Abstract  

Purpose: Tipifarnib is a farnesyltransferase (FTase) inhibitor that has activity in metastatic breast cancer and enhances the efficacy of cytotoxic agents in preclinical models. We evaluated the biological effects of tipifarnib in primary breast cancers in vivo, whether adding tipifarnib to preoperative chemotherapy increased the pathologic complete response rate (pCR) at surgery, and determined whether biomarkers predictive of pCR could be identified.

Experimental Design: Forty-four patients with stage IIB-IIIC breast cancer received up to four cycles of neoadjuvant doxorubicin-cyclophosphamide (AC) every 2 weeks plus tipifarnib and filgrastim followed by surgery. Enzymatic assays measuring FTase activity and Western blotting for phospho (p)-signal transducer and activator of transcription 3 (p-STAT3), phospho-extracellular signal-regulated kinase, p-AKT, and p27 were done in 11 patients who agreed to optional tissue biopsies before therapy and 2 hours after the final dose of tipifarnib during the first cycle, and predictive biomarkers were evaluated by immunohistochemistry in 33 patients. The trial was powered to detect an improvement in breast pCR rate of 10% or less expected for AC alone to 25% for AC-tipifarnib ($\alpha = 0.05$, $\beta = 0.10$).

Results: Eleven patients had a breast pCR (25%; 95% confidence interval, 13-40%). FTase enzyme activity decreased in all patients (median, 91%; range, 24-100%) and p-STAT3 expression decreased in 7 of 9 (77%) patients. Low tumor Ki-67 expression (below the median of 60%) at baseline was significantly associated with resistance to therapy ($P = 0.01$).

Conclusion: Tipifarnib inhibits FTase activity in human breast tumors in vivo, is associated with down-regulation of p-STAT3, and enhances the breast pCR rate, thus meriting further evaluation.

Ras proteins are low molecular weight guanosine nucleotide binding GTPases (G proteins) that play a critical role in cell growth and regulation (1). Oncogenic mutations of the three known human ras genes are found in 30% of all human cancers; these mutations lead to constitutive hyperactivation of the Ras protein. Although the frequency of ras mutations in breast cancer is very low (<2%; refs. 2, 3), hyperactivation of Ras protein and its downstream effectors is very common due to overexpression of upstream components such as epidermal growth factor receptor and HER-2/neu (4, 5); upstream events may also lead to activation of the pathway without Ras protein overexpression (6). In addition, Ras protein overexpression is associated with poor prognosis (7), and RhoC overexpression (a downstream effector of Ras) is associated with regional and/or distant metastases (6) and with inflammatory carcinoma (9).

Posttranslational modification with a 15-C farnesyl lipid at the COOH terminus of Ras is essential for mediation of its downstream signaling effects (10, 11). This modification is catalyzed by farnesyl transferase (FTase), a heterodimeric zinc metalloenzyme. FTase inhibitors cause accumulation of cells in the G2-M or G1 phase (11-14), induce apoptosis of a variety of tumor cell lines (15), inhibit angiogenesis (16), inhibit the growth of MCF-7 human breast cancer xenografts (which have wild-type Ras; ref. 17), induce tumor regression in breast cancer transgenic mouse models (18, 19), and revert the RhoC-GTPase–induced inflammatory breast cancer phenotype (9). Increased Ras/Raf-1/mitogen-activated protein kinase kinase/mitogen-activated protein kinase activity has been implicated in...
doxorubicin-resistant MCF-7 cell line (20), in paclitaxel-resistant cells (21), and in the expression of the P-glycoprotein extrusion pump (22). Objective responses have been observed in about 10% of patients with metastatic breast cancer treated with tipifarnib (formerly R115777; Zarnestra, Johnson & Johnson and Tibotec Therapeutics), an orally available FTase inhibitor (23).

