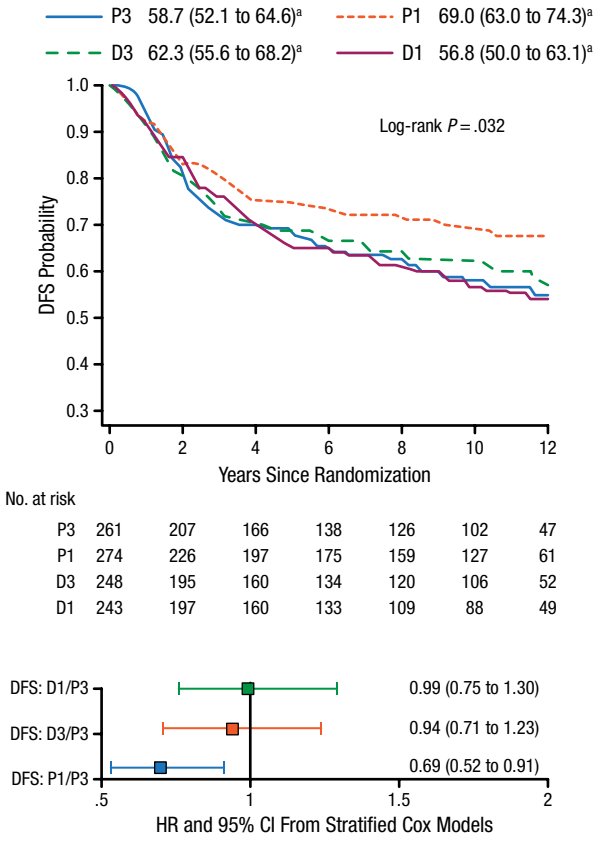
Figure 1. Improvement in DFS With Weekly Paclitaxel in Patients With TNBC



DFS, disease-free survival; D1, weekly docetaxel; D3, every-3-weeks docetaxel; P1, weekly paclitaxel; P3, every-3-weeks paclitaxel; TNBC, triple-negative breast cancer.

[a]10-y rate, % (95% CI).

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or of unknown status, Dr Sparano said that, although 5-year data showed a trend for improved outcomes in the taxane arms, this was not consistently seen in the updated analysis. At a median follow-up of 12.1 years in this patient population, there was a nonsignificant trend toward increased OS (81.6% vs 79.6%; HR, 0.87; 95% CI, 0.69 to 1.08) favoring D3 compared with P3. DFS was also improved in this group compared with P3 (75.3% vs 69.4%; HR, 0.76; 95% CI, 0.63 to 0.91). However, similar benefits were not seen in association with P1.

Although these data demonstrate benefit of AC and weekly paclitaxel therapy in patients with TNBC, Dr Sparano emphasized that outcomes can still be improved in this population. A pending trial [NRG-BR003] will investigate the effect of adding carboplatin to AC and weekly paclitaxel in this setting, he concluded.

TP53 Mutations Are Associated With Increased Pathologic Complete Response in HER2-Positive BC

Written by Lynne Lederman

Katherine A. Hoadley, PhD, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, North Carolina, USA, presented the mutational analysis of the Paclitaxel and Trastuzumab With or Without Lapatinib in Treating Patients With Stage II or Stage III Breast Cancer That Can Be Removed by Surgery trial [CALGB 40601; NCT00770809].

CALGB 40601 was a neoadjuvant trial in which patients with human epidermal growth factor receptor 2 (HER2)–positive clinical stage II or III breast cancer (BC) had a pretreatment biopsy research tissue sample taken at random assignment to weekly paclitaxel (T) plus trastuzumab (H) plus lapatinib (L) for 16 weeks (n = 118); or T plus H for 16 weeks (n = 120); or T plus L for 16 weeks (n = 67) [Carey LA et al. ASCO 2013 (abstr 500)]. A second research tissue sample was obtained at surgery following the neoadjuvant treatment. There was no statistically significant difference between treatment groups in pathologic complete remission (pCR) rates. RNA from pretreatment samples were correlated with pCR by intrinsic subtype in all arms (n = 265). The pCR rate for the HER2-enriched subtype (n = 82) has twice the pCR rate (70%) as luminal A (n = 80; 34%) or luminal B (n = 80; 36%) [Carey LA et al. *J Clin Oncol.* 2014].

The mutational analysis evaluated 181 HER-positive pretreatment tumors and correlated 9 genes (*TP53*, *PIK3CA*, *GATA3*, *AKT1*, *ERBB2*, *MAP3K1*, *MAP2K4*, *TRPS1*, and *MALAT1*) with pCR rates. To increase the power to detect somatic mutations, UNCeqR, a program that integrates RNA and DNA sequencing, was used [Wilkerson MD et al. *Nucleic Acids Res.* 2014].

A median of 62 total mutations (interquartile range 32-118) was found. The number of mutations varied significantly by intrinsic subtype ($P < .001$) and by *TP53* mutation status ($P < .001$). The HER2-enriched and luminal B subtypes had higher numbers of mutations. *TP53* mutations also correlated with higher numbers of mutations.

