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Abstract

Purpose: It has been suggested that a subgroup of human epidermal growth factor receptor 2 (HER2)-negative breast cancer patients with chromosome 17 (Chr-17) polysomy benefit from HER2-directed therapy. This hypothesis was examined using the data from a phase III trial that randomized patients with HER2-negative or HER2-untested metastatic breast cancer to first-line therapy with paclitaxel along with either lapatinib or placebo.

Experimental Design: HER2 expression level by immunohistochemistry, fluorescence in situ hybridization (FISH), and mean HER2 ratio of Chr-17 values were determined centrally using archival tissue. Polysomy means of 2.0 and 2.2 served as thresholds.

Results: Of 580 patients on the original trial, 406 were HER2 negative by FISH. Progression-free survival (PFS) data were available for 405 patients, of whom 44 (11%) met the definition of polysomy (Chr-17 ≥2.2, FISH negative for HER2). Median PFS in the polysomy group was 20.9 and 24.4 weeks for paclitaxel plus lapatinib and paclitaxel plus placebo, respectively. In the nonpolysomy group, median PFS was 24.6 and 23.1 weeks for paclitaxel plus lapatinib and paclitaxel plus placebo, respectively. Log-rank testing showed no treatment advantage for either group. Similar results were found using a Chr-17 polysomy cutoff of 2.0. Response rates in the polysomy group were 17% for paclitaxel plus lapatinib and 10% for paclitaxel plus placebo. In the nonpolysomy group, response rates were 32% for paclitaxel plus lapatinib and 25% for paclitaxel plus placebo. Neither comparison was statistically significant.

Conclusion: This analysis could not confirm the hypothesis that Chr-17 polysomy in HER2-nonamplified patients improved chemotherapy outcome when lapatinib is added as a HER2-targeted treatment.

Human epidermal growth factor receptor 2 (HER2) is a cell membrane surface-bound receptor involved in signal transduction pathways leading to cell growth and differentiation. The HER2 gene is located on the long arm of chromosome 17 (Chr-17; 17q11.2-q12), and the gene is amplified with overexpressed protein product in 20% to 30% of human breast cancers. One currently accepted definition of HER2 positivity, which led to the Food and Drug Administration approval of Herceptin, requires a fluorescence in situ hybridization (FISH) result of more than four HER2 gene copies per nucleus, a FISH ratio (HER2 gene signals to Chr-17 centromere) of ≥2.0, or 3+ staining by immunohistochemistry (IHC). An alternate definition, put forth by American Society of Clinical Oncology/College of American Pathologists, requires six or more HER2 gene copies by FISH, a FISH ratio of ≥2.2 or greater, or 3+ staining by IHC. HER2 amplification or overexpression is associated with poor prognosis in the absence of treatment. HER2 amplification or overexpression is also associated with responsiveness to HER2-directed therapies, and the use of these treatments has resulted in dramatic improvements in clinical outcomes (1–3). Thus, HER2 represents a key molecular marker with prognostic and predictive significance, and the evaluation of HER2 overexpression or amplification has become a requirement for the pathologic assessment of breast cancer. However, debate exists about optimal methods for the assessment of HER2 and the clinical relevance of these assays.

It has been suggested that women whose breast cancers lack HER2 gene amplification but have Chr-17 polysomy
Translational Relevance

The clinical benefits of human epidermal growth factor receptor 2 (HER2)-directed therapies are generally restricted to patients with metastatic breast cancer whose tumors overexpress HER2. However, limited data suggest that subgroups of HER2-negative breast cancer patients, such as those with chromosome 17 (Chr-17) polysomy, may derive benefit from HER2-directed therapy. Using robust data from a phase III trial of patients with HER2 fluorescence in situ hybridization–negative or HER2-untested metastatic breast cancer randomized to receive paclitaxel along with either lapatinib or placebo, we show that Chr-17 polysomy in HER2-nonamplified patients is not associated with improved outcome on chemotherapy when lapatinib is added as a HER2-targeted treatment. These findings argue against a role for Chr-17 polysomy as a mechanism for response to HER2-directed therapy in this patient population.

