Original Study

Clinical Outcomes for Plasma-Based Comprehensive Genomic Profiling Versus Standard-of-Care Tissue Testing in Advanced Non–Small Cell Lung Cancer

Ray D. Page,[1] Leylah M. Drusbosky,[2] Hiba Dada,[2] Victoria M. Raymond,[2] Davey B. Daniel,[3] Stephen G. Divers,[4] Karen L. Reckamp,[5] Miguel A. Villalona-Calero,[6] Daniel Dix,[2] Justin I. Odegaard,[2] Richard B. Lanman,[2] Vassiliki A. Papadimitrakopoulou,[7,8] Natasha B. Leighl[9]

Abstract

Challenges remain with collecting adequate tissue biopsies to successfully perform comprehensive genomic profiling to identify NCCN-recommended biomarkers to inform first-line therapy in patients with newly diagnosed, advanced NSCLC. Plasma-based genotyping (liquid biopsy) has previously demonstrated noninferiority to tissue biopsy for identifying targetable biomarkers in patients with NSCLC and achieves genotyping at a faster rate than tissue. This study analyzed clinical outcomes of 33 patients who were treated with targeted therapy in the first-line setting based on liquid biopsy results and demonstrated that patients respond to therapy at rates similar to those treated based on tissue-genotyping results, while able to initiate targeted therapy significantly faster (18 vs. 31 days, respectively). These findings support the utility of liquid biopsy at diagnosis of advanced disease to inform targeted therapy options in a fast, noninvasive manner.

Background: : Somatic genomic testing is recommended by numerous expert guidelines to inform targeted therapy treatment for patients with advanced nonsquamous non–small cell lung cancer (aNSCLC). The NILE study was a prospective observational study that demonstrated noninferiority of cell-free circulating tumor DNA (cfDNA)-based tumor genotyping compared to tissue-based genotyping to find targetable genomic alterations in patients with newly diagnosed nonsquamous aNSCLC. As the cohort has matured, clinical outcomes data can now be analyzed. **Methods:** : This prospective, multicenter North American study enrolled patients with previously untreated nonsquamous aNSCLC who had standard of care (SOC) tissue genotyping performed and concurrent comprehensive cfDNA analysis (Guardant360). Patients with targetable genomic alterations, as defined by NCCN guidelines, who were treated with physician's choice of therapy had objective response rates, disease control rate, and time to treatment collected and compared to published outcomes. **Results:** : Among 282 patients, 89 (31.6%) had an actionable biomarker, as defined by NCCN, detected by tissue (21.3%) and/or cfDNA (27.3%) analysis. Sixty-one (68.5%) of these were treated with an FDA-approved targeted therapy guided by somatic genotyping results (*EGFR, ALK, ROS1*). Thirty-three patients were eligible for clinical response evaluation and demonstrated an objective response rate of 58% and disease control rate of 94%. Twenty-five (76%) and 17 (52%) achieved a durable response > 6 months and 12 months, respectively. The time

[1]Center for Cancer and Blood Disorders, Fort Worth, TX
[2]Guardant Health, Inc, Redwood City, CA
[3]Tennessee Oncology, Chattanooga, TN
[4]Genesis Cancer Center, Hot Springs, AR
[5]Cedars-Sinai Medical Center, Los Angeles, CA
[6]Miami Cancer Institute, Miami, FL
[7]U of Texas, MD Anderson Cancer Center, Houston, TX
[8]Pfizer, Inc, New York, NY
[9]Princess Margaret Cancer Centre, Toronto, Ontario, Canada

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Address for correspondence: Leylah M Drusbosky, PhD, Guardant Health, Inc, 505 Penobscot Dr, Redwood City, CA 94063.
E-mail contact: ldrusbosky@gmail.com

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to treatment (TtT) was significantly faster for cfDNA-informed biomarker detection as compared to tissue genotyping (18 vs. 31 days, respectively; $P = .0008$). **Conclusions:** cfDNA detects guideline-recommended biomarkers at a rate similar to tissue genotyping, and therapeutic outcomes based on plasma-based comprehensive genomic profiling are comparable to published targeted therapy outcomes with tissue profiling, even in community-based centers.