Based on these considerations, we initiated a phase I/II trial of tipifarnib in combination with preoperative doxorubicin and cyclophosphamide (AC) in patients with stage IV breast cancer (for the phase I trial) and clinical stage IIB-IIIC breast cancer (for the phase II trial), and previously recommended the phase II dose of tipifarnib (200 mg orally twice daily on days 2-7 of therapy) that could be safely used with dose-dense AC plus granulocyte colony stimulating factor (24). Furthermore, we also reported that 7 of the first 21 patients with locally advanced breast cancer treated with up to four cycles of the combination had a pathologic complete response (pCR) in the breast [33%; 95% confidence interval (95% CI), 15-55%], providing a sufficient level of activity to proceed to the second stage of the phase II trial. We herein report the final results of the completed phase II trial in 44 patients with clinical stage IIB-IIIC breast cancer. Our primary objectives were to determine whether tipifarnib enhanced the breast pCR rate associated with standard preoperative AC chemotherapy, to determine the biological effects of tipifarnib in vivo, and to determine whether we could identify biomarkers predictive of breast pCR.

AC chemotherapy and tipifarnib. All patients received “dose-dense AC,” consisting of doxorubicin (60 mg/m² by slow i.v. push over 10-15 min) and cyclophosphamide (600 mg/m² by i.v. infusion over 30-60 min) given on day 1 every 2 wk for up to four cycles, preceded by standard antiemetic therapy. Tipifarnib was given at a dose of 200 mg twice daily on days 2 to 7 of each treatment cycle. Treatment cycles were repeated if the neutrophil count was at least 1,500/μL, platelet count at least 100,000/μL, and if there was adequate recovery from nonhematologic toxicity (to grade 0 or 1). All patients also received granulocyte-colony stimulating factor, 5 mg/kg s.c. on days 2 to 13 of each cycle (pegfilgrastim was not used).

Surgery and additional therapy. All patients with an operable primary breast cancer who were candidates for surgery underwent mastectomy or lumpectomy plus axillary dissection about 4 wk after completion of four cycles of AC. After surgical resection, patients received additional chemotherapy, hormonal therapy, or radiation therapy as clinically indicated.

Centralized pathology review. Pathologic response was assessed by the local pathologist using procedures normally used for evaluation of surgical breast cancer specimens; pCR was defined as no evidence of invasive carcinoma in the specimen. In 35 of 44 cases, pathologic responses were reviewed by two of the coauthors who were breast pathologists for cases at Moffitt Cancer Center (D.C.) and for cases at Montefiore Medical Center plus other centers (S.F.); the specimens were evaluated for “residual cancer burden” (RCB) as described by Symmans et al. (25); in five cases, RCB was determined by review of the pathology report, and the remaining six cases were not evaluable (received nonprotocol therapy before surgery or specimens not available).

Estimation of predicted pCR rate. We performed a post hoc analysis to estimate the expected pCR rate in breast and lymph nodes for each patient enrolled in the trial using the nomogram developed by Rouzier et al. (26), which had not been published at the time that the trial was initiated. For each patient, an expected pCR rate was calculated using information required by the nomogram.

