MYC Amplification as a Prognostic Marker of Early-Stage Lung Adenocarcinoma Identified by Whole Genome Copy Number Analysis

Reika Iwakawa¹, Takashi Kohno¹, Motohiro Kato², Kouya Shiraishi¹, Koji Tsuta³, Masayuki Noguchi⁴, Seishi Ogawa², and Jun Yokota¹

Abstract

Purpose: Even in small-sized (≤2 cm in greatest dimension) and/or pathologic stage I lung adenocarcinoma (ADC), a considerable proportion of the patients will relapse within 5 years and show poor prognosis. The purpose of this study was to identify genetic alterations that define prognosis of patients with early-stage lung ADC.

Experimental Design: Regions of copy number alterations in 65 small-sized lung ADCs and 40 ADC cell lines were determined by using GeneChip Human Mapping 10-K and 250-K single-nucleotide polymorphism (SNP) arrays, respectively. A copy number assay based on real-time genomic PCR (RT-G-PCR) was done for 60 small-sized lung ADCs and 162 stage I lung ADCs.

Results: Several regions on chromosomes 5p, 7p, 8q, and 14q were frequently (>10%) amplified in both small-sized ADCs and lung ADC cell lines. In particular, the MYC gene was mapped in the minimum common region at chromosome 8q24.21, and therefore was indicated to be a target of gene amplification in lung ADCs. MYC amplification correlated with poor prognosis (P = 0.031) of patients with small-sized ADCs. MYC amplification detected by SNP array analysis was well reproduced by RT-G-PCR analysis. Therefore, to investigate the utility of MYC amplification as a prognostic marker for early-stage lung ADCs, 162 stage I lung ADCs were subjected to the analysis. MYC amplification was associated with relapse-free survival in these patients (P = 0.013 by multivariate Cox proportional hazard model analysis).

Conclusions: These results strongly indicate that MYC amplification is a prognostic marker of patients with early-stage lung ADCs.

Clin Cancer Res; 17(6); 1481–9. ©2010 AACR.

Introduction

Lung cancer is the leading cause of cancer death worldwide (1, 2). Adenocarcinoma (ADC) is the most common histologic type of lung cancer in many countries (3–5), and with the recent advances of computed tomographic technology, the number of patients diagnosed with small-sized lung ADC as well as stage I lung ADC has been increasing (6, 7). Although both small-sized and stage I ADCs are thought to be early-stage diseases and treated primarily by surgery without adjuvant therapy, a considerable fraction of patients with those ADCs shows unfavorable outcomes after surgical treatment. Therefore, to improve the prognosis of those patients, it is necessary to identify suitable markers to select patients with poor prognosis who can benefit from adjuvant therapy after surgery.

Lung ADC has been considered to develop to invasive carcinoma through atypical adenomatous hyperplasia, ADC in situ, and minimally invasive ADC (8). Bronchioloalveolar carcinoma (BAC) is a well-differentiated ADC showing a lepidic growth through the peripheral airway, and it was classified into a purely in situ lesion by 2004 World Health Organization (WHO) classification (4). Types A and B by Noguchi classification for small-sized lung ADC (2 cm or less in greatest dimension) are non-invasive ADCs showing BAC morphology, while types C and D are invasive ADCs with and without a BAC component, respectively (9). Therefore, types A and B tumors correspond to carcinoma in situ in the 2004 WHO classification (4). Five-year survival rates of patients with BAC and with type A/B ADC are known to be 100%, while prognoses of patients with invasive ADCs are variable (8–11). Therefore, it is absolutely necessary to develop a novel way of prediction for prognosis of patients with those invasive ADCs.

