original contributions

Evaluation of Omics-Based Strategies for the Management of Advanced Lung Cancer

Ravi Salgia, MD, PhD[1]; Isa Mambetsariev, BA[1]; Rebecca Pharaon, BA[1]; Jeremy Fricke, BS[1]; Angel Ray Baroz, BS[1]; Iztok Hozo, PhD[2]; Chen Chen, MS[3]; Marianna Koczywas, MD[1]; Erminia Massarelli, MD, PhD[1]; Karen Reckamp, MD, MS[1,4]; and Benjamin Djulbegovic, MD, PhD[5]

QUESTION ASKED: Does omic-informed therapy decision-making improve survival in patients with advanced non–small-cell lung cancer?

SUMMARY ANSWER: A fast-and-frugal decision tree (FFT) model was developed and showed high predictive value regarding decisions to use tyrosine kinase inhibitor (TKI) targeted therapy. We also found a significant correlation with survival benefit with the omics-driven therapeutic strategy for progression-free survival (PFS; hazard ratio [HR], 0.56; 95% CI, 0.42 to 0.74; $P < .001$) and overall survival (OS; HR, 0.51; 95% CI, 0.36 to 0.71; $P < .001$) as compared with standard therapeutic options.

WHAT WE DID: A cohort of patients (N = 798) with lung adenocarcinoma at a single academic site was evaluated for their molecular testing and for therapeutic decision-making using an FFT framework.

WHAT WE FOUND: A FFT framework can be used to evaluate the accuracy of the management strategies in oncology. Our study shows that omic-informed therapy decision-making was associated with improvement in PFS and OS in metastatic adenocarcinoma of lungs.

BIAS, CONFOUNDING FACTORS: This was a retrospective study performed at a single institution evaluating patients of 4 academic physicians who specialize in thoracic oncology. The relatively small sample size of the study is also a limiting factor preventing additional validation of the model.

REAL-LIFE IMPLICATIONS: The standardized FFT framework can enable oncologists to evaluate their management strategies in their own cohorts of patients in terms of the effects on health outcomes and the utility of molecular testing when making therapeutic decisions. The distinct improvement in PFS and OS due to omic-informed therapy may influence oncologists to consider TKIs as the preferred therapeutic option.

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ASSOCIATED CONTENT

Data Supplement

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VALUE IN CANCER CARE

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abstract

PURPOSE Omic-informed therapy is being used more frequently for patients with non–small-cell lung cancer (NSCLC) being treated on the basis of evidence-based decision-making. However, there is a lack of a standardized framework to evaluate those decisions and understand the association between omics-based management strategies and survival among patients. Therefore, we compared outcomes between patients with lung adenocarcinoma who received omics-driven targeted therapy versus patients who received standard therapeutic options.

PATIENTS AND METHODS This was a retrospective study of patients with advanced NSCLC adenocarcinoma (N = 798) at City of Hope who received genomic sequencing at the behest of their treating oncologists. A thoracic oncology registry was used as a clinicogenomic database to track patient outcomes.

RESULTS Of 798 individuals with advanced NSCLC (median age, 65 years [range, 22-99 years]; 60% white; 50% with a history of smoking), 662 patients (83%) had molecular testing and 439 (55%) received targeted therapy on the basis of the omic-data. A fast-and-frugal decision tree (FFT) model was developed to evaluate the impact of omics-based strategy on decision-making, progression-free survival (PFS), and overall survival (OS). We calculated that the overall positive predictive value of the entire FFT strategy for predicting decisions regarding the use of tyrosine kinase inhibitor–based targeted therapy was 88% and the negative predictive value was 96%. In an adjusted Cox regression analysis, there was a significant correlation with survival benefit with the FFT omics-driven therapeutic strategy for both PFS (hazard ratio [HR], 0.56; 95% CI, 0.42 to 0.74; $P < .001$) and OS (HR, 0.51; 95% CI, 0.36 to 0.71; $P < .001$) as compared with standard therapeutic options.

CONCLUSION Among patients with advanced NSCLC who received care in the academic oncology setting, omics-driven therapy decisions directly informed treatment in patients and was correlated with better OS and PFS.