Optional tumor biopsy and FTase enzyme analysis. Patients who consented to an optional biopsy had paired tumor biopsies done before treatment and during cycle 1, day 6 or 7, 2 h after the last tipifarnib dose. Three core biopsies were obtained from the tumor using a 14-gauge needle after local anesthesia. Specimens were placed in a sterile container, placed on dry ice, and transported to the pathology laboratory where they were wrapped in foil and placed in liquid nitrogen. After freezing in liquid nitrogen, specimens were stored at -70°C until they were analyzed using methods that have been previously described for FTase and GGTase enzyme activity (18) and by Western blots for phospho (p)-signal transducer and activator of transcription-3 expression, and by an enhanced chemiluminescence-based detection. The resulting lysates were normalized for total protein content (50 μg per lane), resolved on 12% SDS-PAGE gels, transferred onto polyvinylidene difluoride membranes, and incubated with anti-p-STAT3, p-ERK1/2, and p27. Frozen breast tumor tissues were mechanically homogenized with TISSUESENDER in radiolabeled precipitation assay buffer (150 mmol/L NaCl, 10 mmol/L Tris at pH 7.4, 0.1% SDS, 1.0% Triton X-100, 5 mmol/L EDTA, 0.1% sodium deoxycholate) containing protease inhibitors. The homogenates were incubated on ice for 30 min and then spun at 10,000 × g for 5 min at 4°C to pellet cell debris. The resulting lysates were normalized for total protein content (50 μg per lane), resolved on 12% SDS-PAGE gels, transferred onto polyvinylidene difluoride membranes, and incubated with total AKT (Santa-Cruz, Inc.), p27 (BD Biosciences), and β-actin (Sigma), followed by horseradish peroxidase-conjugated secondary antibody and enhanced chemiluminescence–based detection. The same blot was reprobed with anti-β-actin polyclonal antisem (Sigma) as a loading control. The immunoblot data were quantified by scanning densitometry using the AlphaEaseFC software and normalized by β-actin.

Materials and Methods

Patient selection. Patients were required to have histologically or cytologically confirmed adenocarcinoma of the breast and clinical stage IIB-IIIC disease and meet other requirements as previously described (24). The study was reviewed, approved, and sponsored by the Cancer Therapy Evaluation Program of the National Cancer Institute (National Cancer Institute study number P5598. Clinical Trials.gov identifier NCT00491144). The protocol was reviewed by the local institutional review board at each participating institution, and all patients provided written informed consent.
**Predictive biomarker analysis.** Primary tumor specimens from pretreatment biopsies were available in 33 patients, including 10 of 11 patients who had a breast pCR. For Ki-67, p27, p-STAT3, p-ERK, and p-AKT, pretreatment paraffin-embedded tumor specimens were evaluated by immunohistochemistry by a single pathologist (D.C.) without knowledge of clinical patient characteristics or response to therapy. This sample included 32 of 44 patients in the phase II trial (including 9 patients with inflammatory carcinoma) and 1 patient with inflammatory carcinoma treated in the phase I portion of the study who did not have a breast pCR but who had a baseline specimen available. Immunohistochemistry was done on a Ventana Benchmark XT automated slide stainer, using the avidin-biotin complex method and the following antibodies: Ki-67 (mouse monoclonal antibody (mAb), clone K2, Ventana, proprietary dilution); p27 (mouse mAb, clone Sc53G8, Cell Marque, proprietary dilution); p21 (mouse mAb, clone EA10, Calbiochem, dilution 1:50); p-STAT3 (rabbit polyclonal antibody, clone 9145, Cell Signaling, dilution 1:1000); p-ERK (mouse mAb, clone 4376, Cell Signaling, dilution 1:100); and p-AKT (mouse mAb, clone Ser473 587F11, Cell Signaling, dilution 1:20). For antigen retrieval, CC1 standard for Ki-67, p27, p21, and p-STAT3 and protease for p-AKT were used. The detection of p-ERK did not require antigen retrieval. The immunostains were evaluated considering the percent of tumor cells staining positive (nuclear staining), and p-AKT staining was evaluated by scoring the staining intensity (0, 1+, 2+ and 3+) and percent of positive cells [0 (0%), 1+ (1-33%), 2+ (34-66%), 3+ (more than 66%)], with the product of intensity and percentage scores used to assign a composite score.