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Keywords: NSCLC, Targeted therapy, Genotyping, Liquid biopsy (cfDNA), Next-generation sequencing

Introduction

First-line targeted therapies in advanced nonsquamous non–small cell lung cancer (aNSCLC) have demonstrated durable 50% to 90% objective response rates (ORR).[1-4] This exceeds outcomes with chemotherapy (29%-49% ORR), immune checkpoint inhibitor monotherapy in patients with >1% PD-L1 (ICI; 38-45% ORR), and even combination chemotherapy plus ICI in aNSCLC (40%-65% ORR).[5-7] Additionally, in never-smoker aNSCLC patients with oncogenic driver alterations in their tumor, first line treatment with ICI leads to poorer outcomes and is not recommended.[8,9] Oncologists must ensure that every patient's tumor undergoes comprehensive genomic profiling (CGP) so that the opportunity for superior targeted therapy outcomes is not lost. Various guidelines and expert consensus statements, including National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) and International Association for the Study of Lung Cancer (IASLC), recommend plasma-based comprehensive genomic profiling (CGP) concurrently with tissue genotyping or when tissue is insufficient to test for all recommended genomic targets in patients with advanced nonsquamous NSCLC.[8,10-12] The IASLC recently published updated recommendations to adopt a "plasma first" approach for biomarker evaluation at the time of diagnosis and for monitoring the efficacy of targeted therapies in aNSCLC, as well as to identify mechanisms of resistance to targeted therapies, with repeat tissue biopsy if plasma ctDNA is uninformative.[12] However, undergenotyping of all 8 NCCN-guideline recommended genomic targets (mutations in *EGFR, BRAF, MET*, *KRAS*, rearrangements in *ALK, ROS1, NTRK, RET*) remains a major concern as a significant number of patients are not tested for all recommended biomarkers at diagnosis.[13,14] The list of targets is rapidly growing, for example the emerging importance of *KRAS* G12C and *NRG-1* fusions, thus comprehensive genomic profiling at diagnosis remains critical to optimize outcomes for patients with advanced lung adenocarcinoma.

After histopathological diagnosis is made on tissue biopsy specimens, many institutions conduct hotspot or single-gene testing for common genomic alterations instead of next-generation sequencing (NGS).[15] However, serial individual-gene interrogation often depletes the small tissue biopsy specimens before all mutations are tested for, contributing to the phenomenon of undergenotyping in advanced cancer patients.[16] In contrast, comprehensive genomic profiling with NGS, whether in tissue or blood, provides comprehensive genomic profiling for all potential targetable alterations in a single step. However, up to 40% of tumor biopsies are inadequate or insufficient for molecular analysis.[17-19] The Noninvasive versus Invasive Lung Evaluation (NILE) prospective, multicenter study reported that guideline-recommended biomarkers were detected by cfDNA genotyping (27.3%) at a rate similar to tissue genotyping (21.3%) ($P < .0001$ for noninferiority of cfDNA molecular testing). This study confirmed noninferiority of cfDNA genotyping as compared to tissue NGS, a higher rate of successful interrogation of 8 NCCN recommended biomarkers, with a faster turnaround time than tissue NGS (9 days vs. 15 days, respectively; $P < .0001$).[14] Additionally, a prospective single-center study of 323 patients with aNSCLC who had genotyping performed on tissue biopsy and plasma cfDNA found that integrating plasma NGS into routine management of stage IV NSCLC led to a 15% increase in the detection of therapeutically targetable mutations and significantly improved patient access to targeted therapy, consistent with other studies comparing plasma versus tissue NGS in aNSCLC.[18,20,21]

The clinical utility of a predictive biomarker assay is whether it optimizes treatment selection and yields superior outcomes for patients. Multiple head-to-head retrospective studies in aNSCLC have shown that plasma-based CGP leads to treatment outcomes comparable to tissue-based genomic testing, and multiple retrospective analyses revealed that the addition of cfDNA testing increased the identification of driver mutations by 15%-65% over SOC tissue-based testing alone at diagnosis.[18,22-25] Additional prospective studies evaluating plasma-based CGP outcomes in first-line aNSCLC are the global FLAURA[26] trial, the Spanish Lung Liquid versus Invasive Biopsy Program (SLLIP).[27-29] Both the FLAURA and SLLIP studies were conducted solely in academic centers, and neither study examined how plasma-based CGP impacted physician treatment choice and subsequent outcomes in a real world, community-based setting.