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INTRODUCTION

Targeted therapy is a promising treatment that has revolutionized the management of lung cancer, a leading cause of cancer mortality in the United States. However, although randomized controlled trials (RCTs) have shown improvement in progression-free survival (PFS) with tyrosine kinase inhibitor (TKI)-based targeted therapy for genes such as epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*) rearrangements, b-raf proto-oncogene (*BRAF*) V600E alterations, ros proto-oncogene 1 (*ROS-1*) rearrangements, and neurotrophic receptor tyrosine kinase (*NTRK*) fusions, the same has not been proven for overall survival (OS) as compared with standard therapy.[1-5] These RCTs evaluated single-agent TKIs in the front-line setting, but real-world oncology practice is complicated further with several lines of therapy. Many patients typically receive serial TKIs during the course of their treatment, which is impossible to evaluate for PFS, and OS evaluation of these patients is not commonly performed. Testing for alterations with therapies approved by the US Food and Drug Administration (FDA) is also now routinely done in practice as part of a molecular testing panel, and this practice is endorsed by the National Comprehensive Cancer Network (NCCN), which has developed clinical pathways and guidelines to direct oncologists to proper genomic treatment management.[1,6,7] Widespread use

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of next-generation sequencing (NGS) and the availability of targeted therapies in the clinics have complicated lung cancer treatment decision-making, with various national guidelines[8] and commercial pathways[9-11] coming to fruition to guide patient care. However, these guidelines and pathways are developed in "theory-free" environments,[12] precluding evaluation of the accuracy of the use of NGS results and proper assignment of patients to appropriate targeted therapies informed by these guidelines and pathways. We recently proposed the use of fast-and-frugal decision trees (FFTs) as a theoretical framework for constructing clinical pathways to enable us to better assess the accuracy and the impact of the recommended management strategies on important health outcomes.[12] Therefore, to address the clinical utility of omics-driven pathways and guidelines in the management of lung cancer, we constructed FFTs to provide a theoretical framework that calculates the accuracy of appropriate TKI selection based on a given mutation, as well as the impact this has on long-term outcomes.

METHODS

Patients

Patients (N = 798) at City of Hope (COH) who had pathology-confirmed metastatic lung adenocarcinoma were enrolled in this analysis and evaluated from 2008 to 2016. The data were collected between 2016 and 2018 and a retrospective chart review was performed. All patients in the study had stage IV disease and their date of diagnosis was recorded as the time of metastasis diagnosis. Patients had molecular testing performed at the discretion of their primary clinical provider, using clinically available molecular testing platforms. However, not all patients were tested on the same panel because of the variability of the treating oncologist and the type of testing available when the testing was ordered. The various NGS platforms of testing included (1) FoundationOne (Foundation Medicine, Cambridge, MA), (2) Onco48 (COH, Duarte, CA), (3) Response DX: Lung (Cancer Genetics, Los Angeles, CA), (4) LabCorp (LabCorp, Burlington, NC), (5) OncoComplete (COH), (6) Caris (Caris Life Sciences, Dallas, TX), (7) MD Anderson (MD Anderson, Houston, TX), (8) Mayo Clinic (Mayo Clinic, Rochester, MN), (9) Hopeseq Lung (COH), (10) Guardant 360 (Guardant Health, Redwood City, CA), and (11) bioT3 (bioTheranostics, San Diego, CA). Single-gene testing results were also available and performed with fluorescent in situ hybridization, immunohistochemistry, Sanger sequencing, or NGS by various pathology laboratories for alternations in the following genes: *EGFR*, *ALK*, *ROS1*, *KRAS*, *BRAF*, *MET*, and *RET*.

Data Source

A thoracic oncology registry (THOR) included de-identified patient data obtained under an institutional review board–approved protocol (No. 18008) with a waiver of informed consent. The study was approved by the ethics review boards and in accord with an assurance filed with and approved by the Department of Health and Human Services at the COH and was conducted according to the Declaration of Helsinki. THOR encompasses the demographically diverse population of patients at COH. The patients were all treated at the COH academic site by 4 physicians with a focus on thoracic oncology. Data collected included patient demographics, stage, age at diagnosis, race and ethnicity, smoking history, date of diagnosis of metastatic disease, metastatic sites, treatment dates, dates of progression, date of death or of last contact, histology, molecular testing results, vital status at last contact, and overall survival (OS). Molecular testing results were abstracted from sequencing reports in patients' charts. Only patients with stage IV disease who had a confirmed diagnosis of metastatic disease were included in this study.

