Comparing Neoadjuvant Nab-paclitaxel vs Paclitaxel Both Followed by Anthracycline Regimens in Women With ERBB2/HER2-Negative Breast Cancer—The Evaluating Treatment With Neoadjuvant Abraxane (ETNA) Trial
A Randomized Phase 3 Clinical Trial

Luca Gianni, MD; Mauro Mansutti, MD; Antonio Anton, MD; Lourdes Calvo, MD; Giancarlo Bisagni, MD; Begoña Bermejo, MD; Vladimir Semiglazov, MD; Marc Thill, MD; Jose Ignacio Chacon, MD; Arlene Chan, MD; Serafin Morales, MD; Isabel Alvarez, MD; Arrate Plazaola, MD; Milvia Zambetti, MD; Andrew D. Redfern, MD; Christian Dittrich, MD; Rebecca Alexandra Dent, MD; Domenico Magazzù, PhD; Raffaella De Fato, PhD; Pinuccia Valagussa, BS; Ignacio Tusquets, MD

IMPORTANCE Studies of neoadjuvant chemotherapy regimens using anthracyclines followed by taxanes have reported a doubling of pathological complete remission (pCR) rates compared with anthracycline-based regimens alone. A reverse sequence did not reduce activity. Nab-paclitaxel is an albumin-bound nanoparticle of paclitaxel that allows for safe infusion without premedication, and its use led to a significantly higher rate of pCR in the GeparSepto trial.

OBJECTIVE To determine whether nab-paclitaxel improves the outcomes of early and locally advanced human epidermal growth factor receptor 2 (ERBB2/HER2)-negative breast cancer compared with paclitaxel when delivered in a neoadjuvant setting.

DESIGN, SETTING, AND PARTICIPANTS In this multicenter, open-label study, in collaboration with Grupo Español de Investigación en Cáncer de Mama (GEICAM) and Breast Cancer Research Center–Western Australia (BCRC-WA), patients with newly diagnosed and centrally confirmed ERBB2/HER2-negative breast cancer were recruited. Participants were randomly allocated to paclitaxel, 90 mg/m² (349 patients), or nab-paclitaxel, 125 mg/m² (346 patients). The 2 drugs were given on weeks 1, 2, and 3 followed by 1 week of rest for 4 cycles before 4 cycles of an anthracycline regimen per investigator choice.

MAIN OUTCOMES AND MEASURES The primary end point was the rate of pCR, defined as absence of invasive cells in the breast and axillary nodes (ie, ypT0/is ypN0) at the time of surgery. A secondary end point was to assess tolerability and safety of the 2 regimens.

RESULTS From May 2013 to March 2015, 814 patients were registered to the study; 695 patients met central confirmation eligibility and were randomly allocated to receive either paclitaxel (349), or nab-paclitaxel (346) (median age, 50 years; range, 25-79 years). The intention-to-treat analysis of the primary end point pCR revealed that the improved pCR rate after nab-paclitaxel (22.5%) was not statistically significant compared with paclitaxel (18.6%; odds ratio [OR], 0.77; 95% CI, 0.52-1.13; P = .19). Overall, 38 of 335 patients (11.3%) had at least 1 serious adverse event in the paclitaxel arm and 54 of 337 patients (16.0%) in the nab-paclitaxel arm. Peripheral neuropathy of grade 3 or higher occurred in 6 of 335 patients (1.8%) and in 15 of 337 (4.5%), respectively.

CONCLUSIONS AND RELEVANCE The improved rate of pCR after nab-paclitaxel was not statistically significant. The multivariate analysis revealed that tumor subtype (triple-negative vs luminal B-like) was the most significant factor (OR, 4.85; 95% CI, 3.28-7.18) influencing treatment outcome.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01822314
Published online January 11, 2018.

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Pathologic complete response (pCR) after neoadjuvant therapy of breast cancer is a surrogate end point of individual long-term benefit, and allows for rapid testing of new therapies, and discovery or validation of predictive or prognostic biomarkers. The growing number of candidate new drugs and the established awareness that breast cancer is a group of different diseases with different molecular characteristics and different sensitivity to therapies has led to a greater interest in evaluating these agents in a neoadjuvant setting. The latter approach is an easily applicable clinical tool to rapidly rank the antitumor activity of new therapies in subgroups of patients selected for homogeneous molecular characteristics of the tumor.