Because stepwise progression of lung ADC has been thought to be attributed to accumulation of multiple genetic alterations in lung epithelial cells, we have attempted to identify genetic alterations associated with...
Translational Relevance

We showed here that MYC amplification is a prognostic marker for patients with small-sized lung adenocarcinoma (ADC) as well as stage I lung ADC. No adjuvant therapy was usually given after surgery for these patients, and a high proportion of patients relapsed within 5 years after surgery if the MYC gene was amplified in tumors. These results imply that micrometastases are often present at the time of surgical resection of the tumors with MYC amplification. For this reason, MYC amplification could be a critical genetic alteration for lung ADC cells to convert their phenotypes from nonmetastatic to metastatic ones. Therefore, lung ADC cases with MYC amplification will be an appropriate target of postoperative adjuvant therapy in clinics.

prognosis of patients with small-sized lung ADC by using several molecular biologic methods (12). In this study, we attempted to identify genes commonly amplified in lung ADCs that show association with prognosis of patients because amplified genes and/or their products could be molecular targets not only for diagnosis but also for therapy of patients with lung ADC. Recent genome-wide analyses for copy number changes in cancer cells have identified various chromosomal loci that are amplified in lung ADCs (13–16). However, because copy number alterations in lung ADC genomes are very complex, target genes often remain unclear in amplified chromosomal segments. In addition, the clinical significance of gene amplification in early-stage lung ADC also remains unclear. Therefore, in this study, we first determined commonly and frequently amplified genes in both small-sized lung ADCs and lung ADC cell lines. The clinical significance of gene amplification was then validated using 2 sets of early-stage lung ADC cases. One is a set of 65 small-sized lung ADCs, and the other is a set of 162 stage I lung ADCs. These analyses revealed that amplification of the MYC gene at chromosome 8q24.21 is a poor prognostic marker of patients with early-stage lung ADC.

Materials and Methods

Patients and tissues

All 254 patients with lung ADC underwent curative pulmonary resections from 1993 to 2004 at the National Cancer Center Hospital (NCCH), Tokyo, Japan. None of them received neoadjuvant therapy before surgery and chemotherapy or radiotherapy after surgery unless they relapsed, and their relapse-free survivals were followed up for at least 5 years, except for 2 patients with small-sized lung ADCs. In 92 cases of small-sized lung ADCs, cancer cells were obtained by laser capture microdissection using the PixCell Laser Capture Microdissection System (Arcturus Engineering) as previously described (17), and noncancerous lung tissues were obtained from regions greater than 5 cm from tumors with macroscopically normal morphology in the resected lobes of the lungs. Sixty-five cases were subjected to 10-K single-nucleotide polymorphism (SNP) array analysis as reported previously (12), and 60 cases were subjected to real-time genomic PCR (RT-G-PCR) analysis. Thirty-three of the 92 cases were subjected to both analyses. Small-sized lung ADCs were classified into 4 histologic types, A to D, according to the Noguchi classification (8, 9). Type A localized bronchioloalveolar carcinoma (LBAC), and type B LBAC with foci of alveolar structural collapse, are noninvasive tumors, while type C, LBAC with foci of active fibroblastic proliferation, and type D, poorly differentiated ADC, are invasive tumors. To efficiently detect the association of copy number alterations with prognosis, all type C cases with relapse and random type C cases without relapse were selected for this cohort; therefore, the relapse-free survival rate of type C cases selected was considerably lower than that of all type C cases, and the population of advanced stages (≥IA) in type C cases was higher than that in all type C cases, as previously described (12). In 162 cases of stage I lung ADCs, the cancer cells and the corresponding noncancerous cells were macrodissected. The tumors were pathologically diagnosed as being stage I according to the tumor-node-metastasis classification of malignant tumors (18). Genomic DNA was extracted as described previously, and the status of epidermal growth factor receptor (EGFR) and KRAS mutations in these tumors were previously determined (12, 17). This study was done under the approval of the Institutional Review Board of the National Cancer Center.

Cell line DNA

DNA from 40 lung ADC cell lines, listed in our recent article (19), was used for 250-K SNP array analysis.

Array hybridization and copy number analysis

Amplified loci were determined by using the GeneChip Human Mapping 10-K and 250-K SNP arrays (Affymetrix, Inc.). Methods used for array analysis were previously described (12). Copy numbers of the 65 primary tumors and 40 cell lines were determined using the Copy Number Analyzer for Affymetrix GeneChip Mapping Array (CNAG) software (20, 21).