Decision-Making Analysis: Clinical Practice Guidelines, Pathways, and FFTs

Clinical practice guidelines, such as those from the NCCN, are commonly used to aid decision-making. They are often converted into easy-to-follow algorithms, flow-charts, or clinical pathways. Pathways are typically ad hoc developed constructs by experts in an unsystematic, "theory-free" environment, which, in turn, precludes the quantitative evaluation of the outcomes based on the management strategies recommended by guidelines and pathways. The quantitative analysis of the accuracy of clinical management strategies (eg, whether the recommendation was true positive or negative) and assessment of its impact on health outcome is possible by converting pathways into FFT heuristics.[12] FFTs are highly effective, simple decision trees composed of sequentially ordered cues (tests) and binary (yes or no) decisions formulated via a series of if-then statements.[13] The binary (yes or no) responses determine the ratio between false-negative and false-positive recommendations, which, in turn, allow the application of Bayesian methods to calculate the accuracy of the entire FFT (ie, the entire clinical management strategy).[13]

Statistical Analysis

We first determined positive and negative predictive values related to the choice of appropriate targeted therapy (ie, whether management was based solely on available mutations, in which case targeted therapy was chosen or was affected by other factors prompting the use of chemotherapy [ie, nontarget therapy]). We then calculated survival and PFS as a function of the management driven by targeted versus nontargeted therapy. PFS was determined on the basis of physician notes from the medical records. Survival and PFS estimates for the study's patients were generated using the Kaplan-Meier method supplemented by a multivariable Cox regression model to adjust the analysis for other relevant clinical factors. The distribution of cohort characteristics and the type of treatment

assignment between targeted therapy and nontargeted therapy groups were compared using χ^2 tests.

RESULTS

The clinical and demographic features of all patients included in this analysis are described in Table 1. In this study, 798 individuals with lung adenocarcinoma were identified in THOR who were treated or were intended to be treated (before their death or hospice care) at COH. The median age at metastatic diagnosis was 65 years (range, 22-99 years) for the entire cohort. The majority of patients were female (56%), the major race groups were White (60%), Asian (32%), and Black (3%); and 398 patients (50%) had a history of smoking, among whom 164 (21%) had a history of > 30 pack-years. For the targeted-therapy group, the majority of patients were female (62%), never smokers (68% *v* 28% in nontargeted-therapy group), and there was a distinctly high percentage of Asians (44%) as compared with 17% Asian patients in the nontargeted-therapy decision group.

The breakdown of NGS testing and the distribution of targeted therapy and nontargeted therapy across the different genes is shown in Figure 1. The most common alterations were in *EGFR* (47%), and these patients mostly were treated with erlotinib (68%; Data Supplement, online only). Of the 662 patients who underwent molecular testing, 485 (73%) had an alteration detected with an available FDA-approved or clinically significant

TABLE 1. Patient Characteristics

Characteristic	Total, No. (%)	Decision (%)		*P*	χ^2
		Targeted Therapy	Nontargeted Therapy		
Patients	798 (100)	439 (55)	359 (45)	NA	NA
Sex					
Female	448 (56)	274 (62)	174 (48)	< .001	15.60
Male	350 (44)	165 (38)	185 (52)		
Age at diagnosis, median, years	65	62	68	NA	NA
Race					
Black	24 (3)	9 (2)	15 (4)	< .001	68.78
Asian	256 (32)	195 (44)	61 (17)		
White	477 (60)	216 (49)	261 (73)		
Other	28 (3)	13 (3)	15 (4)		
Unknown/declined to answer	13 (2)	6 (2)	7 (2)		
Smoking status					
Never smoker	400 (50)	298 (68)	102 (28)	< .001	123.07
Former smoker	398 (50)	141 (32)	257 (72)		
No. of pack-years smoked					
< 10	100	59	41	< .001	69.24
10-29	129	59	70		
≥ 30	164	20	144		
Driver oncogene					
EGFR	377 (47)	340 (77)	37 (10)	< .001	603.67
ALK	64 (8)	62 (14)	2 (1)		
BRAF	11 (1.5)	4 (1)	7 (2)		
RET	8 (1)	2 (1)	6 (2)		
ROS-1	10 (1.5)	10 (2)	0 (0)		
MET	15 (2)	9 (2)	6 (2)		
ERBB2	21 (3)	12 (3)	9 (2)		
KRAS	123 (15)	0 (0)	123 (34)		
Other	33 (4)	0 (0)	33 (9)		
None	136 (17)	0 (0)	136 (38)		

Abbreviation: NA, not applicable.