For RhoA, RhoB, and RhoC, paraffin-embedded specimens were likewise evaluated by another pathologist (C.K.) without knowledge of the clinical patient characteristics or response to therapy. Cytosplasmic RhoA, RhoB, and RhoC protein expression was scored from 0 to 3+ by comparison to the positive internal controls by immunohistochemistry with antibodies against RhoA, RhoB, and RhoC GTPases (which was previously developed, validated, and described by C.K.; ref. 27). A mouse anti-RhoA mAb at 1:50 dilution without pretreatment (Santa Cruz Biotechnology), a rabbit polyclonal anti-RhoB antibody at 1:40 dilution without pretreatment (Santa Cruz Biotechnology), and a chicken polyclonal anti-RhoC antibody at 1:9,000 dilution with microwave citrate buffer (pH 6.0) pretreatment were used. The proteins were expressed in the cytoplasm of myoepithelial cells and vascular smooth muscle cells, which served as consistent internal positive controls. Using this schema, strong diffuse staining was scored 3+, moderate diffuse staining as 2+, low diffuse staining as 1+, and no staining as 0.

**Statistical considerations.** The study was designed to detect an increase in the breast pCR rate from ≤10% to at least 25% (α = 0.05, β = 0.10) using Simon’s two-stage design. Although the breast pCR rate was 13% in National Surgical Adjuvant Breast and Bowel Project (NSABP) B18 and B27 trials after four cycles of AC (28–30), we assumed a slightly lower breast pCR of 10% or less for standard therapy; our trial required to have palpable axillary nodes or a tumor larger than 5 cm (or inflammatory carcinoma), whereas B18 and B27 included patients with less advanced disease (T1c-N3 and N0-N1 disease; refs. 28–30). If two or less breast pCRs (<10%) were observed among the initial 21 patients, the study would be terminated early and declared negative; if at least three breast pCRs were observed, accrual would continue to a total of 50 evaluable patients. If at least eight pCRs (≥16%) were observed among the 50 evaluable patients, this regimen would be considered worthy of further testing. This design yields an at least 0.90 probability of a positive result if the true pCR rate is at least 25%. It yields an at least 0.90 probability of a negative result if the true pCR rate is 10% or less, with at least 0.65 probability of early negative stopping.

With regard to the predictive biomarker analysis, the relationship between each marker and either sensitivity to therapy (as indicated by breast pCR) or resistance to therapy (as measured by a RCB score of 3) was evaluated by Fisher’s exact test with two-sided P < 0.05.

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### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51</td>
</tr>
<tr>
<td>Range</td>
<td>30-70</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td>40 (91)</td>
</tr>
<tr>
<td>Stage, n (%)</td>
<td>13 (30)</td>
</tr>
<tr>
<td>Hormone receptor expression, n (%)</td>
<td>24 (52)</td>
</tr>
<tr>
<td>Positive</td>
<td>22 (48)</td>
</tr>
<tr>
<td>Negative</td>
<td>15 (34)</td>
</tr>
<tr>
<td>HER2/neu positive, n (%)</td>
<td>29 (66)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ECOG, Eastern Cooperative Oncology Group; PgR, progesterone receptor.
Biological effects of tipifarnib in vivo. Twelve patients consented to an optional biopsy before treatment and 2 hours after the final tipifarnib dose in cycle 1, of whom 11 patients had evaluable specimens, including 2 patients who had a breast pCR and RCB score of 0 (patient nos. 31 and 55). The effect of tipifarnib on tumor FTase and GGTase enzyme activities is shown in Fig. 1. GGTase and FTase are similar proteins that consist of two subunits, including an α-subunit, which is common to both enzymes, and a β-subunit, with 25% identity, and have different isoprenoid substrates. There was consistent inhibition of FTase enzyme activity after tipifarnib administration in all patients (median, 91%; range, 21-100%). The effect of tipifarnib on GGTase I enzyme activity was variable, being decreased in six patients, increased in two patients, and unchanged in three patients. Regarding the effects of tipifarnib on expression of signaling proteins, there was consistent inhibition of p-STAT3 that was observed in 7 of 9 (77%) evaluable patients, but there were inconsistent effects on p-ERK, p-AKT, and p27 expression. Representative results from two patients are shown in Fig. 2, including one patient (no. 31) who had a pCR and a second patient (no. 30) who had a posttreatment RCB score of 3 (indicating extensive persistent disease and resistance to therapy). In summary, although tumor FTase enzyme activity was substantially reduced by tipifarnib in most patients, and p-STAT3 decreased in the majority of patients, there was no correlation between FTase enzyme inhibition or p-STAT3 inhibition and breast pCR.