Materials and Methods

Patients. EGF30001 evaluated the efficacy of the addition of lapatinib in women with incurable stage III or IV breast cancer that was HER2-negative or untested at the time of study entry (7). This study was funded and conducted by GlaxoSmithKline. Patients (n = 580) were enrolled between January 2004 and July 2005, stratified by disease site and stage, and randomized (1:1) to either 175 mg/m² paclitaxel every 3 weeks (q3w) and 1,500 mg oral lapatinib daily or 175 mg/m² paclitaxel q3w and oral placebo daily. The primary end point of the trial was time to progression (TTP); secondary end points were progression-free survival (PFS), response rate (RR), clinical benefit rate (CBR), overall survival, quality of life, and safety. Response assessments were done in accordance with the Response Evaluation Criteria in Solid Tumors.

Study design and end points. This study retrospectively assessed HER2 gene amplification and Chr-17 polysomy in patients treated in EGF30001, and compared PFS for the HER2-nonamplified cases across treatment arms by the presence or absence of polysomy. Patients were eligible if a tumor block was available for FISH analyses.

Definitions used in this analysis include the following: (a) HER2 gene amplification (HER2 positive) was a HER2/Chr-17 ratio of ≥2 by FISH as approved by the United States Food and Drug Administration; (b) HER2 nonamplification (HER2 negative) was a ratio of <2 by FISH; (c) polysomy was a Chr-17 centromere average of ≥2.2 (or ≥2 as an exploratory analysis) as described by Kaufman et al. (4).

Sample preparation. FISH assays were done using the HER2 PathVysion FISH assay (Abbott Laboratories) as described elsewhere (8, 9). FISH signals were evaluated by enumeration of the number of red HER2 signals and the number of green Chr-17 centromeres in each of at least 20 interphase carcinoma cell nuclei as approved by the Food and Drug Administration (10, 11). The enumerations were done by a licensed clinical laboratory scientist and confirmed by a board-certified pathologist.

HER2 positive was defined as HER2 gene amplification by FISH (ratio ≥2.0) and HER2 negative was defined as a lack of HER2 gene amplification by FISH (<2.0). Among confirmed HER2-negative cases, exploratory analyses were done for Chr-17 centromere polysomy based on the average Chr-17 centromere score per tumor cell nucleus. For the primary analysis, the definition of polysomy previously described by Kaufman (4), Chr-17 ≥2.2, was used. Exploratory analysis of alternate cut points was done to address the possibility that either more modest or more significant degrees of polysomy might be associated with biological significance and treatment effect.

Statistical analysis. The primary population was the intent-to-treat population, which was defined as all randomized patients who received at least one dose of study

<table>
<thead>
<tr>
<th>Table 1. EGF30001 overall demographics</th>
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<tr>
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<tr>
<td>Paclitaxel plus lapatinib, n = 291</td>
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<tr>
<td>Mean age, y (range)</td>
</tr>
<tr>
<td>ECOG performance status 0/1, %</td>
</tr>
<tr>
<td>Prior adjuvant taxane, %</td>
</tr>
<tr>
<td>Prior adjuvant anthracycline, %</td>
</tr>
<tr>
<td>Stage IIIb-c, %</td>
</tr>
<tr>
<td>Stage IV</td>
</tr>
<tr>
<td>Visceral ± other metastases, %</td>
</tr>
<tr>
<td>Abbreviation: ECOG, Eastern Cooperative Oncology Group.</td>
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<tr>
<td>*No data for 1 of 580 patients, withdrawn before first dose.</td>
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</table>
medication \((n = 579)\). The primary end point in the original clinical study was TTP. For the polysomy analyses, however, the more conservative end point of PFS (time from randomization until disease progression or any death) was selected in addition to RR.

In the HER2-negative patient group, polysomy subgroups were retrospectively defined using the cutoff of 2.2. Kaplan-Meier curves were generated for both treatment arms in the polysomy and nonpolysomy groups, and were used to calculate median PFS. Estimates of hazard ratios (HR) based on log-rank tests and 95% confidence intervals (CI) were calculated comparing the two polysomy subgroups for each treatment arm. Polysomy subgroups were compared using log-rank tests. This same PFS analysis was repeated using the groups divided by a polysomy cutoff of \(\geq 2.0\).

