Association Between Younger Age and Targetable Genomic Alterations and Prognosis in Non–Small-Cell Lung Cancer

Adrian G. Sacher, MD; Suzanne E. Dahlberg, PhD; Jennifer Heng, BS; Stacy Mach, BA; Pasi A. Jänne, MD, PhD; Geoffrey R. Oxnard, MD

**IMPORTANCE** Non–small-cell lung cancer (NSCLC) diagnosed in young patients is rare, and the genomics and clinical characteristics of this disease are poorly understood. In contrast, the diagnosis of other cancers at a young age has been demonstrated to define unique disease biology. Herein, we report on the association of young age with targetable genomic alterations and prognosis in a cohort of 2237 patients with NSCLC.

**OBJECTIVE** To determine the relationship between young age at diagnosis and the presence of a potentially targetable genomic alteration, disease prognosis, and natural history.

**DESIGN, SETTING, AND PARTICIPANTS** A cohort of all 2237 patients with NSCLC who were genotyped at the Dana-Farber Cancer Institute between January 2002 and December 2014 were identified. Tumor genotype, patient characteristics, and clinical outcomes were collected and studied at a National Cancer Institute–designated comprehensive cancer center. Multivariate logistic regression was used to analyze the relationship between age and mutation status, and multivariate Cox proportional hazard models were fitted for survival analysis.

**MAIN OUTCOMES AND MEASURES** The frequency of targetable genomic alterations by defined age categories as well as the association of these age groups with survival. Age categories used in this analysis were younger than 40, 40 to 49, 50 to 59, 60 to 69, and 70 years or older.

**RESULTS** A cohort of 2237 patients with NSCLC was studied. Of the 2237 participants, 1939 (87%) had histologically confirmed adenocarcinoma, 269 (12%) had NSCLC not otherwise specified, and 29 (1%) had squamous histologic findings; 1396 (63%) had either stage IIIB or IV cancers; and median (range) age was 62 (20-95) years. We found that gene mutations for EGFR ($P = .02$) and ALK ($P < .001$) were associated with cancer diagnosis at a younger age, and a similar trend existed for ERBB2 ($P = .15$) and ROS1 ($P = .10$) but not BRAF V600E ($P = .43$). Among patients tested for all 5 targetable genomic alterations (n = 1325), younger age was associated with an increased frequency of a targetable genotype ($P < .001$). Those diagnosed at 50 years or younger have a 59% increased likelihood of harboring a targetable genotype. While presence of a potentially targetable genomic alteration treated with a targeted agent was associated with improved survival, the youngest and oldest age groups had similarly poor outcomes even when a targetable genotype was present.

**CONCLUSIONS AND RELEVANCE** Younger age is associated with an increased likelihood of harboring a targetable genotype and is an underappreciated clinical biomarker in NSCLC. The survival of young patients with NCSLC is unexpectedly poor compared with other age groups, suggesting more aggressive disease biology. These findings underscore the importance of comprehensive genotyping, including next-generation sequencing, in younger patients with lung cancer.
Non-small-cell lung cancer (NSCLC) is increasingly understood as a heterogeneous disease, both in its clinical presentation and its genomic make-up. While older age is a commonly considered factor in selecting treatment, younger age is a relatively minor factor when planning care or therapy for patients with NSCLC. 

This is in contrast to a number of cancers where young age at diagnosis is understood to represent a distinct disease biology. For instance, breast cancer occurring in young patients has been associated with both an increased frequency of BRCA1 and BRCA2 mutations, as well as an increased likelihood of ERBB2 overexpression and triple-negative disease. 

Breast cancer in younger patients has also been demonstrated to exhibit a more aggressive disease biology and has been associated with higher mortality even after controlling for the effect of genetics and therapy. Colon cancer in young patients has been associated with higher rates of microsatellite instability and similarly demonstrates more aggressive disease biology. 

Acute lymphoblastic leukemia in older adolescents and young adults exhibits a poorer prognosis than pediatric patients but better outcomes than older age groups and may benefit from more aggressive treatment regimens.

In contrast, NSCLC occurring in young patients is a poorly studied clinical entity. The median age at diagnosis of NSCLC is 70 years and less than 5% of patients are younger than 50 years at diagnosis. Recent data have suggested that ALK- and ROSI-rearranged lung cancers are associated with a younger age at diagnosis. However, these lung cancers represent only a small portion of all NSCLC and are only 2 potentially targetable genotypes in lung cancer. A higher incidence of EGFR mutations among young patients with advanced NSCLC has also been suggested by prior small retrospective studies. More recent studies of the incidence of EGFR mutations and ALK rearrangements have suggested that age may not be as significant of a predictor of mutation status as previously surmised. 