Regimens of sequential anthracyclines and taxanes are reference adjuvant therapy for high-risk breast cancer. In the sequence, weekly paclitaxel leads to superior disease-free survival compared with taxanes administered every 3 weeks. When considering neoadjuvant treatment, the addition of a taxane after the anthracycline’s portion of treatment has doubled the rate of pCR. In addition, treatment was at least equally effective when the sequence was reversed.

Data from reports in metastatic breast cancer indicated that nab-paclitaxel, the nano-particle, albumin-bound paclitaxel (Abraxane, Celgene Corp), has improved antitumor activity than solvent-based paclitaxel, although this superiority was not confirmed in a more recent trial. The formulation allows for safe infusion without the steroid premedication that is required for the cremophor-formulated paclitaxel.

In view of the possibility that nab-paclitaxel improved the efficacy of commonly used sequential regimens of anthracyclines and taxanes, we designed the Evaluating Treatment with Neoadjuvant Abraxane (ETNA) trial to directly compare the 2 formulations of paclitaxel in women with high-risk human epidermal growth factor receptor 2 (ERBB2/HER2)-negative breast carcinomas. To better interpret the results, we stratified cases in a group of triple-negative disease and 2 groups of hormone-receptor (HR)-positive or prognostic biomarkers. The growing number of candidate new drugs and the established awareness that breast cancer is a group of different diseases with different molecular characteristics of the tumor.

Methods

Study Design

ETNA was an open-label, randomized clinical trial performed in 62 sites in Europe, in collaboration with Grupo Español de Investigación en Cáncer de Mama (GEICAM) for Spanish sites, Breast Cancer Research Center-Western Australia (BCRC-WA), and National Cancer Center Singapore. The study’s primary aim was to compare the proportion of patients achieving a pCR, defined as absence of invasive cells in the breast and axillary nodes (ie, ypT0/is ypN0) at surgery after paclitaxel vs nab-paclitaxel, both followed by an anthracycline-containing regimen given as neoadjuvant therapy (Supplement 1). A list of the participating investigators is provided in the eAppendix in Supplement 2.

Key Points

Question In the neoadjuvant setting, is nab-paclitaxel significantly more effective than paclitaxel in achieving pathological complete remissions (pCR) in ERBB2/HER2-negative breast cancers?

Findings In this randomized clinical trial that included 695 patients, the rate of pCR was 22.5% with nab-paclitaxel therapy vs 18.6% with paclitaxel, a difference that was not statistically significant.

Meaning At the doses selected for this study, nab-paclitaxel and solvent-based paclitaxel had antitumor activity of the same order of magnitude in all patient subgroups; the extensive biobanking performed in the trial will allow for translational studies and better interpretation of the clinical findings.

The study was undertaken in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent. Approvals for the study protocol (and any modifications thereof) were obtained from independent ethics committees at each participating institution and relevant competent authority (the trial protocol is available in Supplement 1). Patients were not compensated for their participation.

Patients

Patients were eligible if they had a previously untreated, unilateral invasive, ERBB2/HER2-negative breast cancer. A central histologic assessment of core biopsy specimens for hormone receptor and ERBB2/HER2 status and determination of Ki67 values was mandatory. Patients had to be 18 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The tumor had to be classified as cT2 to cT4a-d. Key exclusion criteria were metastatic disease (stage IV), bilateral breast cancer, other malignant neoplasms, inadequate bone marrow or renal function, impaired liver or cardiac function, and refusal to use contraception.

Randomization and Masking

Randomization was done centrally via computed-generated blocks, and stratification was by cooperative research group, disease stage (early [T2N0; T3N0] vs locally advanced [T3N1; T4 any N; any T N2-3]), and tumor subtype (triple-negative tumors [ER and progesterone receptor (PgR)<1%; ERBB2/HER2 0/1 positive, or 2 positive and in situ hybridization (ISH) negative] vs luminal B-like high [ER and/or PgR≥1%; Ki67 level >20%, ERBB2/HER2 0/1 positive or 2 positive and ISH negative] vs luminal B-like intermediate [ER and/or PgR≥1%; Ki67 level 14% to 20%; ERBB2/HER2 0/1 positive or 2 positive and ISH negative]). All study data were collected by the Michelangelo Team in Milano, Italy. Participants and investigators were not masked to treatment assignment.