TP53 had a mutation frequency of 56%, *PIK3CA* had a mutation frequency of 20%, and the rest of the 9 genes had a mutation frequency of < 10%. *TP53* mutations were significantly associated with pCR. In the overall population, the odds ratio was 3.67 ($P < .001$) for pCR vs wild type for those with mutated *TP53*; the odds ratio was 5.23 ($P = .007$) for pCR with luminal A mutations vs wild type. No other genes examined were correlated with pCR.

There were 8 *HER2*/*ERBB2* mutations in 7 patients; 2 of the 8 *HER2* mutations were previously shown to be activating mutations [Bose R et al. *Cancer Discov*. 2013]. A patient in the THL arm with HER2-enriched with V777L, preclinically predicted sensitive to L, had pCR. A patient in the TL arm with luminal A with L755S, preclinically predicted resistant to L, did not have pCR.

TP53 was the most frequently mutated gene in this cohort and was associated with increased pCR and a higher somatic mutation rate. Activating *HER2* mutations were uncommon but behaved as predicted from preclinical studies. Future studies to use genomic signatures, somatic mutations, and clinical variables for pCR predictions are underway.

ICE: No Advantage to Adding Capecitabine to Ibandronate in High-Risk Early BC

Written by Lynne Lederman

Elderly individuals are underrepresented in clinical trials. Standard anthracycline or taxane-based adjuvant regimens for breast cancer (BC) are often considered to be intolerable in frail elderly patients, whereas capecitabine has an acceptable toxicity profile and relevant single-agent activity in metastatic BC [O'Shaughnessy JA et al. *Oncologist*. 2012]. Elderly patients have a high incidence of treatment-induced osteopenia/osteoporosis, fractures, and bone surgery, especially from aromatase inhibitors [Chen JS et al. *Osteoporos Int*. 2009]. Adjuvant bisphosphonates reduce distant recurrence and increase overall survival (OS) in postmenopausal patients [Coleman R et al. SABCS 2013 (abstr S4-07)]. Therefore, the effects of adjuvant ibandronate with and without capecitabine was investigated in elderly patients.

Results of the phase 3 Study in Elderly Patients With Early Breast Cancer [ICE; NCT00196859] were reported by Gunter von Minckwitz, MD, PhD, University of Frankfurt, Frankfurt, and Chairman of the German Breast Group (GBG), Germany. This study enrolled 1358 women aged ≥ 65 years with moderate- to high-risk early BC who did not have extensive comorbidities. Patients were randomly assigned to capecitabine 2000 mg/m^2 daily on day 1 to 14 every 3 weeks for 6 cycles plus oral ibandronate 50 mg daily or 6 mg IV every 4 weeks (route of administration chosen by patients) for 2 years, or to ibandronate monotherapy for 2 years. Anastrozole and/or tamoxifen treatment in hormone receptor–positive disease and/or radiotherapy was started after capecitabine. Trastuzumab was not given.

Table 1. Invasive Disease–Free and Overall Survival, Median Follow-Up 61.3 Months

	Capecitabine + Ibandronate	Ibandronate
Invasive disease–free at 3 y	85.4	84.3
Invasive disease–free at 5 y	78.8	75.0
Ibandronate to combination	HR, 1.04; 95% CI, 0.84 to 1.29; *P* = .7012	
Overall survival at 3 y	95.4	94.3
Overall survival at 5 y	90.1	87.6
Ibandronate to combination	HR, 1.14; 95% CI, 0.85 to 1.54; *P* = .3827	

Data in percentage unless otherwise indicated.

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The primary end point was invasive disease–free survival (IDFS). Secondary end points were OS, bone-related events (fractures, surgery, or new osteoporosis; bone metastases were excluded), preference of oral or IV administration of ibandronate, and safety.

Patient and tumor characteristics were well balanced between the combination (n = 677) and monotherapy (n = 681) intent-to-treat arms. Median age was 71 years, with about 25% aged ≥ 75 years. About half of patients had node-positive disease; 81% were hormone-receptor positive, and almost three-quarters received aromatase inhibitors only; 75.8% in each arm completed ibandronate treatment, and 83.3% completed 6 cycles of capecitabine with 7.8% discontinuations due to toxicity. Of the 65.4% who started oral ibandronate, 2.4% switched from oral to IV; of the 34.6% who started with IV, 3.6% switched to oral; and the median duration of ibandronate was similar in the 2 treatment arms.

Toxicities in the capecitabine arm were as expected, including 31.0% of patients experiencing any grade 3 or 4 adverse events; fewer experienced skin disorders, especially hand-foot syndrome (14.6%). Bone-related events occurred in 25.0% of the capecitabine arm and 24.7% of the ibandronate-only arm (*P* = .65).

IDFS and OS are shown in Table 1. Neither treatment was favored in a subgroup analysis. Prof von Minckwitz suggested that given the high OS rate, patient life expectancy in this elderly population should be taken into account when treatment decisions are made.

The ICE study failed to show that adjuvant capecitabine improved IDFS in patients receiving ibandronate. The outcome of elderly patients with moderate- or high-risk early BC receiving ibandronate alone is favorable, although bone-related events were frequent (25%). Longer follow-up may be needed to observe any potential late effects of capecitabine.