However, studying the relationship between age and genotype in young patients is challenging given the presence of multiple confounding factors, including smoking status, sex, and race. The relative rarity of young patients with NSCLC in these studies and the low incidence of many of these targetable genomic alterations further complicates the study of this association.

We hypothesized that young age at diagnosis would define a population of NSCLC patients enriched with targetable genomic alterations. The aim of this study was to examine the relationship between young age, targetable genotypes and prognosis, as well as to establish a definition for young age which delineates this genetically and potentially biologically unique population.

Methods

The cohort for analysis was identified from an institutional database of patients with NSCLC undergoing routine clinical tumor genotyping between January 1, 2002, and January 1, 2014. Patients were eligible if they consented to allow their clinical information to be used in retrospective research studies on an institutional review board (IRB)-approved protocol (Dana-Farber/Harvard Cancer Center protocol No. 02-180) or if they were deceased and data were made available on an IRB-approved waiver of consent. The database was queried for information on age, sex, race, smoking status, date of diagnosis, histologic findings, stage, and date of death. Race was included because of the known associations between tumor genetics and patient race.

Tumor genotyping was performed per the standard clinical practice at our institutions as previously described. Briefly, testing was performed on formalin-fixed paraffin-embedded (FFPE) biopsy samples that were prescreened by board-certified pathologists. Specific genotyping methods used included validated polymerase chain reaction–based assays for EGFR and KRAS mutations; bidirectional Sanger sequencing of EGFR, KRAS, ERBB2, and BRAF; break-apart fluorescence in situ hybridization and immunohistochemical assays for ALK and ROSI; and more recently a targeted next-generation sequencing (NGS) assay including each of these genes. Standard genetic testing was performed on all available tumor specimens; however, not all assays were able to be performed on each tumor specimen owing to tissue availability. As a general practice, genotyping was performed on all patients with nonsquamous NSCLC and with sufficient tissue for testing, either as part of routine clinical care or an institutional genomic analysis protocol. Patients with squamous histology who underwent clinical genotyping based on unique clinical or pathological characteristics suggesting a possible mixed histologic findings were also included in the study.

This analysis focused on targetable genotypes for which approved targeted therapies exist or where compelling clinical trial data suggest the potential for targeted therapy. For this study, targetable genomic alterations were defined as EGFR mutations in the kinase domain, ALK rearrangements, ROSI rearrangements, ERBB2 mutations in the kinase domain.
and BRAF V600E mutations.\(^\text{39}\) As a comparison, oncogenic mutations in KRAS were also studied as a genotype that was not targetable during the study period.\(^\text{40}\) Other rare genotypes were studied more irregularly during the study period (eg, RET rearrangements) or had inadequate data regarding targetability (eg, PIK3CA mutations, non-V600E BRAF mutations) and were therefore not included in this analysis.\(^\text{33,41}\)

**Statistical Analysis**

The genotypes EGFR, KRAS, ALK, ROSI, ERBB2, and BRAF V600E were chosen because they are exclusive of each other and have been previously demonstrated not to overlap.\(^\text{28,42}\) As such, patients with missing results for some genotypes but possessing a known driver genomic alteration in 1 of these 6 genes had their missing values coded to be wild type. We used \(\chi^2\) tests to test for association between categorical variables. Multivariate logistic regression models were fitted to determine if age was an independent predictor of mutation using backward stepwise regression and including age as a continuous variable; categorical variables included never smoking status, female sex, adenocarcinoma histology, Asian race, and cancer stage in the initial models.

A composite variable using the results of EGFR, ALK, ROSI, ERBB2, and BRAF genotyping was used so that anyone with an abnormality of interest in any of these 5 genes was considered to be positive for a targetable genotype; anyone with known wild-type status across all 5 genes was considered negative for this composite variable; and patients negative for some of the genes but with incomplete genotyping for others were excluded from analysis of the composite variable. Overall survival was defined as the time from date of diagnosis of metastatic disease to date of death from any cause, and patients thought to remain alive at the time of analysis have been censored at their last follow-up date. Event-time distributions were estimated using the Kaplan-Meier method, and multivariate Cox models were used to estimate adjusted hazard ratios. The log-rank test was used to compare event-time distributions. All \(P\) values are 2 sided, and significance was defined at \(\alpha = .05\). No adjustments have been made for multiple comparisons. Age categories used in this analysis were younger than 40, 40 to 49, 50 to 59, 60 to 69, and 70 years or older. Age cut-point analysis for patients possessing a targetable genomic alteration based on the previously defined composite endpoint was performed by recursive partitioning.