Treatment

Patients in the paclitaxel group received 90 mg/m² intravenously on weeks 1, 2, and 3, followed by a 1-week rest, for 4 cycles. Patients in the nab-paclitaxel group received 125 mg/m² intravenously on weeks 1, 2, and 3, followed by a 1-week rest,
for 4 cycles. After taxane treatment, all patients received 4 cycles of an anthracycline regimen per the investigator’s choice among doxorubicin and cyclophosphamide; epirubicin and cyclophosphamide; and fluorouracil, epirubicin, and cyclophosphamide. In the presence of severe toxic effects, investigators decided whether to discontinue neoadjuvant therapy and perform surgery immediately. After neoadjuvant chemotherapy and surgery, patients with hormone receptor-positive tumors had to receive endocrine therapy according to local guidelines. Postsurgery irradiation was recommended in accordance with international and local guidelines (see the trial protocol in Supplement 1).

Outcomes

The primary end point was pCR after neoadjuvant therapy assessed by a local pathologist according to provided guidelines requiring examination on serial sections of the surgical specimen. Secondary end points were to compare pCR rates in luminal B-like and triple-negative tumors separately, the rates of clinical overall response after taxane treatment and before surgery, and the tolerability of both neoadjuvant regimens. Clinical response was defined by modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria. Adverse events were categorized according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Other secondary end points were event-free survival and overall survival, but data are still too early and will be reported after a long-term follow-up.

Statistical Analysis

The sample size calculation for the primary end point was based on an estimated pCR rate to paclitaxel of 20% (32% in triple negative tumors and 15% in luminal B-like cancers) and targeting 10% absolute improvement in favor of nab-paclitaxel. A minimum of 632 patients (316 per treatment arm) were required to reject the odds ratio (OR) set by the null hypothesis, with 80% power and a false-positive rate of 5%. The derived OR was then used with a 2-sided Cochran-Mantel-Haenszel design, stratifying the comparison between the 2 treatment arms by breast cancer phenotype.

No patient was removed from the intention-to-treat (ITT) population after central confirmation of eligibility. No interim analyses were planned for the primary end point, but an Independent Data Monitoring Committee regularly reviewed study accrual and safety data. Toxicity-related adverse events were categorized according to the NCI-CTCAE (version 4.0) (the statistical analysis plan is provided in Supplement 1).

Results

Patients

Between May 2013 and March 2015, 814 patients were registered to the study. A total of 695 patients met central confirmation eligibility and were randomly allocated to receive either paclitaxel (349), or nab-paclitaxel (346). Their median age was 50 years (range, 25–79 years). All patients were assessed on an ITT basis for efficacy, regardless of whether they started neoadjuvant treatment (CONSORT diagram shown in Figure 1). The cutoff date for the analysis was February 12, 2016, after all patients had undergone surgery and pCR could be assessed. Most patients (72%) presented with clinical T2 tumors, and half had positive axillary nodes. Disease stage was locally advanced in 170 (24%) of the patients, triple-negative tumors accounted for 219 (32%), and hormonal receptors (HRs), either ER and/or PgR, were positive in 476 (68%) of the tumors (eTable 1 in Supplement 2).

Efficacy

The comparison of pCR between paclitaxel and nab-paclitaxel is reported in the Table. The improved rate of pCR after nab-paclitaxel was not statistically significant (P = .19). As detailed in Figure 2, nab-paclitaxel achieved a marginally improved pCR
rate in all patient subgroups. It is worth noting that patients with triple-negative tumors attained a high rate of pCR, regardless of the taxane delivered (paclitaxel, 37.3%; nab-paclitaxel, 41.3%). The frequency of pCR in the category defined as intermediate B–like tumors was 1 of 50 (2.0%) for paclitaxel and 4 of 49 (8.2%) for nab-paclitaxel; proportions for the high B–like tumors were 12.0% and 15.4%, respectively. Indeed, the multivariate analysis, including treatment, disease stage, tumor subtype, and age category, documented that tumor subtype was the most significant factor influencing treatment outcome (OR, 4.85; 95% CI, 3.28-7.18; \( P < .001 \)) favoring triple-negative tumors (eTable 2 in Supplement 2). A similar multivariate analysis (data not shown) conducted in the luminal B–like subgroup, including treatment, disease stage, age category, and Ki67 as a continuous variable, revealed that this last factor was the only one significantly affecting outcome (OR, 1.05; 95% CI, 1.03-1.07; \( P < .001 \)).