Predictive biomarker analysis. Biomarker data for the pretreatment tumor specimen were available for 33 patients, of whom 11 had inflammatory carcinoma and 10 had a breast pCR. The median value (and range) for each marker expressed as percent of positive tumor cells is shown in Table 2 for Ki-67, p-STAT3, p-ERK, p21, and p27. The median marker values (and range) expressed as a score for RHEB and AKT are also shown. There was no relationship between any marker (evaluated as a dichotomous variable above or below the median) and either sensitivity to therapy (i.e., breast pCR) or resistance to therapy (i.e., RCB score 3) with the exception of Ki-67; low Ki-67 score (below the median of 60%) was significantly associated with resistance to therapy (P = 0.01).

For RhoA, RhoB, and RhoC, the proportion of samples that were graded as 0, 1+, 2+, and 3+ is represented in Fig. 3. There was no significant association between expression of RhoA, RhoB, or RhoC protein (evaluated as a dichotomous variable comparing 2+/3+ versus 1+/0 expression) and either response or resistance to therapy. There was no association between RhoA, RhoB, or RhoC expression and inflammatory phenotype. Three of 10 (30%) evaluable cases with inflammatory disease were 3+ for RhoC, compared with 4 of 18 (22%) evaluable noninflammatory cases.

Treatment information. A total of 158 cycles of AC-tipifarnib combination were given. Thirty-five of 44 (80%) patients received all four cycles of the combination. Nine patients (20%) received less than four cycles of the AC-tipifarnib combination, including three patients who received one cycle, four who received two cycles, and two who received three cycles. Reasons for discontinuing the tipifarnib included gastrointestinal side effects of nausea, vomiting, and/or dyspepsia in five patients (11%), patient preference in two patients (5%), persistent neutropenia and thrombocytopenia in one patient (2%), and death due to pneumonitis in one patient (2%; described in the next paragraph). The dose of AC was reduced in four patients (9%) due to toxicities including febrile neutropenia (n = 2), thrombocytopenia (n = 1), and anemia (n = 1). Of 114 second or subsequent cycles of therapy given to 41 patients who received at least two treatment cycles of the AC-tipifarnib combination, all cycles were given on schedule in
30 patients (73%). Twelve treatment cycles were delayed 1 week or more in 10 patients (24%) due to adverse events including three patients with grade 2 skin infection (7%) and one patient each with grade 4 chest pain resulting in hospitalization (2%), grade 1 to 2 thrombocytopenia (2%), grade 2 stomatitis (2%), grade 2 anemia (2%), febrile neutropenia (2%), and persistent sinus tachycardia (2%).

**Overall toxicity.** The worst grade toxicity observed at the recommended phase II dose is shown in Table 3 (using the National Cancer Institute Common Terminology for Adverse Events, version 3). Neutropenia and leukopenia were the most common grade 3 to 4 toxicities. Neutropenia occurred in 50% of all patients (including 32% who had grade 4 neutropenia). The duration of neutropenia was brief, however, resulting in only one patient (5%) developing grade 3 febrile neutropenia and a second patient (5%) developing grade 3 infection (cellulitis) unassociated with neutropenia. The incidence of grade 3 toxicity was 5% or less for all other categories.