**Results**

**Patient Characteristics**

A total of 2237 eligible patients with NSCLC and tumor genotyping results were identified (Table). Overall, 1939 patients (87%) had histologically confirmed adenocarcinoma; 269 patients (12%) had NSCLC not otherwise specified; and 29 patients (1%) had squamous histologic findings. Of the 2237 eligible patients, 1936 (63%) had either stage IIIB or IV cancers. There was a preponderance of female patients (n = 1379 [62%]) in our cohort, and 594 (27%) patients in our study had never smoked. Patients were primarily white (n = 1975 [90%]); the remainder were Asian (n = 98 [5%]), black (n = 87 [4%]), or Hispanic (n = 31 [1%]).

The median age of patients included in this study was 62 years (range, 20-95 years). Younger age was associated with increased likelihood of having never smoked \(P < .001\), being a female \(P = .002\), and initial presentation with stage IV disease \(P < .001\). Overall, 81 patients (4%) were diagnosed with NSCLC at age 40 or younger (Table).

**Association Between Genotype and Age**

Across the entire patient cohort, 712 patients (32%) possessed a targetable genomic alteration (ie, EGFR kinase mutation, ALK or ROSI rearrangement, ERBB2 kinase mutation, or BRAF V600E). Patients diagnosed with NSCLC at a younger age had an increased likelihood of harboring a KRAS mutation decreased with younger age at diagnosis \(P < .001\) (Figure 1) (Table). In contrast, the likelihood of harboring a KRAS mutation decreased with younger age at diagnosis \(P < .001\) (Figure 1) (Table). A multivariate analysis of the relationship between age and presence of a targetable genotype (composite variable) was then performed. As expected, smoking status \(P < .001\), female sex \(P = .02\), and Asian race \(P = .03\) were significantly associated with presence of a targetable genotype. Controlling for these factors, we found that this model maintained a significant association between age and the presence of a targetable genotype \(P = .006\) (Table). Examining the individual targetable mutations using this multivariate model, we found that only the genotype associated with a younger age at diagnosis was ALK rearrangement \(P < .001\), whereas the association between EGFR mutations and age was no longer significant \(P = .28\). In this multivariate analysis, KRAS mutations \(P = .04\) and, unexpectedly, BRAF V600E mutations \(P = .008\) were both associated with older age at diagnosis.

**Defining Criteria for Young Age at NSCLC Diagnosis**

The frequency of targetable genomic alterations across 5-year age groups was studied to look for a cut point where the likelihood of harboring a targetable genotype changes dramatically (eFigure 2 in the Supplement). An apparent drop in the likelihood of harboring a targetable alteration increased with younger age at diagnosis in patients who had undergone testing for all 5 alterations (n = 1325) \(P < .001\) (Figure 1) (eTable 1 in the Supplement). A multivariate analysis of the relationship between age and presence of a targetable genotype (composite variable) was then performed. As expected, smoking status \(P < .001\), female sex \(P = .02\), and Asian race \(P = .03\) were significantly associated with presence of a targetable genotype. Controlling for these factors, we found that this model maintained a significant association between age and the presence of a targetable genotype \(P = .006\) (eTable 1 in the Supplement). Examining the individual targetable mutations using this multivariate model, we found that only the genotype associated with a younger age at diagnosis was ALK rearrangement \(P < .001\), whereas the association between EGFR mutations and age was no longer significant \(P = .28\). In this multivariate analysis, KRAS mutations \(P = .04\) and, unexpectedly, BRAF V600E mutations \(P = .008\) were both associated with older age at diagnosis.
dently validate the age cut point observed in the data. An age cut point of 50 years was identified using this methodology with 160 patients (78%) younger than 50 years harboring a genomic alteration compared with 547 patients (49%) 50 years and older. Thus, there existed a 59% increased chance of detecting a targetable alteration in a patient younger than 50 compared with an older patient.