The NILE study is a prospective first-line aNSCLC study that included multiple community oncology centers. The primary endpoint of noninferiority to SOC tissue-based CGP was demonstrated, however the patient outcomes had not matured at the time of the initial publication.[14] Treatment in NILE was based on physician choice, and not defined by study protocol. Here we evaluate the impact of plasma-based CGP on physician choice of targeted therapy and subsequent outcomes based primarily in a real-world community care setting in North America.

Patients and Methods

Patients

The NILE study (ClinicalTrials.gov; NCT03615443) enrolled 307 patients at 28 North American Centers (27 community enrolled 82% of patients, 2 academic sites enrolled 18% of patients) with

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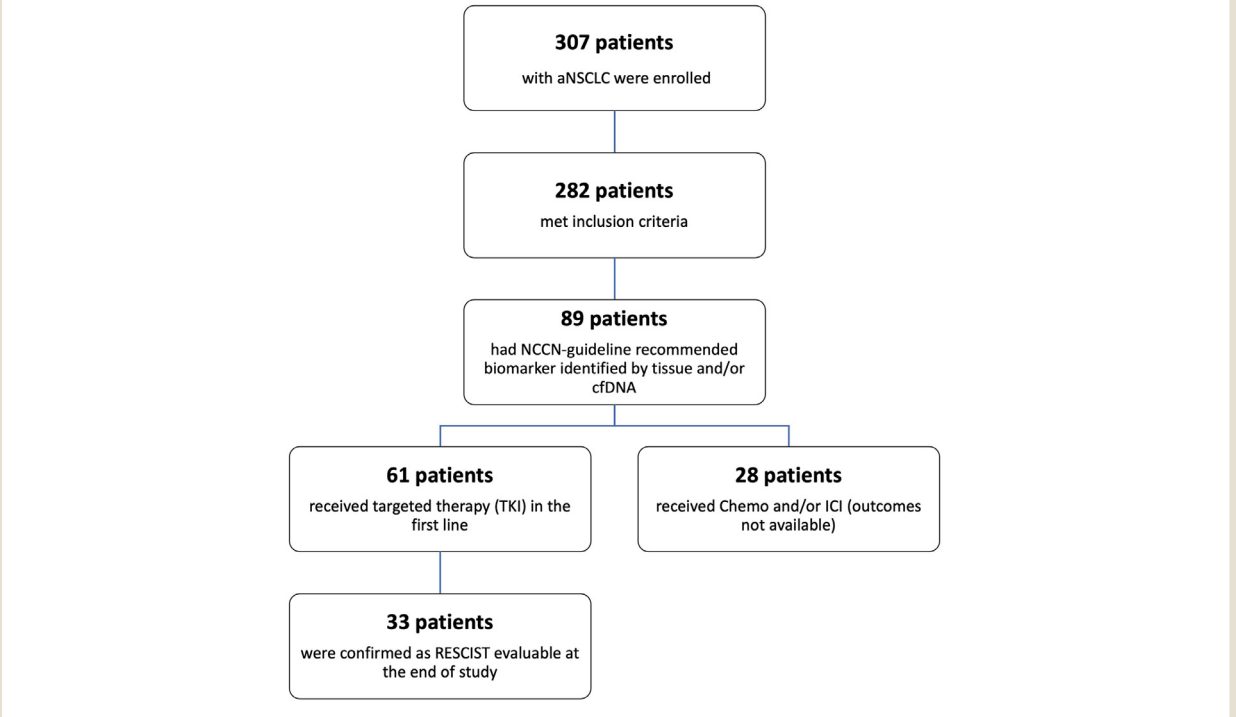
Figure 1 Consort diagram of patients enrolled onto NILE study.



previously untreated, stage IIIB/IV nonsquamous advanced NSCLC undergoing physician's choice of SOC tissue genotyping. Patients were prospectively consented between July 2016 and April 2018 to this institutional review board-approved study.

This study was conducted in accordance with the U.S. Common Rule and GCP. Written informed consent was obtained from each patient or their guardian.

Study Procedures

SOC tissue genotyping included genomic testing (NGS, PCR "hotspot" testing, FISH and/or IHC, or Sanger sequencing) and PD-L1 expression analysis. SOC tissue genotyping was required per study protocol; each site performed the tissue testing currently in process at each respective which may vary across sites. Patients provided a pretreatment blood sample for cfDNA analysis using a CLIA-certified, CAP-accredited, comprehensive NGS assay (Guardant360; Guardant Health). The cfDNA test interrogated single-nucleotide variants (SNV) in 73 genes, insertion-deletion (indel) and fusion events, and copy number amplifications in select genes including all 8 NCCN guideline-recommended biomarkers , including *KRAS*. The cfDNA test has demonstrated extensive analytical and clinical validity and clinical utility.[18,22-25,30] A clinical report of the cfDNA NGS results was issued to the ordering provider.