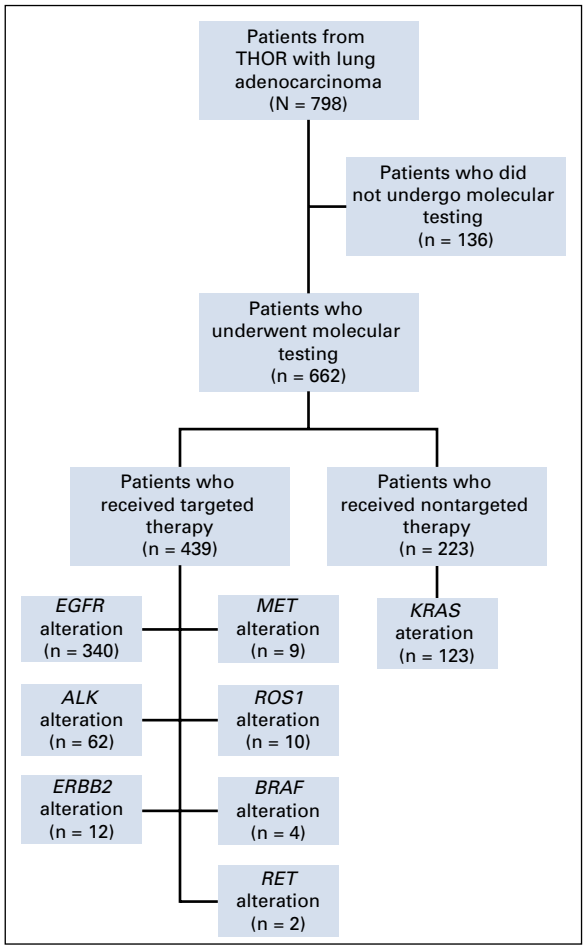

FIG 1. Flow diagram for patient participation. THOR, thoracic oncology registry.

therapy and 88% of the patients (n = 427 of 485) were appropriately matched to a targeted therapy based on the oncologist's decision. Overall, 90.18% of patients (n = 340 of 377) with an *EGFR* mutation, 96.87% of patients (n = 62 of 64) with an *ALK* rearrangement, and 100% of patients (n = 10 of 10) with a *ROS1* fusion were appropriately treated with targeted therapy based on their mutational status. Similar rates were not observed in *BRAF* V600E (36.6%; n = 4 of 11), *MET* exon 14 (59.99%; n = 9 of 15), or *RET* fusion (24.98%; n = 2 of 8); Fig 1).

Although stage IV lung adenocarcinoma with *MET* exon 14 alterations, *ERBB2* mutations, and *RET* fusions did not have an FDA-approved therapy at the time of our analysis, which is common in the real-world, off-label use in oncology practice, information related to these mutations informed treatment decisions in our cohort. Alternative therapeutic options for patients who had actionable alterations, such as in *EGFR*, *ALK*, and *BRAF*, included chemotherapy, immunotherapy, palliative care, hospice, among others (Data Supplement). The majority of patients with a nontargeted-therapy decision had a *KRAS* alteration (n = 123 of 359; 34%) or no molecular testing performed (n = 136 of 359; 38%) and were treated with chemotherapy (54%) or immunotherapy (13% single; 5% combination).

FFT for lung Cancer Management

Figure 2 shows FFT representing a comprehensive strategy for the management of metastatic lung cancer based on molecular testing and administration of targeted therapy. The overall positive predictive value of our FFT for predicting decisions regarding the use of TKI targeted therapy was 88% and the negative predictive value was 96%, suggesting that lung cancer management strategies are almost entirely driven by the availability of targeted therapy and other clinical factors played a relatively minor role.