### Table. Patient Demographic Information and Genotype

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<th>Characteristic</th>
<th>Total, No. (%)</th>
<th>Age, No. (%), y</th>
<th>P Value</th>
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<td></td>
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<td>&lt;40 40-49 50-59</td>
<td>60-69 ≥70</td>
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<td>2237 (100)</td>
<td>81 (4) 252 (11)</td>
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<td>214 (36) 262 (38) 273 (45)</td>
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<td>383 (64) 435 (62) 337 (55)</td>
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<td>25 (32) 80 (34) 149 (26) 157 (24) 129 (23)</td>
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<td>6 (9) 28 (13) 131 (26) 197 (34) 131 (27)</td>
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<td>Nonmutant</td>
<td>1353 (73)</td>
<td>60 (91) 182 (87) 373 (74) 390 (66) 348 (73)</td>
<td>&lt;.001</td>
</tr>
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Abbreviations: NA, not applicable; NOS, not otherwise specified; NSCLC, non–small-cell lung cancer.

*Patients not tested for a given gene or with indeterminate results excluded from each subcategory.

### Survival Analysis

Given the findings that younger patients with advanced NSCLC exhibited a unique biology enriched for targetable genomic alterations, we next sought to determine whether prognosis was similarly unique. Overall survival by predefined age categories revealed the lowest median overall survival occurring for patients younger than 40 years (18.2 months; 95% CI, 13.6-
25.7 months) and those older than 70 years (13.6 months; 95% CI, 11.4-15.7 months) compared with those between 40 and 49 years of age (22.9 months; 95% CI, 19.1-28.3 months), 50 and 59 years (21.3 months; 95% CI, 18.5-25.1 months) and 60 to 69 years (18.3 months; 95% CI, 16.5-20.6 months) (P < .001). Under the hypothesis that targetable genotypes may be associated with survival, the relationship between targetable genotypes and overall survival was tested in a univariate analysis and found to be significant (P < .001) (eFigure 3 in the Supplement). Overall survival analysis by age category was explored separately in those patients with and without targetable genotypes, and a significant difference was found between age categories (P = .009) (Figure 2A) for patients harboring a targetable genotype. In this subset analysis, the lowest median overall survival was found in patients younger than 40 years (21.4 months; 95% CI, 13.6-47.3 months) and patients older than 70 years (22.3 months; 95% CI, 16.9-28.6 months). The longest median overall survival occurred among those patients between 50 and 59 years of age (35.4 months; 95% CI, 29.6-41.4 months). In contrast, no difference in overall survival was found between age categories in patients that did not harbor a targetable genotype (P = .41) (Figure 2B).

A survival analysis was then performed by Cox regression examining the effect of age on survival and controlling for the presence of a targetable genomic alteration, use of targeted therapy, metastatic disease at diagnosis, sex, histologically confirmed adenocarcinoma, presence of brain metastases, and the year of metastatic disease. This revealed that the oldest age category had a significantly poorer chance of survival (eTable 2 in the Supplement) compared with all age categories except the youngest, but there was no significant difference in overall survival between the oldest and youngest age groups (hazard ratio [HR], 0.73; 95% CI, 0.32-1.67; P = .46) (eTable 2 in the Supplement). The presence of a targetable genomic alteration that received targeted therapy was associated with improved survival in this model (HR, 0.66; P < .001), whereas a targetable alteration that did not receive targeted therapy was not (HR, 1.06; P = .71). Metastatic disease at diagnosis was also associated with poorer survival (HR, 1.48; P < .001), as was the presence of brain metastases (HR, 1.25; P < .001).

**Discussion**

This study tested the hypothesis that young age at diagnosis is an underappreciated marker of disease biology in NSCLC. Studying 5 targetable genotypes across 1325 patients, we identified with univariate and multivariate analysis that younger age at diagnosis was significantly associated with the presence of a targetable alteration. Specifically, patients diagnosed at younger than 50 years have a 59% increased likelihood of harboring a targetable genotype. This supports the proposition that NSCLC in the young may represent a biologically distinct subgroup of lung cancer that is enriched for targetable genomic alterations. Furthermore, it suggests that age...
50 years constitutes a useful age cutoff by which NSCLC in the young may be defined. This finding is consistent with previous studies demonstrating an association between young age and specific targetable genomic alterations, including EGFR, ALK, and ROS1. The findings of this study are particularly notable because recent studies have suggested that this association may be more tenuous than previously demonstrated. It is important to note that these studies have not directly addressed the frequency of such alterations by age group because of the rarity of young patients with NSCLC.