RT-G-PCR analysis

The copy number of the MYC gene was measured by a TaqMan Copy Number Assay (Applied Biosystems). The assay kit contains a FAM dye-based assay for the MYC gene on chromosome 8 as a target locus and a VIC dye-based assay for the RPH1 gene on chromosome 14 as a reference locus. PCR was carried out in duplicate using 5 ng DNA as a template. Primer and probe concentrations were optimized for each target according to the manufacturer’s instructions. The PCR program consisted of 95°C for 15 minutes followed by 45 cycles of 95°C for 15 seconds and 60°C for 1 minute. Standard curves for the copy numbers of the
target and reference loci were generated using serially diluted (0.04–134 ng) normal Human Genomic DNA (Promega KK). Data analysis was carried out using ABI Prism 7900HT Sequence Detection Software v2.3.

Statistic analysis
Fisher’s exact test was used to assess the association of MYC amplification with clinicopathologic characteristics or mutations of the EGFR and KRAS genes. Relapse-free survival of patients with and without MYC amplification was compared by Kaplan-Meier curves and the log-rank test. The Cox proportional hazard model was used to compute univariate and multivariate HRs and a 95% CI. Statistic analyses were done using IMP software (version 5.1; SAS institute, Inc.), and a P value of less than 0.05 was considered as being statistically significant.

Results
Common and frequent amplification of the MYC gene in lung ADC
We first determined regions of somatic copy number alterations in 65 cases of small-sized ADCs by GeneChip Human Mapping 10-K SNP array analysis using the CNAG software (12, 20, 21). Regions of amplification were defined as segments of at least 5 consecutive SNP loci with an estimated copy number of 5 or more. Various chromosomal regions showed amplification in small-sized ADCs, and in particular, 11 regions on chromosomes 5p, 7p, 8q, and 14q showed amplification with high frequencies (>10%; Supplementary Fig. 1 and Supplementary Table 1A). Therefore, to define common regions of amplification in lung ADCs, we selected 40 cases of lung ADC cell lines to the GeneChip Human Mapping 250-K SNP array analysis. In accordance with the results of primary small-sized ADCs, regions on chromosomes 5p, 7p, 8q, and 14q were also frequently (>10%) amplified in these cell lines, and 13 regions on these chromosomes were defined as common regions of amplification in lung ADC cell lines (Supplementary Table 1B). Therefore, common regions of amplification in both 65 small-sized ADCs and 40 ADC cell lines were defined by a comparison of amplified segmental regions among all the samples. No region on chromosomes 5p, 7p, and 14q was commonly amplified in both primary tumors and cell lines. However, 5 regions at chromosome 8q24 were commonly amplified in both of them (Supplementary Table 1C), and the MYC gene at 8q24.21 was mapped to the common and most frequent region of amplification in lung ADC (Fig. 1A). The MYC gene was amplified in 7 (10.8%) of the 65 small-sized ADCs and in 10 (25.0%) of the 40 ADC cell lines examined. PVT1, a noncoding RNA gene, and MIR1208, a microRNA gene resided within the PVT1 locus, were mapped to another common region but less frequently amplified than the MYC gene, and no other gene, including noncoding RNA genes and microRNA genes, existed in 3 other common regions of amplification at 8q24. Accordingly, the target gene of amplification at 8q24 was defined as being the MYC gene in a set of lung ADCs analyzed in the present study. Representative results of copy number analysis for chromosome 8 are shown in Figure 1B.