Impact of FFT-Driven Targeted Therapy on Survival and PFS

In an intention-to-treat analysis, the targeted-therapy treatment decision was correlated with survival benefit as compared with nontargeted-therapy decisions. FFT-based targeted-therapy decision-making showed a significant benefit, with a median survival of 38 months as compared with 26 months in the nontargeted-therapy decision-making group ($P < .001$; Fig 3A). This was also evident in the PFS analysis, where patients in the targeted-therapy decision-making group had a median survival of 9 months, as compared with 5 months in the other group ($P < .001$; Fig 3B). In the unadjusted Cox regression analysis, the hazard ratio (HR) was 0.53 (95% CI, 0.43 to 0.65; $P < .001$) for OS and 0.54 (95% CI, 0.45 to 0.64; $P < .001$) for PFS, both favoring better outcomes with the FFT-driven therapy decision (Data Supplement). An adjusted Cox regression analysis demonstrated that, as expected, OS benefits were associated with age (HR, 1.03; 95% CI, 1.01 to 1.05; $P < .001$), with younger patients faring better. More importantly, OS was improved with the FFT-driven therapeutic strategy (HR, 0.51; 95% CI, 0.36 to 0.71; $P < .001$; Data Supplement). However, in the PFS adjusted Cox analysis, the FFT-driven therapy decision was the only significant variable (HR, 0.56; 95% CI, 0.42 to 0.74; $P < .001$; Data Supplement).

DISCUSSION

Overall, patients who received targeted therapy had improved short-term PFS long-term OS when compared with patients who received a nontargeted standard-of-care therapy. This survival advantage was correctly predicted by our FFT analysis, especially when taking into account the entire treatment management plan, which used a number of cues. Although targeted therapy has been shown in several RCTs to have superior PFS,[14-18] the same has not been proven for OS. This is partly because the advantage of treatment effects related to PFS is diluted by crossover or subsequent therapies.[19] However, statistically proven incremental gains in OS are difficult to achieve without negative effects on quality of life.[19] Although first-generation TKIs such as geftinib and erlotinib showed minimal median