The suggestion that younger patients with NSCLC represent a genetically unique subgroup has potential implications for the treatment of lung cancer. As the list of rare but potentially targetable genomic alterations increases, the potential cost and complexity of comprehensive genetic testing will continue to grow in parallel. A recent study by Drilon et al examined the use of comprehensive genotyping with targeted NGS among patients with advanced lung adenocarcinoma and a light smoking history, another population enriched for targetable genomic alterations. This study demonstrated that comprehensive genomic profiling using NGS could detect potentially targetable alterations missed by standard genotyping in 65% of these patients, including 26% where a targeted agent based on National Comprehensive Cancer Network guidelines was readily available. This highlights that clinical characteristics can be used to better apply a tool like tumor NGS. Given our finding that patients diagnosed at a younger age are similarly enriched for targetable genotypes, it could be advocated that age at diagnosis is an appropriate clinical characteristic to consider when determining the potential use of comprehensive genotyping for a NSCLC patient. We are not suggesting substandard genotyping in older patients but rather advocating more aggressive efforts to routinely search for rare and even potentially novel targetable alterations in young patients. Because not all patients have access to comprehensive tumor genotyping, a prospective study to test the use of targeted NGS for patients younger than 40 years diagnosed with lung cancer has been initiated through a collaboration between the Addario Lung Cancer Medical Institute and Foundation Medicine (NCT02273336).

The realization that NSCLC in the young is a genetically unique disease naturally lends itself to the question of whether the natural history and underlying disease biology of NSCLC is also distinct in this subgroup. Our study has found evidence that the prognosis of patients younger than 40 years with metastatic disease is no better than that of patients older than 70 years, whereas patients in other age categories exhibit improved prognosis compared with the oldest age group. This association was found when the presence of a potentially targetable genomic alteration was controlled, which itself was associated with an improved prognosis as demonstrated in previous studies. This finding would not normally be expected if disease biology was similar across age groups, even when the small size of this patient group is considered, particularly given the markedly lower rate of comorbidities and functional impairment in younger patients. The poor survival associated with NSCLC in this age group potentially suggests that disease biology is distinctly aggressive in the youngest patients and may support the role of young age as a marker of lung cancer biology. Other factors (eg, late diagnosis, disease awareness, and financial challenges obtaining optimal medical care among young patients) represent potential contributors or alternative explanations for this phenomenon. Although the rarity of young patients with NSCLC makes such analyses challenging, further examination of the prognosis of...
young patients with NSCLC in larger cohorts of patients is warranted to better understand this phenomenon.

Although the focus of this study was young age, the incidental findings of an association between older age and BRAF V600E alterations is noteworthy. Although BRAF V600E is clearly targetable in melanoma,\textsuperscript{45} the use of BRAF inhibitors has exhibited mixed results in cancers of the colon and lung.\textsuperscript{39} Preliminary results of a phase-2 trial of dabrafenib in advanced NSCLC with a BRAF V600E mutation demonstrated a modest overall response rate of 32%, in contrast to a 53% overall response rate in melanoma and approximately 70% overall response rate with EGFR-kinase inhibitors in EGFR-mutant lung cancer.\textsuperscript{40,45,46} Of note, other non-V600E BRAF mutations may not be targetable at all.\textsuperscript{51} These characteristics suggest that BRAF V600E may be less easily targeted in NSCLC compared with other rare genotypes like ALK and ROS1.

In interpreting these findings, several limitations inherent in this study must be considered. Our data were retrospective, and we had limited comprehensive data on individual patient treatment. The patients included in this study are drawn from a single institution and are subject to referral bias. Notably, the overall rate of targetable genomic alterations was higher in the study population than expected from the general population. Although genetic testing was performed based on institutional standard of care for all patients, this standard has evolved over time and was limited by the availability of tissue for comprehensive genotyping. Thus, all patients in this study did not undergo identical genotyping, and genotyping data were not comprehensive for all patients. A composite end point examining patients who had undergone comprehensive genetic testing was used to account for these differences.

**Conclusions**

Despite the aforementioned limitations, the findings of this study expand the current understanding of the genetics and biology of lung cancer in young patients. These patients possess a uniquely high incidence of targetable genomic alterations paired with an unexpectedly poor prognosis. This combination of opportunity and risk defines the treatment of NSCLC in young patients and requires unique therapeutic and research strategies. These data suggest that exhaustive genotyping methods such as NGS should be used when available for young patients with lung cancer to detect targetable alterations that may guide therapy.\textsuperscript{44} These methods may also facilitate detection of rare uncharacterized genomic drivers that may become targets in the future. Such an approach will both maximize the chance of these young patients having access to the most appropriate targeted therapies and provide more comprehensive knowledge of the genomics of lung cancer in the young.

**References**