Association of MYC amplification with relapse-free survival of patients with small-sized lung ADC
We next examined the association of MYC amplification with several clinicopathologic parameters in 65 small-sized ADCs (Fig. 2A). MYC amplification was not associated with age, gender, and smoking history. MYC amplification was detected in 3 of 37 stage I tumors and in one of 14 noninvasive tumors (type B in Noguchi classification), indicating the occurrence of MYC amplification in various stages of lung ADC progression, including early stages without invasion and metastasis. According to the accumulated genetic alterations, lung ADCs can be classified into 3 types: EGFR type, KRAS type, and non-EGFR/KRAS type (5, 12, 19). MYC amplification was observed in both EGFR and KRAS types, and also in non-EGFR/KRAS type. The results indicate that MYC amplification occurs in any progression stage and in any molecular pathway, irrespective of smoking history, in lung ADCs. MYC gene amplification has been shown to occur late in lung cancer progression, in particular in small cell lung cancer (SCLC) (22–25), suggesting the association of MYC amplification with clinical aggressiveness of lung ADC. Therefore, we next examined the association of MYC amplification with prognosis of ADC patients. Because, in 63 of the 65 patients with small-sized ADC, tumors were resected by surgery, no adjuvant therapy was given after surgery and their prognoses were followed-up for 5 or more years; we examined the association of MYC amplification with relapse-free survival of these 63 patients. As reported previously (8–11), the prognosis of patients with type A+B noninvasive tumors, corresponding to carcinoma in situ by the 2004 WHO classification (4), was 100% and was significantly better than that of patients with type C+D invasive tumors, and the pathologic stage was also significantly associated with prognosis (Fig. 2B and C). Importantly, MYC amplification was also associated with poor prognosis of patients with small-sized ADC (Fig. 2D). We then attempted to perform multivariate analysis with those clinicopathologic and molecular variables to define whether MYC amplification is an independent prognostic marker or not. However, it was not possible to control for Noguchi classification of tumor types because no relapse was observed among patients with type A+B noninvasive tumors. Therefore, multivariate analysis was limited to patients with type C+D invasive tumors (n = 49). In these 49 patients, statistically significant associations with relapse-free survival were observed for pathologic stage and MYC amplification (by the log-rank test in Fig. 2E and F, and by the Cox proportional hazard model in Fig. 2G). Therefore, it was indicated that MYC amplification is an independent marker of pathologic staging for relapse-free survival of patients with small-sized lung ADC. Because type A+B noninvasive tumors correspond to carcinoma
in situ and are classified into stage 0 by the 2004 WHO classification (4), it was considered to be proper to analyze only type C+D invasive tumors for the association between MYC amplification and prognosis.

Concordance of SNP array data with RT-G-PCR data for MYC amplification

For the use of MYC amplification as a prognostic marker in a clinical setting, a rapid and simple method for detection of the MYC copy number in the human genome should be applied. For this purpose, we next evaluated the MYC copy number in small-sized ADCs by RT-G-PCR analysis using a commercially available method named TaqMan Copy Number Assays, and compared the result of RT-G-PCR analysis with that of GeneChip Human Mapping 10-K SNP array analysis. Thirty three of the 65 ADCs, including 6 ADCs with MYC amplification, analyzed by the 10-K SNP arrays were subjected to RT-G-PCR analysis with 20 corresponding normal lung tissue samples (Fig. 3A). The copy number of the MYC gene in 6 ADCs with MYC amplification by 10-K SNP array analysis (mean ± SD = 1.89 ± 0.46) was significantly higher than that in the 20 normal lung tissues (mean ± SD = 1.05 ± 0.11) and 27 ADCs without MYC amplification by 10-K SNP array analysis (mean ± SD = 1.03 ± 0.28). The cut-off value of MYC amplification by the RT-G-PCR analysis was then set as 1.59 because the mean + 2SD value of 27 ADCs without MYC amplification was 1.59. All the 20 normal lung tissues and 27 ADCs without MYC amplification showed MYC copy numbers of less than 1.59, whereas 5 of the 6 ADCs with MYC amplification showed copy numbers of >1.59. In one of the 6 ADCs with MYC amplification, the control locus in the RT-G-PCR analysis also showed amplification by 10-K SNP array analysis. Therefore, it was concluded that the cut-off value of 1.59 could differentiate ADC cases with MYC amplification
from those without MYC amplification by RT-G-PCR analysis.

We then analyzed the association of MYC amplification with relapse-free survival of patients with small-sized ADC by RT-G-PCR analysis. For this study, we freshly prepared 27 small-sized ADCs and a total of 60 cases including the 33 cases described above were subjected to the analysis. The newly prepared 27 cases were either type C or type D invasive tumors. Because stage I tumors with poor prognosis were preferentially collected for the efficient detection of the association, associations of staging with relapse-free survival were weaker than the former 63 patients (Fig. 3B and C). MYC amplification was detected in 7 of the 60 cases and