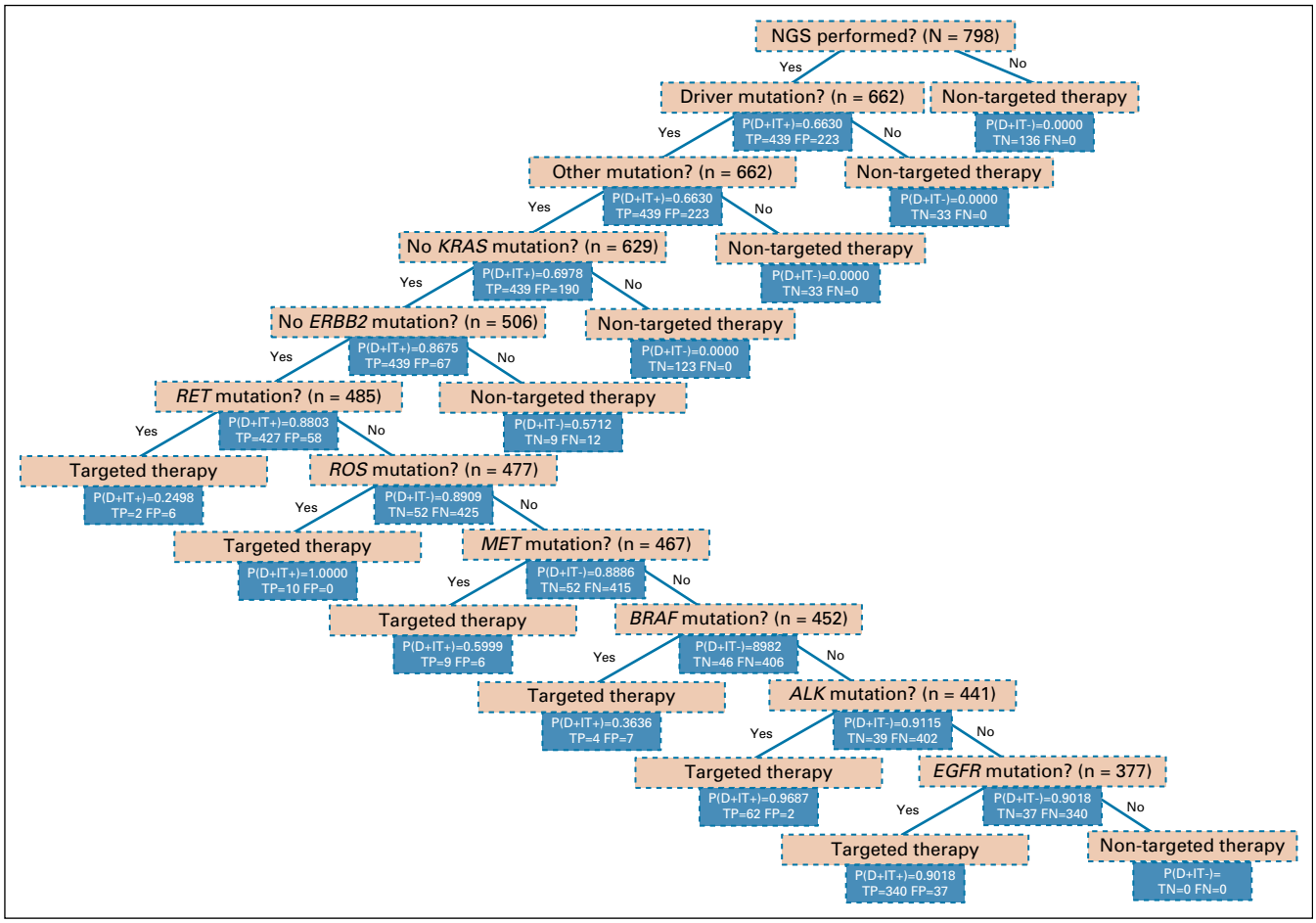

FIG 2. A model fast-and frugal decision tree (FFT) showing cues that represent a comprehensive management strategy for lung cancer decision-making based on molecular testing and administration of targeted therapy. An FFT comprises sequentially ordered cues where cues (eg, was next-generation sequencing [NGS] performed?) and accompanying decisions (eg, targeted therapy *v* nontargeted therapy) are binary (yes or no), thus we can frame their relationship with "if-then" statements. In this example, if a patient had an *EGFR* mutation, they would be given targeted therapy. Furthermore, the FFT also evaluates whether the decision made was a true positive (TP) or a false positive (FP), based on the detected alteration. P(D+IT+), probability of selecting targeted therapy (ie, probability of selection of a tyrosine kinase inhibitor [TKI] given a positive mutation [positive predictive value]); P(D+IT−), probability of selecting nontargeted therapy (ie, probability of selecting a non-TKI therapy given the absence of mutation). The figure shows the predictive value after using each cue (mutation). Using Bayes formula for taking into consideration conditional dependency of cues, we calculated that the overall positive predictive value of the entire FFT strategy for predicting decisions regarding the use of TKI targeted therapy was 88%, whereas the negative predictive value (NPV) was 96%.[12,13] FN, false negative; FP, false positive.

OS improvements, more mature data from gefitinib and erlotinib trials showed that patients who received sequential combination of EGFR-TKI and chemotherapy had significantly improved OS, suggesting that TKI-related improvement in OS lies in sequential therapy.[2,20] Furthermore, recent trials, including the FLAURA trial, have shown incremental improvements in OS alongside improvements in quality of life, as compared with first-generation TKIs.[21] However, the ARCHER 1050 trial showed that although OS was improved with dacomitinib compared with gefitinib, the improvements in quality of life were only seen in patients treated with geftinib.[22,23] We had previously shown in a retrospective meta-analysis of > 1,000 clinical trials that enrolled > 80,000 patients with oncologic malignancies that the long-term outcomes in patients with personalized treatment strategies were superior to those in patients in nonpersonalized therapy arms.[24-28] However, to our knowledge, this is the first formal study that applied a standardized theoretical framework to evaluate lung cancer decision-making demonstrating that an omic-based management strategy leads to superior outcomes compared with standard chemotherapy or immunotherapy (ie, non–omics-based treatment). Therefore, we believe the widespread availability of NGS testing would improve outcomes beyond our single-institution experience. Indeed, we had previously shown that adherence to clinical guidelines improves biomarker testing and appropriate first-line therapy in academic and community settings.[11,29] In our current study, overall testing rates for *ALK*, *EGFR*, and other actionable mutations was 83% (n = 662 of 798). The

