Prevalence, Clinicopathologic Associations, and Molecular Spectrum of ERBB2 (HER2) Tyrosine Kinase Mutations in Lung Adenocarcinomas

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Abstract

Purpose: Activating mutations in the tyrosine kinase domain of HER2 (ERBB2) have been described in a subset of lung adenocarcinomas (ADCs) and are mutually exclusive with EGFR and KRAS mutations. The prevalence, clinicopathologic characteristics, prognostic implications, and molecular heterogeneity of HER2-mutated lung ADCs are not well established in U.S. patients.

Experimental Design: Lung ADC samples (N = 1,478) were first screened for mutations in EGFR (exons 19 and 21) and KRAS (exon 2), and negative cases were then assessed for HER2 mutations (exons 19–20) using a sizing assay and mass spectrometry. Testing for additional recurrent point mutations in EGFR, KRAS, BRAF, NRAS, PIK3CA, MEK1, and AKT was conducted by mass spectrometry. ALK rearrangements and HER2 amplification were assessed by FISH.

Results: We identified 25 cases with HER2 mutations, representing 6% of EGFR/KRAS/ALK-negative specimens. Small insertions in exon 20 accounted for 96% (24/25) of the cases. Compared with insertions in EGFR exon 20, there was less variability, with 83% (20/24) being a 12 bp insertion causing duplication of amino acids YVMA at codon 775. Morphologically, 92% (23/25) were moderately or poorly differentiated ADC. HER2 mutation was not associated with concurrent HER2 amplification in 11 cases tested for both. HER2 mutations were more frequent among never-smokers (P < 0.0001) but there were no associations with sex, race, or stage.

Conclusions: HER2 mutations identify a distinct subset of lung ADCs. Given the high prevalence of lung cancer worldwide and the availability of standard and investigational therapies targeting HER2, routine clinical genotyping of lung ADC should include HER2.

Introduction

The human epidermal growth factor receptor 2 (HER2/ERBB2) is a receptor tyrosine kinase of the ERBB family which includes 3 additional members: EGFR (HER1/ERBB1), HER3 (ERBB3), and HER4 (ERBB4). Ligand binding to the extracellular domain of EGFR, HER3, and HER4, results in the formation of catalytically active homo- and heterodimers which, in turn, activate several downstream pathways involved in cellular proliferation, differentiation, migration, and apoptosis (1–3). Despite extensive structural homology with all other members of its family, both along the catalytic intracellular domain and the extracellular putative ligand-binding region, HER2 has no identified direct ligand. Instead, it functions as the preferred dimerization partner for all other ERBB family receptors (4–6). This observed superior ability for dimerization, coupled with a unique basal tyrosine kinase activity, confers to HER2 a pivotal role in signal transduction with corresponding significant roles in cancer development and progression when its function is deregulated.

Deregulation of the HER2 gene, through protein overexpression and/or gene amplification, is found in many human cancers most notably breast, ovarian, gastric, and some biologically aggressive forms of uterine carcinomas (7–10). In most cases, overexpression correlates with poor prognosis and, in breast and gastric cancers, it can also predict benefit from HER2-targeted therapy. Trastuzumab, a humanized monoclonal antibody targeting the extracellular domain of HER2, has shown significant survival advantage in the treatment of HER2 overexpressing breast cancer (8, 11) when combined with cytotoxic chemotherapy.
ERBB2 (HER2) Mutations in Lung Carcinoma

**Translational Relevance**

The incidence, clinicopathologic characteristics, and prognostic implications of activating mutations in the tyrosine kinase domain of HER2 in lung adenocarcinomas (ADCs) are not well established. The current study represents the largest assessment for HER2 mutations (N = 1,478) in predominantly Caucasian population and the most comprehensive concurrent analysis for other recurrent oncogene mutations. We show that mutations in HER2 identify a distinct subset of lung ADCs with highest prevalence among never-smokers (5%) and which are mutually exclusive with other known driver oncogene mutations, making up 6% of lung ADCs lacking EGFR, KRAS, and ALK alterations. Given the high incidence of lung ADC, it is estimated that there are between 1,000 and 2,000 patients with HER2-mutated lung ADC diagnosed every year in the United States, and their identification would allow for assignment to one of many investigational agents targeting this pathway.