Clinical response to either paclitaxel or nab-paclitaxel was assessed at the end of the 4 cycles of either taxane and after anthracycline regimens before surgery (eTable 3 in Supplement 2). As for pathological remission, neither taxane was able to achieve a statistically significant difference. Of note, the addition of an anthracycline regimen after a single taxane doubled the rate of clinical complete remission (paclitaxel, 20.1% to 41.8%; nab-paclitaxel, 20.8% to 42.2%). The overall clinical response rate after taxane therapy was 66.5% vs 69.4%, respectively. Disease progression while receiving treatment was documented in 23 patients (6.6%) in the paclitaxel regimen (locoregional, 21; distant, 2) and in 19 patients (5.5%) in the nab-paclitaxel arm (locoregional, 16; distant, 3).

Safety

The safety population includes all patients who received at least 1 dose of either paclitaxel (335 patients), or nab-paclitaxel (337 patients), with attribution of adverse effect classified according to the treatment administered, regardless of any discrepancy with respect to the treatment they were assigned. Twenty-seven patients (8.1%) discontinued paclitaxel mainly because of adverse events (12) or disease progression while receiving therapy (10). The remaining 5 patients discontinued for other reasons. In the nab-paclitaxel arm, the figures were, respectively, 32 patients (9.5%), 13 due to adverse events, and 16 due to disease progression. The remaining 3 patients discontinued for other reasons.

During taxane treatment, 94.9% of patients treated with paclitaxel had at least 1 drug-related adverse event compared with 95.5% of those treated with nab-paclitaxel. Drug-related adverse events of grade 3 or higher were 17.3% and 22.3%, respectively, and serious adverse events categorized as taxane-related were 2.7% and 2.1% (eTable 4 in Supplement 2). Peripheral sensory neuropathy was the most frequently reported adverse event and more common with nab-paclitaxel than paclitaxel at any grade and at grades 3 or higher, with a statistically significant risk difference (RD). Rates of neutropenia of grade 3 or higher was 30.6% in the nab-paclitaxel arm and 19.7% in the paclitaxel arm with a statistically significant RD of −10.9%.

The dose of paclitaxel had to be reduced in 27 patients (8.4%) because of adverse events, and this occurred more frequently for nonhematological toxic effects (7.5%). The respective figures for nab-paclitaxel were dose reduced in 37 patients (11%), accounting for 8.6% of nonhematological events (eTable 5 in Supplement 2).

Drug-related adverse effects of grade 3 or higher reported during the subsequent anthracycline regimen accounted for 24.0% in the paclitaxel arm and 23.0% in the nab-paclitaxel arm (eTable 6 in Supplement 2).

Six patients in each of the 2 taxane groups had a left ventricular ejection fraction (LVEF) value below 50%, with 3 patients in each group experiencing a decrease of 10 to 19 points from baseline. One patient per arm had a decrease from baseline by more than 20 points, but in both patients the LVEF remained greater than 50%. Electrocardiographic abnormalities were observed in 3.0% of patients in the paclitaxel arm and 3.2% in the nab-paclitaxel arm.

One patient in the paclitaxel arm was reported to have died from hepatic failure, which subsequently was confirmed to be associated with liver metastases.

Discussion

The ETNA study was a randomized clinical trial in which neoadjuvant paclitaxel was compared with nab-paclitaxel given

<table>
<thead>
<tr>
<th>Category</th>
<th>Subgroup</th>
<th>Nab-paclitaxel, %</th>
<th>Paclitaxel, %</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor subtype</td>
<td>Luminal B-like</td>
<td>13.9</td>
<td>10.0</td>
<td>0.69 (0.39-1.21)</td>
</tr>
<tr>
<td></td>
<td>Triple-negative</td>
<td>41.3</td>
<td>37.7</td>
<td>0.85 (0.49-1.45)</td>
</tr>
<tr>
<td>Stage</td>
<td>Early</td>
<td>23.1</td>
<td>20.7</td>
<td>0.87 (0.57-1.31)</td>
</tr>
<tr>
<td></td>
<td>Locally advanced</td>
<td>20.7</td>
<td>12.5</td>
<td>0.55 (0.24-1.25)</td>
</tr>
<tr>
<td>Age, y</td>
<td>≤50</td>
<td>22.0</td>
<td>20.7</td>
<td>0.90 (0.53-1.51)</td>
</tr>
<tr>
<td></td>
<td>&gt;50</td>
<td>23.1</td>
<td>16.1</td>
<td>0.63 (0.35-1.14)</td>
</tr>
</tbody>
</table>

OR indicates odds ratio.
before an anthracycline-containing regimen to women with ERBB2/HER2-negative high-risk breast cancer. Rates of pCR at surgery, the primary end point of the study, did not show superiority of nab-paclitaxel. The nanoparticle formulation of the taxane afforded a numerically higher rate of pathologic response that was not statistically significant. The clinical response by RECIST criteria was similar after either taxane as well as after completion of the anthracycline-based regimen. Finally, nab-paclitaxel was associated with higher incidence of neutropenia and peripheral neuropathy than paclitaxel, but the different tolerability did not affect the overall drug delivery.