With regard to other serious, unusual, or treatment-limiting toxicities, three patients (7%) had grade 3 gastrointestinal side effects (e.g., nausea, vomiting, dyspepsia, and gastritis) that prompted discontinuation of tipifarnib. One patient was hospitalized with grade 4 cardiac pain associated with dyspnea, migraine headache, and vomiting, which resolved spontaneously; no cardiac or pulmonary etiology was identified. Additionally, one patient was hospitalized and expired during cycle 1 due to pneumonitis associated with severe neutropenia. The patient had a several-week history of cough and exertional dyspnea that was not reported to her treating physician. Physical exam before beginning therapy revealed bibasilar rales, and computerized tomography of the chest revealed bilateral pulmonary infiltrates. She developed rapidly progressive pulmonary symptoms several days after beginning therapy, developed acute respiratory distress syndrome in association with neutropenia, and died 8 days after initiating AC-tipifarnib.

**Discussion**

Previous studies have shown that pCR in the breast after preoperative chemotherapy correlates strongly with improved disease-free survival and overall survival, indicating that breast pCR may be a useful short-term surrogate for predicting improved long-term outcomes (28). Because most patients with locally advanced breast cancer require preoperative chemotherapy, and some patients with operable breast cancer may require preoperative therapy to facilitate breast conservation, these settings represent an appropriate model to determine whether the addition of targeted therapies enhances the effectiveness of standard cytotoxic therapy. We hypothesized that the addition of tipifarnib might enhance the effectiveness of standard AC chemotherapy, and we designed this trial to determine whether the addition of tipifarnib improved the breast pCR rate from the ~10% to 15% historical rate to 25% or higher (28). The study design required observing at least 8 breast pCRs among 50 evaluable patients; we observed 11 breast pCRs among 44 (25%) evaluable patients, and therefore met our primary prespecified end point. Although it is possible that these improved results may be attributed in part to the dose-dense administration of AC, this seems unlikely given the particular efficacy of the combination in estrogen receptor (ER)–positive disease, a subset that has not been clearly shown to benefit from adjuvant dose-dense therapy (32). We also showed that most tumors exhibited near-complete inhibition of the target enzyme, FTase, when biopsied on the 6th and final day of tipifarnib therapy ~2 hours after the last 200-mg
Table 3. Worst grade toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td></td>
<td>1</td>
<td>(2)</td>
<td>7</td>
<td>(16)</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td>16</td>
<td>(36)</td>
<td>1</td>
<td>(2)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>1</td>
<td>(2)</td>
<td>0</td>
<td>(0)</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td>4</td>
<td>(9)</td>
<td>2</td>
<td>(5)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td></td>
<td>0</td>
<td>(0)</td>
<td>1</td>
<td>(2)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td></td>
<td>9</td>
<td>(20)</td>
<td>0</td>
<td>(0)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td></td>
<td>17</td>
<td>(39)</td>
<td>2</td>
<td>(5)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td></td>
<td>4</td>
<td>(9)</td>
<td>1</td>
<td>(2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>1</td>
<td>(2)</td>
<td>0</td>
<td>(0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>5</td>
<td>(11)</td>
<td>0</td>
<td>(0)</td>
</tr>
<tr>
<td>Cardiac pain</td>
<td></td>
<td>0</td>
<td>(0)</td>
<td>0</td>
<td>(0)</td>
</tr>
</tbody>
</table>

tipifarnib dose. Notably, there were variable changes in GGTase I enzyme activity, indicating a specific effect of tipifarnib on FTase. The inhibition of FTase was also associated with reduction in p-STAT3 expression in the majority of samples evaluated, although there were variable effects on other signaling molecules. STAT3 may be an important therapeutic target in breast cancer and other tumors, and STAT3 inhibition potentiates the cytotoxicity of doxorubicin (33, 34).