**Results**

**Patient demographics.** Patient demographic characteristics were balanced for the EGF30001 clinical trial (Table 1). Tumor blocks were available for 492 patients; of these, 406 patients were HER2 negative, and 86 patients were HER2 positive. Patient demographics in the polysomy analyses were similar to the demographics in the clinical trial intent-to-treat population.

**Clinical outcomes by HER2 status in primary clinical trial.** In the intent-to-treat population analysis, there were no statistically significant differences in TTP, PFS, or overall survival for the combination of lapatinib plus paclitaxel compared with paclitaxel alone. Analysis of available data from 405 HER2-negative patients also revealed no benefit with the addition of lapatinib. Median PFS in the HER2-negative group was 23.3 weeks for the paclitaxel plus lapatinib arm compared with 23.1 weeks for the paclitaxel plus placebo arm (HR, 1.10; 95% CI, 0.88-1.37; \(P = 0.395\)). However, in a subset analysis of the 86 HER2-positive patients, the addition of lapatinib to paclitaxel resulted in a statistically significant improvement in PFS, with the combination resulting in a PFS of 35.1 versus 21.9 weeks for paclitaxel plus placebo (HR, 0.52; 95% CI, 0.31-0.86; \(P = 0.004\)). For these HER2-positive patients, the combination also resulted in significant improvements in RR, TTP, and clinical benefit rate. See Table 2 for a summary of PFS results for each group.

**Distribution of Chr-17 polysomy.** Among the 406 HER2-negative patients in this analysis, 44 (11%) had Chr-17 polysomy, 361 (89%) did not have Chr-17 polysomy, and 1 subject (<1%) had indeterminable data. Additional exploratory analyses were done using chromosome copy number cutoffs of \(\geq 2.0\), \(\geq 2.5\), or \(\geq 2.75\). Using a lower cutoff of 2.0, 69 (17%) of patients had Chr-17 polysomy; using higher cutoffs of 2.5 and 2.75, 26 (6%) and 13 (3%) had Chr-17 polysomy, respectively.

The HER2 IHC results for HER2 FISH-negative patients with and without Chr-17 polysomy are shown in Table 3. The HER2 IHC results for HER2 FISH-negative patients with Chr-17 polysomy using the higher exploratory cutoff of 2.75 are also shown in Table 3.

**Chr-17 polysomy and PFS among HER2-negative patients.** Using the chromosome copy number \(\geq 2.2\) cutoff for Chr-17 polysomy, median PFS in the paclitaxel plus lapatinib arm was 20.9 weeks for patients with polysomy \((n = 23)\) versus 24.6 weeks for those without polysomy \((n = 178; HR, 0.77; 95\% CI, 0.43-1.37; P = 0.3209)\). The median PFS in the paclitaxel plus placebo arm was 24 weeks for

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**Table 2. Summary of PFS for patients treated in EGF30001**

<table>
<thead>
<tr>
<th></th>
<th>Median PFS (wk)</th>
<th>For paclitaxel plus lapatinib vs paclitaxel plus placebo</th>
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<tbody>
<tr>
<td></td>
<td>Paclitaxel plus lapatinib</td>
<td>Paclitaxel plus placebo</td>
</tr>
<tr>
<td>HER2-positive patients ((n = 86))</td>
<td>35.1</td>
<td>21.9</td>
</tr>
<tr>
<td>HER2-negative patients ((n = 405)^*)</td>
<td>23.3</td>
<td>23.1</td>
</tr>
<tr>
<td>Polysomy ((n = 44))</td>
<td>20.9</td>
<td>24.0</td>
</tr>
<tr>
<td>No polysomy ((n = 361))</td>
<td>24.6</td>
<td>23.1</td>
</tr>
<tr>
<td>For polysomy vs no polysomy HR</td>
<td>0.77</td>
<td>0.68</td>
</tr>
</tbody>
</table>

*Of 406 HER2-negative patients, data were available for 405 patients.