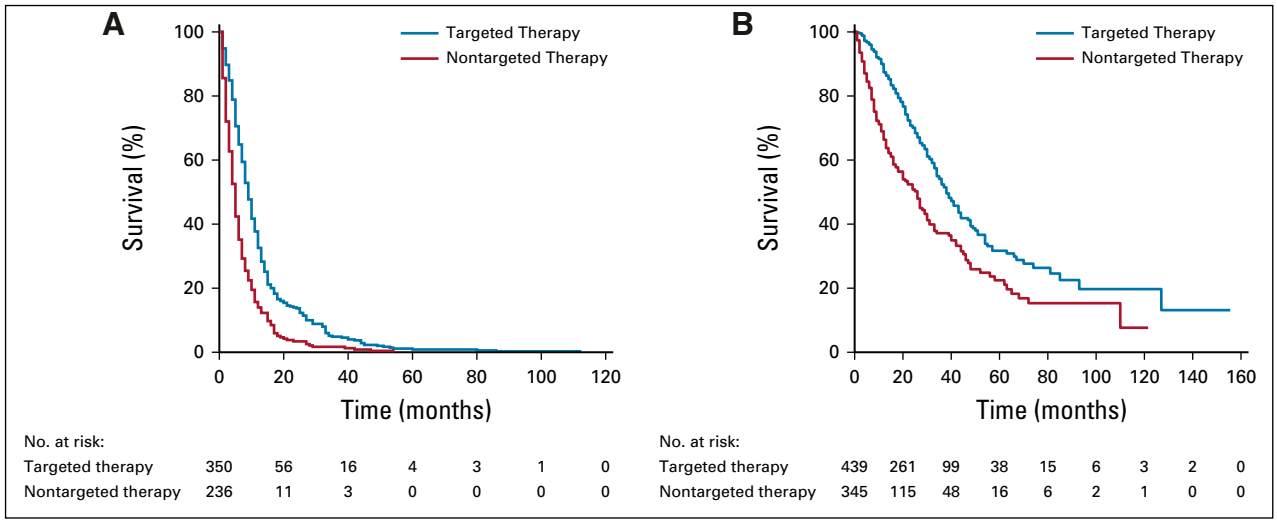

FIG 3. Association of survival with the decision made based on targeted versus nontargeted therapy. (A) Kaplan-Meier estimates of progression-free survival between a targeted therapy and nontargeted therapy decision. (B) Kaplan-Meier estimates of overall survival between a targeted therapy and nontargeted therapy decision.

rates were similarly high for appropriate assignment to treatment upon detection of targeted alterations in *EGFR* (n = 340 of 377; 90%), ALK (n = 62 of 64; 97%), and ROS1 (n = 10 of 10; 100%), but were much lower with BRAF (n = 4 of 11; 36%), RET (n = 4 of 8; 25%), and MET (n = 9 of 15; 60%). This may be because the guidelines have only recently incorporated the other actionable alterations, and other alterations, such as *MET* exon 14, *ERBB2* mutations, and *RET* fusions, at the time these patients were treated (2008-2016), did not yet have FDA-approved therapies.[30,31]

With these biomarker testing and adherence rates in mind, our FFT approach was able to identify a distinct pattern of improved OS of 38 months in the FFT-driven targeted-therapy decision-making group as compared with 26 months in the nontargeted-therapy decision-making group. Therefore, we have shown that the confluence between omics-driven therapeutics and lung cancer decision-making yields significant benefits to the patient and that applying the FFT approach may simplify the decision-making process for oncologists beyond what could be offered by the available clinical pathways and guidelines. In our Cox regression analyses, 2 factors were significantly associated with better survival: younger age and FFT-driven therapeutic decisions. In regard to PFS, the FFT-driven therapeutic decision was the sole significant factor associated with better outcomes signifying the superiority of omic-driven management strategies as compared with standard therapeutic options. Although previous studies have attempted to evaluate specific cases using limited-panel molecular testing for specific mutations,[25,32-34] this study shows a statistically significant increase in both PFS and OS based on a molecular-informed therapy strategy in patients with lung cancer at a single academic site.

A limitation of this study is that this is a single-institution study that focused on a retrospective analysis, with relatively few but key variables of prognostic or predictive significance. With a relatively small sample size in our study, it would be important to perform a large multi-institutional study to better understand the utility of the FFT as a theoretical framework for lung cancer decision-making. This would also alleviate the concern that our study only included patients of 4 oncologists at a single academic institution who undoubtedly confer with each other for their academic expertise when evaluating patients. Inclusion of community sites or oncologists from the community setting in future studies would offer a more robust conclusion. It would also be important in the future to delineate the immunotherapy subgroups into prognostic factors such as PD-L1 to better understand the effect it may have on targeted therapy.[35] Nevertheless, it remains a remarkable finding that the availability of mutation- or targeted-therapy dominated decision-making in almost 90% of cases with improved durable survival.

In conclusion, among patients who received care for advanced non–small-cell lung cancer in the academic setting, omics-driven therapy decision directly informed treatment in patients and was closely correlated with better survival.

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EQUAL CONTRIBUTION

R.S. and I.M. contributed equally to this work.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Administrative support: Ravi Salgia
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Manuscript writing: All authors
Final approval of manuscript: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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