Similar findings have also been recently reported in a phase II study of patients with HER2-positive gastric carcinoma (12). In contrast, whereas overexpression and amplification of HER2 has been reported in up to 1 of 3 of non–small cell lung carcinomas (NSCLCs; refs. 13, 14), statistically significant differences in survival have not been observed (15), and trials exploring the advantage of treatment with trastuzumab have shown only modest or minimal clinical benefits (16).

In 2004, activating mutations within the tyrosine kinase domain of the HER2 gene were discovered in a small subset of NSCLCs (17–22). Their prevalence is reported to be up to 4% (20, 22), and both in vitro and in vivo studies confirm the oncogenic potential of these mutations (23–25). In vitro studies have shown that tumor cells harboring the most prevalent HER2 insertion (YVMA) not only exhibit ligand-independent tyrosine phosphorylation and stronger association with downstream signal transducers that mediate cell survival and proliferative processes, but also potently induce EGFR transphosphorylation, even in the presence of a kinase-dead EGFR (23). Tumor cells harboring HER2 mutations are resistant to EGFR inhibitors but remain sensitive to both HER2 inhibitors and dual EGFR/HER2 inhibitors (25–27). The most commonly encountered mutations are in-frame insertions in exon 20, but point mutations along the tyrosine kinase domain have also been identified; all are mutually exclusive with common activating mutations in EGFR and KRAS (17, 20, 28). On the basis of published studies, the clinical and pathologic characteristics of patients with HER2 mutations have been reported to be very similar to those with EGFR mutations, being more common in women, Asians, never-smokers, and in adenocarcinoma (compared with squamous carcinoma; ref. 20). To date, however, only a few studies focusing on HER2 mutations have been published (17–22) and most were conducted predominantly in Asian patient populations. The incidence, clinicopathologic characteristics, and prognostic implications of HER2 mutant lung cancer in the U.S. population remain to be more thoroughly defined.

In the current study, we aimed to (i) determine the frequency and spectrum of HER2 mutations in a large cohort of U.S. patients with adenocarcinoma, (ii) assess the clinical and histopathologic characteristics of HER2-mutant tumors, (iii) confirm the mutually exclusive nature of mutations in other genes, including major and minor mutations in EGFR, KRAS, BRAF, NRAS, PIK3CA, MEK1, and AKT as well as ALK rearrangements, and (iv) compare the survival of patients with HER2-mutant tumors to those harboring other mutually exclusive mutations.

**Materials and Methods**

**Patient selection and mutation analysis**

Clinical cases of lung adenocarcinoma received for routine, reflex clinical EGFR and KRAS testing at Memorial Sloan-Kettering Cancer Center (New York, NY) between January 1, 2009, and December 31, 2010 were selected for the study. Hematoxylin and eosin–stained sections of formalin-fixed paraffin-embedded tissue were reviewed for each sample to identify and circle the areas of highest tumor density. Macrodissection was conducted on corresponding unstained sections to ensure at least 25% tumor content. Genomic DNA was extracted using the DNeasy Tissue kit (Qiagen) following the manufacturer’s standard protocol. Clinical testing for EGFR mutations was carried out using fragment analysis for the detection of small indels in exons 19 and 20 and the L858R mutation in exon 21 using previously described methods refs. (29, 30). KRAS testing was conducted by a combination of standard sequencing and mass spectrometry genotyping (Sequenom) based on methods previously described (31). As a part of our standard panel of mutation analysis by mass spectrometry, all samples were also concurrently tested for other recurrent point mutations in EGFR, KRAS, BRAF, NRAS, AKT, MAPK1, and PIK3CA (Supplementary Table S1; refs. 32, 33). When sufficient tissue was available, samples that were EGFR/KRAS wild-type (WT) were tested for ALK rearrangements by FISH (Vysis ALK Break Apart FISH Probe Kit) using standard protocols (Supplementary Fig. S1).