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**Table 3. Correlation between IHC and polysomy**

<table>
<thead>
<tr>
<th>IHC result, (n (%))</th>
<th>Chr-17 &gt;2.2 Chr-17 ≤2.2 Chr-17 &gt;2.75</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>22 (50) 248 (69) 7 (15)</td>
</tr>
<tr>
<td>1+</td>
<td>11 (25) 86 (24) 2 (15)</td>
</tr>
<tr>
<td>2+</td>
<td>7 (16) 20 (6) 2 (15)</td>
</tr>
<tr>
<td>3+</td>
<td>3 (7) 2 (&lt;1) 2 (15)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (2) 5 (1) 0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>44 361 13</td>
</tr>
</tbody>
</table>
patients with polysomy (n = 21) versus 23.1 weeks for those without polysomy (n = 183), resulting in a HR of 0.68 (95% CI, 0.36-1.27; \(P = 0.1444\)) for the lack of polysomy. There was no association between the presence and absence of polysomy and outcome for either treatment arm.

Similarly, among patients with Chr-17 polysomy, there was no significant advantage to the combination of paclitaxel plus lapatinib versus paclitaxel and placebo. The HR for progression in polysomy patients who received lapatinib was 0.85 (95% CI, 0.42-1.72), which was not statistically significant (\(P = 0.639\)). The statistical power was limited for these analyses due to the small number of subjects (Fig. 1).

Similar results were seen in the exploratory analyses using the alternate polysomy cutoff of 2.0 (data not shown). An insufficient number of patients precluded the statistical analyses on the groups defined by the higher cutoffs of 2.5 and 2.75.

**Chr-17 polysomy and response among HER2-negative patients.** Among the 44 patients with Chr-17 polysomy, objective responses were seen in 4 of 23 (17%) patients on the paclitaxel plus lapatinib arm versus 2 of 21 (10%) patients on the paclitaxel plus placebo arm. In the nonpolysomy group, RRs were 32% for the paclitaxel plus lapatinib arm and 25% for the paclitaxel plus placebo arm. This resulted in an odds ratio of 2.0 (95% CI, 0.24-24.2) that was not statistically significant (\(P = 0.756\)). The statistical power was limited for this analysis. Similarly, there was no significant difference in RR between the treatment arms for patients without polysomy.

**Discussion**

Initial studies of a HER2-directed monoclonal antibody, trastuzumab, showed that antitumor effect was limited to cell lines with HER2 overexpression. A phase II study of trastuzumab monotherapy as first-line metastatic treatment revealed that trastuzumab was effective in women with HER2 3+ overexpression by IHC or HER2 gene amplification by FISH (1). Similarly, Cancer and Leukemia Group B (CALGB) protocol 9840, a phase III study of the addition of trastuzumab to paclitaxel in metastatic breast cancer, revealed that the benefit from the addition of trastuzumab was seen only in patients with HER2 overexpression by IHC or gene amplification (2). However, in a subset analysis of CALGB 9840, patients who were HER2 FISH-negative but had polysomy for Chr-17 (n = 31), defined as Chr-17 copy number \(\geq 2.2\), were also found to have a statistically significant benefit in RR associated with the addition of trastuzumab (4). Importantly, this was a small number of patients with HER2 FISH-negative polysomic tumors.

A meta-analysis of five studies of adjuvant trastuzumab in combination with chemotherapy in HER2-positive breast cancer reveals a significant benefit to the addition of trastuzumab, with a relative risk for disease-free survival (DFS) and mortality of 0.62 and 0.66, respectively (12). In the central review of HER2 status in the National Surgical Adjuvant Breast and Bowel Project B-31, 174 of 1,787 patients, previously characterized as HER2 positive in local laboratories, were instead found to be HER2 negative (i.e., FISH negative, and <3+ by IHC) by central analysis. These central HER2-negative patients still seemed to benefit from the addition of trastuzumab, with a relative risk for DFS of 0.34 (\(P = 0.014\); refs. 13, 14). Similarly, in a central review of the HER2 status in patients treated on NCCTG N9831, in which HER2-positive patients were randomized to adjuvant chemotherapy plus or minus trastuzumab, those with central HER2-negative disease still showed a nonsignificant trend toward the benefit from the addition of trastuzumab. One hundred three of the total 3,969 patients enrolled on the trial were centrally HER2 negative, and the HR for DFS for the addition of trastuzumab was 0.51, but with a nonsignificant \(P\) value of 0.13 (15).
Lapatinib is a dual tyrosine kinase inhibitor of HER2 and epidermal growth factor receptor, and has shown efficacy in HER2-positive breast cancer as a single agent and in combination with chemotherapy. In two phase II studies of its single agent efficacy in advanced breast cancer, patients with HER2-negative tumors did not respond (3).