Figure 2. Association of MYC amplification with relapse-free survival of 63 patients with small-sized lung adenocarcinoma. A, association of MYC amplification with clinicopathologic factors and genetic alterations. $E^{(\dagger)}$, EGFR mutation ($\dagger$); $K^{(\dagger)}$, KRAS mutation ($\dagger$). B-D, Kaplan-Meier survival curves for relapse-free survival of 63 patients according to Noguchi classification (B), pathologic stage (C), and MYC amplification (D). Kaplan-Meier survival curves for relapse-free survival of 49 patients with type C-D tumors according to pathologic stage (E) and MYC amplification (F). G, hazard ratios for relapse-free survival of 49 patients with type C-D tumors by univariate and multivariate analyses.
was significantly associated with poor prognosis of the patients by the log-rank test \( (P = 0.00058; \text{Fig. 3D}) \). Univariate \( (HR = 2.70, 95\% \text{CI} = 1.59–4.34, P = 0.00068) \) and multivariate \( (HR = 2.68, 95\% \text{CI} = 1.54–4.46, P = 0.0011) \) analyses of patients with type C+D invasive tumors also showed that MYC amplification is a prognostic marker independent of pathologic staging in small-sized ADCs (Fig. 3E–G).

### Association of MYC amplification with relapse-free survival of patients with stage I lung ADC

The above results strongly indicated that MYC amplification could also be a prognostic marker of stage I lung ADC patients. Therefore, we next investigated the association of MYC amplification with prognosis in a set of 162 stage I lung ADC cases by RT-G-PCR analysis. Those cases were randomly selected from the patients who were treated at...
NCCH during the period from 2000 to 2004, and none of the cases overlapped with the 92 cases of small-sized lung ADC analyzed above. MYC amplification was detected in 11 cases and, as in small-sized ADCs, was neither associated with age, gender, and smoking history nor with EGFR type, KRAS type, and non-EGFR/KRAS type (Fig. 4A). Therefore, the occurrence of MYC amplification in the development of lung ADCs in any molecular pathway, irrespective of smoking history, was confirmed by this study, although none of the 16 KRAS types showed MYC amplification in this set of stage I lung ADC cases.

We next examined the association of several clinical variables and genetic alterations in the EGFR, KRAS, and MYC genes with relapse-free survival of these patients (Fig. 4B and C). Age, gender, smoking history, and KRAS mutation did not show association with survival. However, MYC amplification showed significant associations by either the log-rank test ($P = 0.016$) or the univariate (HR = 1.74, 95% CI = 1.01–2.70, $P = 0.043$) and multivariate (HR = 2.10, 95% CI = 1.19–3.40, $P = 0.013$) analyses. Thus, it was concluded that MYC amplification is a prognostic marker for patients with stage I lung ADC. In this set of stage I lung ADC cases, EGFR mutations showed a marginal association with better prognosis by univariate analysis and significant association by multivariate analysis.

**Discussion**

We showed here that MYC amplification is a molecular marker for prognosis of patients with small-sized lung ADC as well as those with stage I lung ADC. Usually for these patients, no adjuvant therapy is given before or after surgery. Therefore, a few cases that received adjuvant therapies were excluded from the analysis in this study. Accordingly, the present results imply that micrometastases are often present at the time of surgical resection of the tumors with MYC amplification. For this reason, MYC amplification could be a critical genetic alteration for lung ADC cells to convert their phenotypes from nonmetastatic to metastatic ones. A recent genome-wide scanning study for gene amplification indicates that the MYC locus is the most frequently amplified region among the 3,131 cases of cancer cell genomes analyzed (16). In this study, we also found that MYC is the most frequently amplified gene

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<th>Case ( % )</th>
<th>MYC Amplification ( % )</th>
<th>$P$</th>
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<td>82 (91)</td>
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<td>E(−)/K(−)</td>
<td>56 (35)</td>
<td>3 (5)</td>
<td>53 (95)</td>
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</table>

