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Tumor biomarker testing in non-small-cell lung cancer: A decade of change

Paul A. VanderLaan[a,1], Deepa Rangachari[b,1], Adnan Majid[b,c], Mihir S. Parikh[b,c], Sidharta P. Gangadharan[c], Michael S. Kent[c], Danielle C. McDonald[b], Mark S. Huberman[b], Susumu S. Kobayashi[b], Daniel B. Costa[b,*]

[a] Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States
[b] Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States
[c] Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States

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ABSTRACT

Introduction: Although a growing list of essential genomic/immune-based biomarkers are linked to approved non-small-cell lung cancer (NSCLC) therapies worldwide, few reports have detailed the evolution of NSCLC predictive biomarker assessment in routine clinical practice.

Methods: We retrospectively reviewed the first one thousand plus NSCLC patient specimens from our institution analyzed for predictive biomarkers from 2004 to 2017 and evaluated patterns of testing as well as correlation with clinical-pathologic characteristics.

Results: The majority of 1009 NSCLC patients had advanced stages of adenocarcinoma with most tissues obtained from the lung, mediastinal/hilar nodes, or pleura. The majority of testing was performed on cytology or small biopsy specimens. All were tested for *EGFR* mutations, 895 for *ALK* rearrangement, 841 for *KRAS* mutation, 537 for *ROS1* rearrangement, and 179 using comprehensive genomic profiling. Implementation of near-universal genomic biomarker testing at our institution for *EGFR*, *ALK*, *ROS1* and PD-L1 all occurred within the first year following evidence of clinical activity or regulatory body approval of an associated inhibitor. The overall testing failure rate after use of the best specimen for the most common tests was ≤5.5%. A quarter of tumors had a driver oncogene identified (*EGFR/ALK/ROS1/BRAF* V600E) with an approved oral targeted therapy, with the highest prevalence in those patients with no or light (≤15 pack-years) history of tobacco use.

Conclusions: Tumor biomarker testing using clinical NSCLC specimens in routine oncologic care evolves rapidly following approval of targeted therapies linked to diagnostic assays. Our practice's decade plus experience highlights the rapid evolution of biomarker testing and confirms the therapeutic relevance of such testing in all patients—particularly those patients with light/no history of tobacco use.

1. Introduction

As recently as a decade ago, the management of advanced non-small-cell lung cancer (NSCLC) was relatively uniform, with limited/absent ability to optimally match patients with best selected systemic therapies using tumor-based predictive biomarkers. Much has changed since then, with tumor genomic and/or immunologic biomarker testing now imperative in the initial assessment and management of advanced NSCLC, particularly adenocarcinomas. The growing list of essential biomarkers that are linked to approved therapies worldwide include: epidermal growth factor receptor (*EGFR*) gene mutations, anaplastic lymphoma receptor tyrosine kinase (*ALK*) gene rearrangements, ROS proto-oncogene 1 receptor tyrosine kinase (*ROS1*) gene rearrangements, B-Raf proto-oncogene serine/threonine kinase (*BRAF*) V600E gene mutations, and programmed death-ligand 1 (PD-L1) expression using immunohistochemistry (IHC). In addition, the rapid evolution of tumor genotyping platforms with the advent of commercially-available comprehensive genomic profiling sequencing technologies has allowed for the identification of other potentially actionable driver oncogenes such as: MET proto-oncogene receptor tyrosine kinase (*MET*) gene mutations or amplification, Erb-B2 receptor tyrosine kinase 2 (*ERBB2*) gene mutations and amplifications, Ret proto-oncogene (*RET*) gene rearrangements, and neurotrophic receptor tyrosine kinase (*NTRK*) gene rearrangements among others. However, the most common genomic events in lung cancer – tumor protein P53 (TP53) and KRAS proto-oncogene GTPase (*KRAS*) gene mutations – remain elusive

* Corresponding author at: Division of Hematology/Oncology, Beth Israel Deaconess Medical Center, 330 Brookline Av., Boston, MA, United States.
E-mail address: dbcosta@bidmc.harvard.edu (D.B. Costa).
[1] These authors contributed equally.

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drug targets.

The rapid pace of drug approvals with matched companion diagnostic assays has been documented in intermittent snapshots focusing on a particular year, technology, or therapeutic agent. Few, if any, reports have described the evolution of biomarker assessment in routine clinical practice. The Cancer Genome Atlas (TCGA) dataset represents the most comprehensive genomic profiling efforts in NSCLC to date; however, specimens analyzed were from surgically-resected tumors and thus may not fully capture the process and outcomes of tumor genomic profiling in de novo advanced/recurrent metastatic disease, where genomic profiling and therapeutic stratification is often accomplished using much smaller pathologic specimens from metastatic sites of disease. Therefore, we sought to compile our medical center's decade plus evolving experience with diagnostic tumor-based predictive biomarker testing in routine clinical care in order to provide a historical perspective on and highlight future opportunities for the implementation of precision oncology into thoracic oncology clinics.