**HER2 mutation analysis**

Cases which were negative for the predominant activating EGFR (Exon 19 deletion and L858R) and KRAS (G12 and G13) mutations were selected for HER2 testing, given the known mutually exclusive nature of these mutations. HER2 molecular analysis was carried out by 2 methods: a sizing assay to detect small indels in exon 20 and a Sequenom assay panel to detect specific point mutations including L755S, D769H, V777L, and V777M. Testing by fragment analysis followed a protocol similar to EGFR testing with fluorescently labeled HER2 primers (29, 30). Briefly, a 300-bp genomic DNA fragment encompassing the entire
coding region of exon 20 was amplified using the primers FW1: 5'-GTT TG GGG TGT GTG TCT-3' and REV: 5'-Hex - CCT AGC CCC TTG TGG ACA TA-3'. PCR products were subjected to capillary electrophoresis on an ABI 3730 Genetic Analyzer (Applied Biosystems). Testing for recurrent point mutations was incorporated into the standard Sequenom testing panel with procedures as previously described. All positive cases were confirmed and further characterized by Sanger sequencing using the above primers without fluorescent label.

To confirm the mutually exclusivity of HER2 exon 20 insertions with major EGFR and KRAS mutations, as well as other rarer mutations not well represented in our cohort, we also tested a separate set of adenocarcinomas with a known positive mutation profile and sufficient DNA. Also, to also tested a separate set of adenocarcinomas with a known positive mutation profile (HER2/CEP17 ratio per cell > 2.2) confirmed the mutually exclusive nature of HER2 rearrangements and insufficient DNA.

Analysis of HER2 gene copy number alterations by FISH

Assessment of HER2 gene copy number was conducted on the same formalin-fixed paraffin-embedded specimens used for DNA extraction. The Vysis PathVysion HER2 DNA Probe Kit (Abbott Laboratories) was used following standard manufacturer's protocol. At least 40 cells were analyzed for each case by 2 reviewers and were classified according to published criteria (34, 35) as disomy, low polysomy (≤4 copies of HER2 in ≤40% of cells), high polysomy (>4 copies of HER2 in >40% of cells), or amplified (HER2/CEP17 ratio per cell ≥ 2, or homogeneously staining regions with ≥15 copies in ≥10% of the cells). Cases with a ratio between 1.8 and 2.2 were reviewed, and wider areas recounted to confirm their status as amplified or not amplified.

Statistical analysis

The association between HER2 status and clinical and biologic characteristics was analyzed by Fisher exact test. Age differences were compared using the t test for independent samples. The 2-sided significance level was set at P < 0.05.

Overall survival was calculated using the Kaplan–Meier method. Patients were followed from date of diagnosis of stage IIIb/IV disease to date of death or last follow-up. Survival data were obtained through medical records and the Social Security Death Index and were updated as of January 8, 2018. © 2012 American Association for Cancer Research. clincancerres.aacrjournals.org Downloaded from clincancerres.aacrjournals.org on January 8, 2018. © 2012 American Association for Cancer Research.
**HER2**-mutant patients presenting at age 64 or younger (64%) was greater than that of the **HER2** WT population (46%, \( P = 0.04 \)). Significantly, more never-smokers harbored **HER2** mutations (5% vs. 1%, \( P < 0.0001 \)), but there were no significant differences in sex ratios (female 2% vs. male 2%, \( P = 0.83 \)) or in the stage at presentation. **HER2** mutations were not significantly more common among Asian patients (2/61, 3%) vs. Caucasian patients (23/1290, 2%; \( P = 0.31 \)).