Treatments and Clinical Outcomes

Patients were treated with physician's choice of first-line therapy. Re-staging scans were obtained per SOC, at approximately every 8 weeks for the first 6 months, then every 12 weeks afterwards. Variability in timing of scans may have occurred depending on the study schedule for specific treatment regimens. Patients were followed for 12 months after starting first line therapy or until disease progression or death.

ORR were measured for patients whose tumors were positive for *EGFR* activating mutations, *ALK* or *ROS1* fusions by Guardant360 and/or tissue testing, defined in accordance with RECIST v1.1 and confirmed by the treating oncologist.[31] Disease control rate (DCR) was defined as the percentage of patients who achieved complete response, partial response, or stable disease for at least 12 months. Progression-free survival was defined as the time of treatment initiation to the time of progression, defined as the rate of tumor progression, either by physical examination or imaging, or death, as defined by RECIST v1.1.

Data on tumor stage, treatment regimens, start and stop dates of therapy, baseline and follow-up imaging dates and results, target lesion diameter at baseline and follow-up, overall response rate and progression-free survival by RECIST v1.1 were collected.

Statistical Analysis

Descriptive analyses were performed for this study and included ORR as defined by the number of responders divided by the number of patients qualified for tumor response analysis; DCR as defined by the number of patients who achieved clinical CR, PR, or SD; PFS as defined by the time between treatment initiation and identify disease progression on CT scan; and Time to treatment defined as

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Table 1 Demographics of 33 RECIST Evaluable Patients

	Evaluable Patients	Evaluable Percentage
Sex		
Female	18	55
Male	15	45
Median age (range) at diagnosis		
	66 (26-85) y	-
Race		
White	23	70
Black or African American	2	6
Asian	7	21
Native American		
Unknown	1	3
Ethnicity		
Hispanic	3	9
Non-Hispanic	30	91
ECOG status at enrollment		
0	7	21
1	22	67
2	2	6
3		
Unknown	2	6
History of prior chemotherapy for early-stage NSCLC		
Yes	3	9
No	30	91
Stage of NSCLC at enrollment		
IIIb	1	3
IV	32	97
Type of NSCLC at enrollment		
Adenocarcinoma	33	100
Large cell		
Other		
Smoking status at enrollment		
Nonsmoker	19	58
Current smoker	1	
Previous smoker	13	39
Unknown		
Oncogenic driver identified at diagnosis by plasma and/or tissue		
EGFR	26	79
Exon 19 del	16	48
L858R	5	15
G719A	3	9
T790M	1	3
L833V	1	3
ALK Fusion	6	18
ROS1 Fusion	1	3

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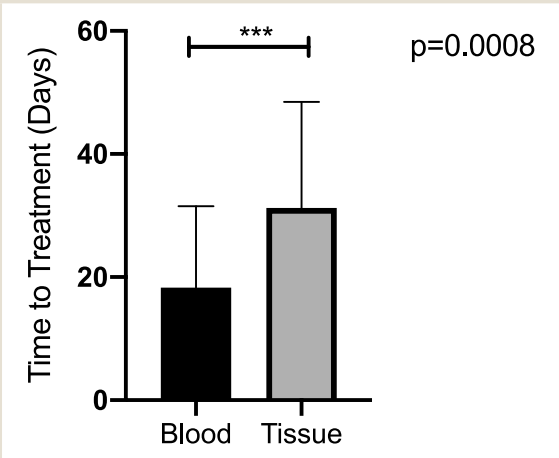
Figure 2 Time to targeted therapy initiation (in days) based on molecular results derived from blood versus tissue ($P = .0008$).



the median number of days between ordering molecular testing and date of initiating targeted therapy; the median of this metric was calculated for each testing modality (blood and tissue). Statistical significance was calculated by unpaired t-test using GraphPad Prism version 8.4.2 for macOS, GraphPad Software, San Diego, CA, www.graphpad.com

Results

A total of 307 patients with newly diagnosed advanced nonsquamous NSCLC were enrolled across 28 centers onto the NILE study, and 282 were eligible for analysis (Figure 1). Eighty-nine patients (31.6%) had an NCCN-guideline recommended biomarker identified by tissue (n = 60, 21.3%) and/or cfDNA profiling (n = 77, 27.3%). cfDNA testing identified a therapeutically targetable alteration in 29 patients that was not identified in tissue. Sixty-one of the 89 patients (68.5%) were treated with a targeted therapy in the first line setting and the reasons for choosing an alternate therapy were not provided by clinicians. A total of 33 patients were confirmed as evaluable at the end of the study. Many patients were nonevaluable as they did not receive targeted therapy in the first line, were lost to follow up, discontinued therapy due to toxicity, or had lack of tumor assessment during the study (N = 28).