2. Methods

2.1. Tumor and data collection

Patient and tumor specimen pairs diagnosed and/or followed at Beth Israel Deaconess Medical Center (BIDMC) with a diagnosis of NSCLC were recorded through an ongoing Institutional Review Board-approved study. The genomic cohort of this report was designed to match evolving evidence-based genomic biomarker testing in advanced NSCLC. *EGFR* genotyping, either through single gene assay or next generation sequencing (NGS), as the initial predictive biomarker receiving evidence-base status was a pre-requisite for initial inclusion of our tumor-patient pairs [1,2]. As such, this design results in a skewing of the data towards testing in non-squamous tumors [1,2]. When multiple tumors were tested, only the best available diagnostic specimen for testing was entered. Clinical-pathologic data, tumor genotype, and other tumor biomarkers were obtained from retrospective electronic chart extraction. Data was managed using the REDCap electronic data capture held at BIDMC. The dates for data assessment for this study spanned from January 1st, 2004 through April 19th, 2017.

2.2. Tumor genomic analyses and other biomarker tests

Tumor genotype was performed by analyzing *EGFR* (at least Sanger sequencing of exons 18–21 until 2016 or multiplex PCR for common exon 18–21 mutations since 2016), *ALK* (fluorescence in situ hybridization [FISH] break-apart probe, IHC, or NGS), *ROS1* (FISH break-apart probe, IHC, or NGS), *KRAS* (sequencing of codons 12–13 or NGS), *BRAF* (sequencing of exon 15 or NGS) in tumor samples using a commercial vendor, as described previously [1]. NGS-based comprehensive genomic profiling and other FISH-based assays were evaluated using different commercially-available assays as described previously [2]. PD-L1 IHC testing was performed and interpreted by a commercial vendor using the PD-L1 clone 22C3 pharmDx kit as described previously [3].

2.3. Statistical methods

Fisher's exact test was used to compare categorical variables. All *p*-values reported are two-sided, and tests were conducted at the 0.05 significance level.

3. Results

3.1. Patient and tumor characteristics

The majority of patients in our cohort with NSCLC were older than 65 years, more frequently women, of White self-reported race, and former smokers (median 30 pack-years). Their tumors were most often of advanced stages with adenocarcinoma histology, obtained from thoracic sites (lung, mediastinal nodes, or pleura), and collected by minimally invasive techniques (small biopsies or needle aspirates/fluids made into formalin fixed paraffin embedded cell blocks). However, the studied population broadly includes a diverse and representative patient population (Table 1). The most frequent biomarker tested for was *EGFR* mutation at 100% testing rate, as this was an initial prerequisite for inclusion at the inception of this cohort in 2004 (Table 1). *ALK* rearrangement testing was ordered in 88.7% of cases, *KRAS* mutation testing in 83.3%, *ROS1* rearrangement testing in 53.2%, and NGS-based testing and/or additional genotyping in 17.7% of tumors (Table 1).

Table 1
Baseline Clinical, Pathologic, and Biomarker Testing Characteristics of Non-Small Cell Lung Carcinomas from 2004 to 2017.

Age at time of tissue acquisition	
Median years-old (range)	66 (27–92)
Gender	
Women n (%)	594 (58.9%)
Men n (%)	415 (41.1%)
Race n (%)	
White	789 (78.2%)
Asian	108 (10.7%)
Black	74 (7.3%)
Other/Multiple	38 (3.7%)
Ethnicity n (%)	
Non-Hispanic	980 (97.1%)
Hispanic	29 (2.9%)
Smoking status n (%)	
Current smoker	240 (23.8%)
Former smoker	529 (52.5%)
Never smoker	238 (23.6%)
Pack-years smoking	
Median (range)	30 (0–240)
Stage at tumor analyses n (%)	
I	47 (4.7%)
II	67 (6.7%)
III	145 (14.4%)
recurrent	61 (6.1%)
IV	687 (68.2%)
Histology n (%)	
Adenocarcinoma	899 (89.1%)
NSCLC (NOS)	55 (5.5%)
Squamous cell carcinoma	38 (3.8%)
Other	17 (1.7%)
Type of tissue n (%)	
Surgical specimen	359 (35.6%)
Small biopsy	264 (26.2%)
Cytology block from aspirate/fluid	385 (38.2%)
Anatomic site of tissue acquisition n (%)	
Lung	445 (44.1%)
Mediastinal/hilar lymph node	224 (22.2%)
Pleura	132 (13.1%)
Soft tissue/bone	57 (5.6%)
Brain	53 (5.3%)
Liver	31 (3.1%)
Extra-thoracic lymph node	29 (2.9%)
Adrenal	8 (0.8%)
Other	30 (3.0%)
Tumor biomarker testing n (%, from total cases)	
EGFR mutation (exons 18–21)	1009 (100%)
ALK rearrangement (FISH, IHC or NGS)	895 (88.7%)
ROS1 rearrangement (FISH, IHC or NGS)	537 (53.2%)
KRAS mutation	841 (83.3%)
BRAF mutation	143 (14.2%)
ERBB2 mutation	144 (14.3%)
NGS-based testing/other technology	179 (17.7%)