Comparison of **HER2** mutants versus specific molecular subsets. When the **HER2** WT group is stratified into molecular subsets (Table 1), we find that the younger age association is lost with most groups but remains significant only when compared with the cohort with **KRAS** mutations (\( P = 0.04 \)). Significant differences were identified in the smoking status of **HER2**-positive patients when compared with both **KRAS** and **BRAF** (\( P < 0.0001 \)). Similar smoking differences were observed when **HER2**-mutated patients were compared with the **EGFR**/**KRAS**/**ALK** negative and the negative for all mutations assayed groups (\( P < 0.0001 \)). In contrast, no significant differences in smoking were identified between the **HER2**-mutated and the **EGFR**-mutated groups. The stratification by molecular subtype also uncovered differences in the stage at presentation of the **HER2**-mutated group compared with both **ALK**-rearranged and **BRAF**-mutated cohorts, the latter 2 being associated with later stage (III–IV) presentation (\( P = 0.003 \) and 0.03, respectively).

**Clinical outcomes**

Because of the small sizes of stage- and mutation-specific cohorts, only overall survival was assessed. During follow-up, 468 patients presented with or developed advanced disease (stage IIIb or IV). This included 102 **EGFR**, 117 **KRAS**, 28 **ALK**, 10 **BRAF**, and 16 **HER2** patients. The median follow-up after the diagnosis of advanced disease for all patients was 19 months. The median overall survival by molecular cohort was: **HER2** 19 months, **EGFR** 30 months, **KRAS** 14 months, **ALK** 25 months, and **BRAF** 21 months. In this series, the overall survival of the **HER2** cohort did not differ significantly from the other molecularly defined cohorts (Fig. 2).
Morphologic spectrum of HER2 mutant lung adenocarcinomas

The vast majority of tumors harboring HER2 mutations (92%, 23/25) were moderate (11) to poorly (12) differentiated and most (80%, 20/25) had high-grade morphology. Eighty-percent (80%, 20/25) were tumors of mixed phenotype with papillary, acinar, solid, and micropapillary, components as the most predominant patterns. Three cases had a mucinous component. A bronchoalveolar component was present in 6 tumors, but it was minimal in most cases (67%, 4/6). Only 3 tumors showed a pure phenotype (1 papillary, 1 micropapillary, and 1 solid) but all were small samples and may reflect limited sampling. Two cases were classified as poorly differentiated adenocarcinoma, not otherwise specified because of limited sampling, both with high-grade cytologic features (Fig. 3).

HER2 gene copy alterations by FISH

Analysis for HER2 gene copy number alterations by FISH was conducted on 11 of the 25 HER2 mutated cases based on tissue availability and in 39 HER2 WT cases. None of the mutant cases showed HER2 amplification. Instead, 2 cases (18%) showed high polysomy (>4 copies of both HER2 and CEP17) and 8 (73%) had low polysomy. Among the WT group, one case was amplified (3%, 1/39) with a HER2/CEP17 ratio of 5.9. In this group, 4 cases (10%) had high polysomy and 27 (69%) had low polysomy (Table 2). Of note, the HER2-amplified case was also found to harbor an EGFR exon 19 deletion.

Discussion

The management of lung adenocarcinomas has been transformed in the past decade by the identification of key genetic alterations that activate driver oncogenes. These alterations allow the assignment of patients to targeted treatments based on the specific molecular lesions detected in their tumors.

Mutations in the HER2 gene identify a distinct subset of lung adenocarcinomas. Although less common than EGFR and KRAS, these mutations represent an additional target with already proven sensitivity to HER2 inhibitors in preclinical models (23–25, 36) and anecdotal clinical reports.
that parallel those seen with remain poorly defined. Previous studies report attributes
HER2 implications of patients each year in the United States and elsewhere.

Given the high prevalence of lung adenocarcinomas, the clinical trials specifically for this indication (36, 39, 40). Both trastuzumab and lapatinib are available and newer agents, such as dacomitinib and afatinib, are in
(37, 38). Both trastuzumab and lapatinib are available and newer agents, such as dacomitinib and afatinib, are in clinical trials specifically for this indication (36, 39, 40). Given the high prevalence of lung adenocarcinomas, the targeting of these mutations could benefit thousands of patients each year in the United States and elsewhere.