Although the vast majority of preclinical and clinical work suggests that the benefit from HER2-directed therapy is limited to those with HER2 overexpression or amplification, there are limited data from both CALGB 9840 and the National Surgical Adjuvant Breast and Bowel Project B-31 that indicate that HER2-negative patients may also benefit from HER2-directed therapies. Chr-17 polysomy is a condition in which cells contain an increased total Chr-17 number without specific gene amplification. That increase in total Chr-17 number may result in increased HER2 protein expression, and this was proposed as a possible mechanism by which HER2-negative patients might benefit from HER2-targeted therapy.

The proposed mechanism for the association of polysomy with HER2-related growth and treatment effect lies in the supposition that polysomy for Chr-17 should result in increased HER2 copy number, even in the absence of specific gene amplification (16). This raises the question of the threshold of HER2 copy number above which the increased copy number is clinically relevant. It has previously been shown that in breast cancers with HER2 amplification, changes in clinical outcome do not occur until HER2 copy number is greater than or equal to four copies per nucleus (14). If the proposed mechanism for polysomy effect is correct, one would expect that the clinically relevant HER2 copy number threshold would be similar regardless of the mechanism of increase (polysomy versus gene amplification). In our series, even with the very inclusive definition of polysomy (Chr-17 copy number of ≥2.2), only 11% of patients showed polysomy. Moreover, only 3% of cases had a Chr-17 copy number >2.75, suggesting that there would be a very small proportion of patients with a clinically relevant elevation in HER2 copy number by this mechanism.

We could not conclude from this trial that Chr-17 polysomy, as defined here in HER2 FISH-negative patients, was associated with improved outcome with the addition of lapatinib to paclitaxel. In this trial, neither PFS nor RR was significantly different in cross-treatment comparisons based on the presence or absence of polysomy. This conflicts with the results from CALGB 9840, as reported by Kaufman et al. (4), in which the presence of Chr-17 polysomy in HER2 FISH-negative patients was associated with a significantly increased RR with paclitaxel plus trastuzumab versus paclitaxel alone (63% versus 25%, \( P = 0.043 \)). Notably, the sample size from that study is small (see Table 4), limiting the statistical power of any conclusion. However, CALGB 9840, as with this study, revealed no improvement in PFS for the addition of HER2-directed therapy in patients with FISH-negative polysomy. This is in contrast to the data of HER2-positive patients (by FISH or IHC) for whom HER2-directed therapy does result in improved PFS and overall survival. As described above, in adjuvant trials of standard chemotherapy plus or minus trastuzumab, Chr-17 polysomy was not associated with the efficacy of trastuzumab as defined by DFS, in either HER2-amplified or a small group of HER2-nonamplified patients (5, 6).

Furthermore, it is unclear if Chr-17 polysomy increases HER2 protein product. In a review of >1,200 FISH-negative breast cancers (without assessment for polysomy) from clinical material, only 2.1% (range, 1.2-3.5%) had IHC staining of 3+ (17–19). In the series reported here, of FISH-negative cases with polysomy, only 7% had staining of 3+ by IHC. Similar results were reported in a series of 900 unselected breast cancer specimens, in which only 45 of 678 (6.6%) FISH-negative tumors were IHC positive at 3+ (20). This is in contrast to the data of HER2-positive patients (by FISH) for whom HER2-directed therapy does result in improved PFS and overall survival. As described above, in adjuvant trials of standard chemotherapy plus or minus trastuzumab, Chr-17 polysomy was not associated with the efficacy of trastuzumab as defined by DFS, in either HER2-amplified or a small group of HER2-nonamplified patients (5, 6).