In the ETNA study design, central evaluation of the expression of estrogen, progesterone, and ERBB2/HER2 receptor status, together with Ki67 values, was performed before randomization for an accurate stratification of triple-negative tumors and the 2 different groups of hormone receptor (HR)-positive tumors with intermediate (14%-20%) and high (>20%) Ki67 values. This allowed for a more accurate analysis of treatment activity in triple-negative and luminal B-like groups.

Results showed a significantly higher rate of pCR in the triple-negative group irrespective of the taxane to which patients were randomized. The triple-negative phenotype was the only variable that was significantly associated with a greater probability of pCR in multivariate analysis. This was in part expected because neoadjuvant chemotherapy is consistently associated with higher rates of pCR in triple-negative breast cancer, as reported by others. However, no significant superiority of nab-paclitaxel over paclitaxel in the separate analysis of the triple-negative tumors and in the luminal-like tumors was observed.

In the group of tumors expressing HR, the rate of pCR was around 10%. The lower propensity of HR-expressing tumors to respond to chemotherapy is well known. However, to our knowledge, ETNA is the first trial that prospectively selected HR-positive tumors based on central laboratory assessment and excluded tumors with low Ki67 based on the expectation that lower proliferation would have a lesser likelihood of response to chemotherapy. Clearly, proliferation within the boundaries of the values assessed in the study did not confer a sensitivity of HR-positive, luminal B-like tumors that could match the one reported for triple-negative breast cancer. The lower rate of pCR is not necessarily indicating lesser, or even lack of, activity, and it should be pointed out that in the ETNA study, the clinical response rates in HR-positive tumors were similar to those in the triple-negative cohort.

GeparSepto is the other reported neoadjuvant study that compared nab-paclitaxel and paclitaxel in women with early-stage breast cancer. Although the ETNA and GeparSepto studies have many similarities, a number of important differences exist in study design and conduct that deserve consideration and limit cross-trial comparisons. The German trial was designed at the same time of the ETNA study and was recently reported. Overall, the ETNA and GeparSepto trials have ORs for pCR in the same order of magnitude. However, in GeparSepto nab-paclitaxel led to statistically significant higher rates of pCR than paclitaxel in the study overall and in each subgroup of triple-negative, ERBB2/HER2-positive, and luminal-like tumors, respectively. The superiority of nab-paclitaxel was especially prominent in the subgroup of triple-negative tumors. A possible explanation for the superior efficacy of nab-paclitaxel is improved uptake in tumors owing to active transport via the secreted protein acid rich in cysteine (SPARC)-caveolin system. However, in the GeparSepto study, patients were stratified according to the level of SPARC expression in tumors, and no association was found between pCR and SPARC expression level. Data on SPARC expression in the ETNA study are not available.

The most relevant difference between the 2 trials relates to the schedule and dose of the taxanes. In GeparSepto, the dose of nab-paclitaxel was initially 150 mg/m² weekly and later decreased to 125 mg/m² weekly after observing excessive peripheral sensory neuropathy and the need for dose discontinuation in the first 464 of the 1206 patients of the trial. However, the schedule was maintained at weekly intervals continuously, while in the ETNA study, the dose of 125 mg/m² was given weekly for 3 weeks followed by 1 week of rest. In addition, the German trial adopted a continuous weekly schedule for cremophor-formulated paclitaxel at 80 mg/m². The latter dose is lower than the single dose of 90 mg/m² in the ETNA study, which was, however, delivered for 3 weeks of every 4 weeks. Thus, when comparing dose delivery between the 2 studies (ie, dose in mg/m² per week), this was 93.75 and 125.00 for nab-paclitaxel and 67.75 and 80.00 for paclitaxel in the ETNA study and GeparSepto study, respectively. Therefore, in ETNA, the planned total dose of paclitaxel was about 85% of that in GeparSepto and the ratio of albumin-bound vs solvent-formulated paclitaxel in the 2 studies was 1.39 and more than 1.56, respectively. In other words, in ETNA the paclitaxel doses were closer to each other in the arms of solvent-based and nano-particle formulations, and the schedule was discontinuous.