The clinicopathologic characteristics and prognostic implications of HER2-mutated lung adenocarcinoma remain poorly defined. Previous studies report attributes that parallel those seen with EGFR mutations, including associations with female sex, Asian ethnicity, never-smoker status, and adenocarcinoma subtype. Most studies, however, have been conducted in Asia. Only 2 studies have included Caucasian patients, a single study of 157 U.S. patients in whom no mutations were detected (20), and a study of 402 European patients in which a mutation rate of 2% was identified (17). To our knowledge, our study, a study of 402 European patients in which a mutation rate of 2% was identified (17). To our knowledge, our study included Caucasian patients, a single study of 157 U.S. patients in whom no mutations were detected (20), and a study of 402 European patients in which a mutation rate of 2% was identified (17). To our knowledge, our study among patients with HER2 mutations, insertions in exon 20 represented the vast majority of the alterations detected (96%, 24/25 patients). As a group, these mutations resemble activating mutations found within exon 20 of EGFR (non-T790M) which have been associated with primary resistance to both first and second generation tyrosine kinase inhibitors (41). In both cases, insertions are in-frame, ranging from 3 to 12 base pairs and confined to a short stretch within the most proximal region of the exon (between the 7th and the 12th codon of the exon). Compared with EGFR, HER2 insertions are less heterogeneous, with over 80% of cases showing the A775_G776insYVMA insertion/duplication (Fig. 4). Two of the mutations

### Table 1. Comparison of clinical characteristics of HER2 mutant patients versus other molecularly defined subsets

<table>
<thead>
<tr>
<th></th>
<th>HER2 (n = 25)</th>
<th>HER2 WT (n = 1359)</th>
<th>EGFR (n = 359)</th>
<th>KRAS (n = 495)</th>
<th>EML4-ALK (n = 35)</th>
<th>BRAF (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female/male</td>
<td>17/8</td>
<td>862/497</td>
<td>260/99</td>
<td>326/169</td>
<td>19/16</td>
<td>17/8</td>
</tr>
<tr>
<td>Median age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>64 (51–84)</td>
<td>66 (32–90)</td>
<td>66 (32–90)</td>
<td>67 (38–86)</td>
<td>56 (39–78)</td>
<td>70 (54–79)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never/smoker</td>
<td>17/8</td>
<td>340/1,019</td>
<td>192/167</td>
<td>30/465</td>
<td>21/14</td>
<td>3/22</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–II/III–IV</td>
<td>15/10</td>
<td>631/728</td>
<td>147/212</td>
<td>246/249</td>
<td>7/28</td>
<td>11/14</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian/Caucasian</td>
<td>2/23</td>
<td>59/1,267</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: P values in parentheses based on comparison with HER; only significant values are annotated.

### Table 2. HER2 copy number alterations in HER2 mutant tumors

<table>
<thead>
<tr>
<th>HER2 copy number alterations</th>
<th>HER2 mutant (n = 11)</th>
<th>HER2 WT (n = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplified</td>
<td>0</td>
<td>1 (3%)</td>
<td>NS</td>
</tr>
<tr>
<td>High polysomy</td>
<td>2 (18%)</td>
<td>4 (10%)</td>
<td>NS (P = 0.29)</td>
</tr>
<tr>
<td>Low polysomy</td>
<td>8 (73%)</td>
<td>27(69%)</td>
<td>NS</td>
</tr>
<tr>
<td>Disomy (or near disomy)</td>
<td>1 (9%)</td>
<td>7 (18%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