**Figure 4.** Association of MYC amplification with relapse-free survival of patients with stage I lung adenocarcinoma. A, association of MYC amplification with clinicopathologic factors and genetic alterations. B, Kaplan-Meier survival curves for relapse-free survival of 162 patients according to MYC amplification. C, hazard ratios for relapse-free survival by univariate and multivariate analyses.
among 65 cases of small-sized lung ADCs and 40 lung ADC cell lines. Common amplification of the MYC gene in lung ADC as well as in various other types of cancers supports the importance of MYC amplification in human carcinogenesis. A recent study showed that the MYC gene is often coamplified with the PVT1 gene and the PVT1 gene is rearranged and coamplified with the CHD7 gene in SCLCs (26). However, none of the ADC tumors and none of the cell lines examined in this study showed coamplification of the CHD7 gene at 8q12 with the MYC/PVT1 loci at 8q24.21. Therefore, coamplification of the CHD7 gene with the PVT1 gene would occur rarely (or would not occur) in lung ADCs. Coamplification of the PVT1 gene with the MYC gene has been reported in several other types of human cancers, and oncogenic roles of PVT1 have been also suggested (27–30). In addition, several microRNAs, including MIR1208, are expressed from the PVT1 locus (31, 32). Therefore, it is possible that the target gene of amplification at 8q24.31 is PVT1 or MIR1208 and not MYC. Further functional studies will be required to elucidate the functional role of 8q24.31 amplification in lung ADC.

Previous genome-wide copy number analysis of lung ADC revealed that gene amplification occurs in diverse chromosomal loci and a number of candidate oncogenes, in addition to MYC, have been mapped to amplified genomic regions (13–16). In this study, frequent amplification was observed not only on chromosome 8q but also on chromosomes 5p, 7p, and 14q. The results indicate that amplification of these chromosome arms also occurs relatively early in the progression of lung ADC. Although there were no common regions of amplification on these chromosome arms in this study, TERT, EGF, and TTF1 (also called NKX2-1) were identified as candidate oncogenes amplified in lung ADC on chromosomes 5p, 7p, and 14q, respectively, in previous studies (15, 16). Therefore, we examined frequencies of TERT, EGF, and TTF1 amplifications in 65 small-sized ADCs and associations of these amplifications with prognosis of the patients. TERT, EGF, and TTF1 were amplified in 7 (10%), 4 (6%), and 8 (12%) of them. Amplification of these genes was not associated with relapse-free survival of the patients (P = 0.38, 0.60, and 0.36, respectively, by the log-rank test). These results further support that amplification of the MYC gene has better predictive value for patients’ outcome than amplification of the TERT, EGF, or TTF1 gene, although TERT and TTF1 are amplified as frequently as MYC in small-sized lung ADC.

Both small-sized ADCs and stage I ADCs are considered to be at early stages in lung ADC progression. In particular, pure BACs (corresponding to types A and B in Noguchi classification) are defined as being noninvasive carcinomas and are known to show extremely good prognosis of 100% in 5-year survival (8–11). However, in the case of invasive carcinoma even in pathologic stage I, a considerable proportion of the patients will relapse within 5 years and show poor prognosis. Therefore, a prognostic marker for stage I invasive ADCs is definitely needed for the improvement of patients’ outcome. However, at present, no clinically applicable markers are available. Therefore, we should further confirm the results of the present study by a prospective study for the introduction of MYC amplification as a molecular marker for prediction of prognosis in patients with early-stage lung ADC.

MYC is a classical oncogene, and its amplification in lung cancer was first reported in 1983 (33). Although association of MYC amplification with poor prognosis in SCLC was suggested (22), the biologic as well as clinical significance of MYC amplification in lung ADC has not been fully understood. The present result strongly indicates that MYC amplification occurs not only in late stages but also in early stages of lung ADC progression and will be a prognostic molecular marker of patients with lung ADC. MYC expression has been shown to be associated with the stemness of cancer cells (34); therefore, we should also validate the biologic significance of MYC amplification in lung ADC cells. The possibility of targeting therapy for MYC in cancer treatment has been shown recently (35). Therefore, lung ADCs will be an appropriate target of MYC-targeted therapy in clinics.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Yoko Shimada and Yuto Ishii for DNA extraction of stage I lung ADCs and Mami Ishikawa for copy number analysis of small-sized lung ADCs and lung ADC cell lines.

Grant Support

Grants-in-Aid from the Ministry of Health, Labor and Welfare for the 3rd-term Comprehensive 10-year Strategy for Cancer Control and from the Program for Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation (NIBIO10-41).

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Received September 16, 2010; revised November 14, 2010; accepted December 6, 2010; published OnlineFirst December 10, 2010.

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Clin Cancer Res; 17(6) March 15, 2011
1489

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