Table 4. Comparison of RRs for patients with metastatic breast cancer with polysomy treated with HER2-directed therapy on EGF30001 and CALGB 9840

<table>
<thead>
<tr>
<th>Polysomy,* n (%)</th>
<th>EGF30001 (n = 21)</th>
<th>CALGB 9840 (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response, n (%)</td>
<td>Paclitaxel plus lapatinib Paclitaxel plus placebo</td>
<td>Paclitaxel plus trastuzumab Paclitaxel plus placebo</td>
</tr>
<tr>
<td>4 (19)</td>
<td>2 (10)</td>
<td>12 (63)</td>
</tr>
<tr>
<td>( P = 0.756 ) ns</td>
<td></td>
<td>( P = 0.043 )</td>
</tr>
</tbody>
</table>

Abbreviation: ns, not significant.

*Chr 17 ≥2.2.
overexpression by IHC or increased HER2 mRNA levels by reverse transcription-PCR (23). This study also reported that Chr-17 polysomy was not associated with clinicopathologic features often associated with HER2 positivity, such as high tumor grade, hormone receptor negativity, or reduced DFS. In fact, the editorial review of this report points out that the tumors showing polysomy were more pathologically similar to HER2-negative tumors than to HER2 gene-amplified tumors, raising doubt that polysomy would be associated with a benefit from HER2-directed therapy (24). In sum, the available literature indicates that Chr-17 polysomy per se does not have a significant effect on HER2 protein or mRNA levels. This supports the results from this analysis that HER2-directed therapy does not add benefit to cytotoxic chemotherapy in metastatic HER2 FISH-negative patients.

If polysomy for Chr-17 is not the explanation for benefit from HER2-directed therapy in some FISH-negative patients, what are potential alternative explanations? Specifically, for HER2-directed therapy in the adjuvant setting, a treatment effect on focally HER2-amplified cells may be important, as suggested by Paik (13). This suggestion has been called focally HER2-amplified clones (FHAC) or HER2 heterogeneity in the primary tumor. In this scenario, there are focal HER2-amplified cells within the primary tumor; however, the majority of cells are not amplified, resulting in an overall FISH ratio of <2.2. Over time and with standard treatment, these HER2-positive cells may have a selective survival advantage and develop into HER2-positive metastases. However, with the early addition of HER2-directed therapy, these cells could be killed along with the HER2-negative cells. However, results reported elsewhere for the EGF30001 and EGF100151 trials show only ~0.5% of breast cancers have this type of HER2 heterogeneity, making this an unlikely possibility (3). Of course the definition of FHACs, or HER2 heterogeneity, has not been clearly defined or accepted. Until an accepted definition is defined, it is impossible to compare incidence of FHAC, or RR in patients with FHAC, across trials.

Several studies have shown that portions (range, 18-60%) of patients with HER2-negative primary tumors have HER2-positive circulating tumor cells or disseminated tumor cells in the bone marrow (23–25). The clinical significance of these HER2-positive circulating tumor cells or disseminated tumor cells is not clear, and has not been supported by the available information about the incidence of HER2-positive clinically detected metastases observed in women with HER2-negative primaries. In Table 5, we review the published series of clinical cases of HER2-negative primary tumors with HER2-positive metastases (26–36). If these series are considered in sum, the overall percentage of patients with a HER2-negative primary and a clinical metastasis that is HER2 positive is low (9%) and is even lower (5%) when one considers only those studies using the more accurate FISH assay for assessment of HER2 status. The relevance of HER2-positive asymptomatic circulating tumor cells and disseminated tumor cells, compared with HER2-positive clinically significant metastases, is not known.

In conclusion, the value of HER2-directed therapy in HER2-negative patients remains unclear. Most studies suggest that the benefit of such therapies is limited to HER2-amplified or overexpressing tumors. A key concern in understanding this issue is the accuracy of HER2 testing, with some series suggesting that as many as 20% of HER2 assays done in the field are inaccurate when the same specimen is reevaluated at a central validated laboratory (27, 28).
References


Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Armen Gasparian at the University of Southern California, Los Angeles, California for the technical assistance.

Grant Support

GlaxoSmithKline.

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Received 6/26/09; revised 11/20/09; accepted 12/13/09; published OnlineFirst 2/9/10.

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Clin Cancer Res; 16(4) February 15, 2010

1287

Published OnlineFirst February 15, 2010; DOI: 10.1158/1078-0432.CCR-09-1643

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Clinical Cancer Research


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