KRAS, BRAF, NRAS, PIK3CA, MEK1 and AKT, as well as ALK rearrangements. Additional testing of a separate set of cases known to be positive for major EGFR and KRAS further confirmed the mutually exclusive nature of these mutations. The incidence of HER2 mutations was 5% and 6% among the EGFR/KRAS-negative and the EGFR/KRAS/ALK-negative groups, respectively. On the basis of these mutually exclusive relationships, the proportion of tumors negative for EGFR, KRAS, and ALK, and the prevalence of HER2 mutations in the latter group, we estimate the overall prevalence in the entire group (1,478 patients) to be approximately 2%, which is similar to that observed by Tutill and colleagues (17), in their smaller study of European patients.
detected in our series have not been reported in previous studies (V777_G778insCG and G776C). The significance of the G776C mutation found concurrently with a 6-bp insertion is unknown.

Having confirmed the mutually exclusive nature of HER2 mutations with other driver oncopgenes, we then compared the clinical characteristics of HER2-positive patients with the WT group (cases confirmed HER2-negative by testing plus cases with mutations in another gene). In agreement with other groups (17, 20, 42), we found a significant association with never-smoker status ($P < 0.0001$). In contrast, we did not identify a significant difference by sex or race, although the low number of Asian patients limited the power of this analysis. Patients with HER2 mutations presented at a slightly younger age compared with the overall HER2 WT group and patients with KRAS mutations. While we noted differences in stage at presentation between the HER2 and both the BRAF and ALK subsets, this is difficult to explain biologically and of unclear clinical significance. In this cohort of patients with HER2-mutated lung cancers, survival was numerically similar to other molecularly defined cohorts.

Previous studies have shown that HER2 mutations are confined to the adenocarcinoma subtype of NSCLCs but specific histologic subtype associations have only been assessed by a single group (17). In this study, Buttita et al reported that HER2 mutations are significantly more frequent in ADC with bronchioloalveolar carcinoma features (43). In our study, we do not find this association. Instead we observe significant heterogeneity and a predominance of high grade morphologic features. Most tumors (82%) were of mixed phenotype with papillary, acinar, solid and micropapillary patterns representing the most common components, in decreasing order. The vast majority of tumors (92%) were moderately or poorly differentiated, as also reported in an Asian cohort (28).

In our analysis of HER2 copy number status, we did not find an association of HER2 mutations and gene amplification. While copy number gains were present in most of the cases studied, either as high or low polysomy, this finding was also present among the WT group without significant differences. Although the number of samples studied is small, this suggests that the presence of a HER2 mutation does not necessarily drive copy number gains of the mutated allele. By comparison, a recent study by Li and colleagues reports a significant association with 7 of 8 mutant tumors showing HER2 gains (4 amplification and 3 high polysomy). While copy number variations in their WT group was not reported, previous studies in unselected patients report the presence of HER2 gene amplification by FISH in up to 23% of unselected NSCLC cases (14, 34, 35), suggesting that both amplification and high copy number gains can be present in a significant proportion of cases in the absence of mutations. Although discrepancies could be attributed to the limited number of cases, the combined findings would seem to suggest that, similar to what has been found in EGFR-mutated lung cancer, amplification cannot serve as a surrogate marker for activating HER2 mutations.

In summary, mutations in the tyrosine kinase domain of HER2 identify a distinct subset of lung adenocarcinomas with a higher prevalence among never-smokers. HER2 mutations are mutually exclusive with other activating mutations and independent of HER2 gene amplification. Given the high incidence of lung adenocarcinomas, there may be several thousand patients with this uncommon, yet important, mutation diagnosed every year in the United States, and their identification will allow for assignment to one of many investigational agents targeting this pathway. Testing for activating HER2 kinase domain aberrations, both point mutations and exon 20 insertions, should therefore be incorporated into standard multiplex molecular screening in lung ADC.

Disclosure of Potential Conflicts of Interest
M.G. Kris has a commercial research grant from Pfizer, Inc and Boehringer Ingelheim and is a consultant/advisory board member of Pfizer Inc, Boehringer Ingelheim, and Genentech. No potential conflicts of interest were disclosed by the other authors.
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