We also evaluated a panel of biomarkers to determine whether markers predictive of breast pCR could be identified in pretreatment tumor specimens. The markers evaluated included Ki-67, p27, p-ERK, p-STAT3 (and total STAT3), p-AKT (and total AKT), RhoA, RhoB, and RhoC, all of which were chosen because of evidence that they might identify tumors sensitive to cytotoxic therapy and/or FTase inhibitor therapy. The only marker found to be predictive was Ki-67, which is known to reflect cellular proliferation, and which also is more likely to be elevated in ER-negative tumors. This is consistent with previous reports that an elevated Oncotype DX Recurrence Score predicted response to preoperative doxorubicin-containing chemotherapy because proliferation genes comprise a significant component of the algorithm used to compute Recurrence Score (35). It is also consistent with previous studies showing higher breast pCR rates in ER-negative disease, as this phenotype is usually associated with higher expression of proliferation-associated genes than ER-positive disease (30). It is notable that tipifarnib seemed to augment the breast pCR rate in patients with ER-positive and ER-negative disease, although the trial was not adequately powered to establish this with certainty.

The incremental improvement in breast pCR associated with AC-tipifarnib combination is comparable to the effect of administering a longer duration of chemotherapy. For example, in the NSABP B27 trial, the breast pCR was significantly higher in patients treated with four cycles of AC followed by four cycles of docetaxel compared with four cycles of AC alone (27% versus 13%). Although our results are encouraging, it is noteworthy that the NSABP B27 trial failed to show an improvement in disease-free survival or overall survival for the docetaxel arm despite a significant improvement in the breast pCR rate (30), indicating that a greater improvement in breast pCR rates may be required. In addition, although a higher breast pCR rate was observed when docetaxel was used in ER-positive (14% versus 6%) and ER-negative (23% versus 14%) disease, the breast pCR rate was substantially lower in the ER-positive subgroup in docetaxel-treated patients (14% versus 23%), which is consistent with adjuvant trials showing relatively greater benefit from adjuvant taxane therapy in ER-negative disease (36). In contrast to the modest improvement in breast pCR rate observed in B27, a randomized phase II trial comparing preoperative chemotherapy used alone and in combination with trastuzumab in HER2/neu-positive breast cancer showed significantly higher pCR rate in the trastuzumab-containing arm (65% versus 25%; ref. 37), which was consistent with several trials showing a 50% reduction in the risk of recurrence associated with adjuvant postoperative trastuzumab (38–40). Taken together, these findings suggest that if breast pCR rate is to be used as a short-term surrogate to screen for promising strategies to subsequently test in phase III adjuvant trials, the target breast pCR rates should be substantially higher than the 25% rate observed in the B27 trial, and that different thresholds may be required for different phenotypic subsets (i.e., hormone receptor–positive versus hormone receptor–negative disease).

In conclusion, we found that the combination of dose-dense doxorubicin-cyclophosphamide (AC) was feasible and tolerable when combined with tipifarnib given orally at a dose of 200 mg twice daily for 6 days following each chemotherapy dose. We also found that tipifarnib inhibited tumor FTase in vivo, inhibited p-STAT3 activation in most patients, and produced a significantly higher breast pCR rate than expected for chemotherapy alone. Based on these encouraging results, we have initiated a second trial combining tipifarnib plus paclitaxel followed sequentially by tipifarnib plus dose-dense AC chemotherapy (ClinicalTrials.gov identifier NCT00470301). Addition of tipifarnib to the paclitaxel component of sequential dose dense therapy represents a logical continuation of our previous effort for two reasons. First, compared with every 3 week paclitaxel, weekly paclitaxel has been shown to produce higher breast pCR rates when given preoperatively and to improve overall survival when given postoperatively, irrespective of hormone receptor expression (41, 42). Second, preclinical evidence suggests that FTase inhibitors synergistically augment the effect of anti-tubulin agents such as paclitaxel (43–46). This trial may establish whether FTase inhibitors such as tipifarnib merit further evaluation in definitive, large-scale phase III adjuvant trials.

Disclosure of Potential Conflicts of Interest

J.A. Sparano, advisory board, Johnson & Johnson.

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Phase II Trial of Tipifarnib plus Neoadjuvant Doxorubicin-Cyclophosphamide in Patients with Clinical Stage IIB-IIIC Breast Cancer

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