B for investigator assessment. With independent assessment, the 16-week PFS rates were 61% in arm A and 75% in arm B. With investigator assessment, they were 57% in arm A and 78% in arm B. The median PFS for independent assessment was 23 weeks (22 weeks for investigator assessment) in arm A, and 40 weeks (35 weeks for investigator assessment) in arm B.