The doses and schedule of taxanes in ETNA were selected to reduce the severity and duration of the peripheral neuropathy linked to paclitaxel, which is consistently more prominent with nab-paclitaxel. This is supported by a comparison of the rates of peripheral neuropathy seen in ETNA and GeparSepto. Any grade neuropathy was reported in 53.7% and 62.6% of patients receiving paclitaxel or nab-paclitaxel, respectively, in ETNA, compared with 66% and 86% in paclitaxel or nab-paclitaxel, respectively in the German trial. In addition, neuropathy of grade 3 or higher was observed in 1.8% and 4.5% in patients receiving paclitaxel or nab-paclitaxel in the ETNA study, and 3% and 11%, respectively, in GeparSepto.

Cremophor-formulated paclitaxel follows nonlinear kinetics, so that dose and infusion duration have profound effects on exposure, tolerability, and most likely antitumor effects. In addition, solvent-based paclitaxel is increasingly maintained in micellar bodies and made unavailable to tumor in spite of increasing doses. Nonlinear kinetics and the fraction of drug entrapped in micellar bodies may lower the exposure to free active drug. Instead, nab-paclitaxel has a linear pharmacokinetics, and the known larger volume of distribution and more rapid clearance compared with solvent-based paclitaxel are in keeping with better tissue and tumor distribution and a predictable dose-effect response.
It is therefore possible that the different dose ratio of nab-paclitaxel to paclitaxel and the different schedule intensities adopted were a relevant reason for the different outcomes of the ETNA and the GeparSepto trials.

Limitations
The present ETNA study was designed at the same time of the GeparSepto trial, but a number of important differences exist in study design, and conduct. ETNA was restricted to women with centrally confirmed triple-negative breast cancer, or with centrally confirmed hormone receptor(s)-positive disease and Ki67 of at least 14%. Patients with ERBB2/HER2-positive tumors were excluded, and the schedule and doses of paclitaxel and nab-paclitaxel were different. In ETNA, in contrast with GeparSepto, the numerically higher rate of pCR with nab-paclitaxel was not statistically significant in the IIT population as well as in the 2 main subgroups of cases. The study has secondary end points of event-free survival, and continuous follow-up will define whether exposure to higher doses of paclitaxel with nab-paclitaxel will provide an efficacy advantage.

Conclusions
In the ETNA trial, the nab-paclitaxel and paclitaxel at the selected doses had antitumor activity of the same order of magnitude, with a trend for higher rates of pCR with nab-paclitaxel and a higher incidence of grade 3 or higher neuropathy and neutropenia. The data do not show a different outcome of paclitaxel vs nab-paclitaxel in triple-negative or in HR-positive tumors selected to approximate the luminal-B subtype and do not support direct substitution of paclitaxel with nab-paclitaxel at the doses and schedule adopted in the ETNA trial. The extensive biobanking performed in the trial will allow for translational studies and better interpretation of the clinical findings.

Role of the Funder/Sponsor: The study sponsor (Fondazione Michelaangelo) developed the study design, reviewed, and approved the reports.

Previous Presentation: This study was an oral presentation at the S22nd Annual Meeting of the American Society of Clinical Oncology, June 3-7, 2016, Chicago, Illinois.

Additional Contributions: We are indebted to all the patients who have participated in our clinical trial and to the many associates, in particular medical oncologists, surgeons, radiation therapists, pathologists, research nurses, and data managers, for their cooperation during the study. We are particularly indebted to the members of the Independent Data Monitoring Committee: Hervé Bonnefoi, MD, Bordeaux University and Bergonié Cancer Center, Bordeaux, France; Lisa Carey, MD, UNC Lineberger Comprehensive Cancer Center, Chapel Hill; and Urania Dafni, ScD, School of Health Sciences, National and Kapodistrian University of Athens, Athens, Greece; and the members of the ETNA Pathology Committee: John Bartlett, BC, PhD, FRCPath, Ontario Institute for Cancer Research, Toronto; Giuseppe Viale, MD, European Institute of Oncology, Milan, Italy; Stephen Fox, BSc(Hons), MBChB, FRCPath, FFSc, FRCPA, DPhil, Peter MacCallum Cancer Center; Victoria, Australia; Claudio Doglioni, MD, San Raffaele Scientific Institute, Milan, Italy; Federico Rojo, MD, PhD, Fundación Jimenez Diaz, Madrid, Spain; and Giampaolo Bianchini, MD, San Raffaele Scientific Institute, Milan, Italy. They were not compensated for their participation.

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