The time to treatment in this 33-patient cohort was significantly faster for blood-based profiling as compared to tissue-based profiling (median 18 vs. 31 days, respectively; $P = .0008$; Figure 2).

Patient demographics for the 33 evaluable and patients are listed in Table 1. The driver gene alterations identified in the cohort were *EGFR* exon 19 deletion (n = 16), *EGFR* L858R (n = 5), *EGFR* G719A (n = 3), *EGFR* T790M (n = 1), *ALK* fusion (n = 6), and *ROS1* fusion (n = 1). Nineteen of the 33 patients achieved a CR or PR resulting in an ORR of 58% by RECIST 1.1. One (3%) had a complete response (CR), 18 (55%) had a partial response (PR), 12 (36%) had stable disease (SD), and 2 (6%) had progressive disease (PD) as their best response to first-line targeted therapy, resulting in a DCR of 94%. Thirteen of the 26 (50%) patients with activating *EGFR* alterations, and 6 of 6 (100%) *ALK*-fusion positive, achieved a best overall response of CR or PR (Table 2). Of the 13 patients with *EGFR*-positive disease who achieved CR+PR, 12 were common driver mutations (exon 19 del, L585R), and 1 patient had a rare L833V mutation. Interestingly, one T790M alteration was detected as a germline alteration at diagnosis. This patient was treated with Osimertinib and achieved a stable disease and remained on therapy >12 months. A swimmer's plot of the duration of targeted therapy and clinical response of the target lesion at each scan is shown in Figure 3

Twenty-five (76%) patients achieved a durable response of at least 6 months and 17 (52%) achieved a durable response of at least 12 months or longer. The majority of patients had a decrease in target lesion size while on targeted therapy (Figure 4). The median progression-free survival (PFS) was not determined, as the majority of patients did not progress while on study, and 52% of patients exhibited event-free survival at 12 months. For patients who did progress on study, the median time to progression was 185 days.

Discussion

In a large prospective, North American multicenter study conducted in mostly community-based sites, the real-world impact of cfDNA genotyping on physician first-line treatment choice and patient outcomes is evaluated for the first time in previously untreated nonsquamous aNSCLC. This study demonstrated a significant advantage for blood-based NGS to reduce the time to treatment initiation in the first line setting as compared to tissue-based profiling. Objective response and disease control rates for patients treated with targeted therapy in this cfDNA study were consistent with prior results of phase III trials comparing the efficacy of targeted therapies based on tissue-detected genomic targets in advanced NSCLC patients.[1-4] In the current study, patients with *EGFR* alterations achieved an ORR of 50%, while patients with *ALK* or *ROS1* fusions achieved an ORR of 100%. PFS for the entire cohort was not determined, as a majority of patients did not progress while on study. For patients who did progress on study, the median time to progression was 185 days. Importantly, the VAF of the target alteration did not impact the patient's response to targeted therapy. Additional noteworthy findings include 3 patients with *EGFR* G719A alterations treated with afatinib, all achieving stable disease, with 2 patients having a durable response for ≥12 months, confirming the importance of *EGFR* whole exon testing versus hotspot testing that might miss uncommon *EGFR* mutations.[32] Patient 14 harbored *EGFR* L833V, a mutation not included in NCCN guidelines, and was treated with Osimertinib and achieved a partial response for a duration of >12 months, continuing therapy after the study period ended. Patient 17 harbored an *EML4-ALK* fusion at 0.05% variant allele frequency (VAF) and achieved a PR on crizotinib, consistent with retrospective analyses finding that the VAF of the target driver gene alteration does not affect clinical response to targeted therapy in aNSCLC.[22,33-35]

There are several limitations to address in this study. Physicians' choice of SOC tissue testing varied across the cohort. Tissue testing varied significantly and consisted of hot-spot PCR-based, IHC/ISH,

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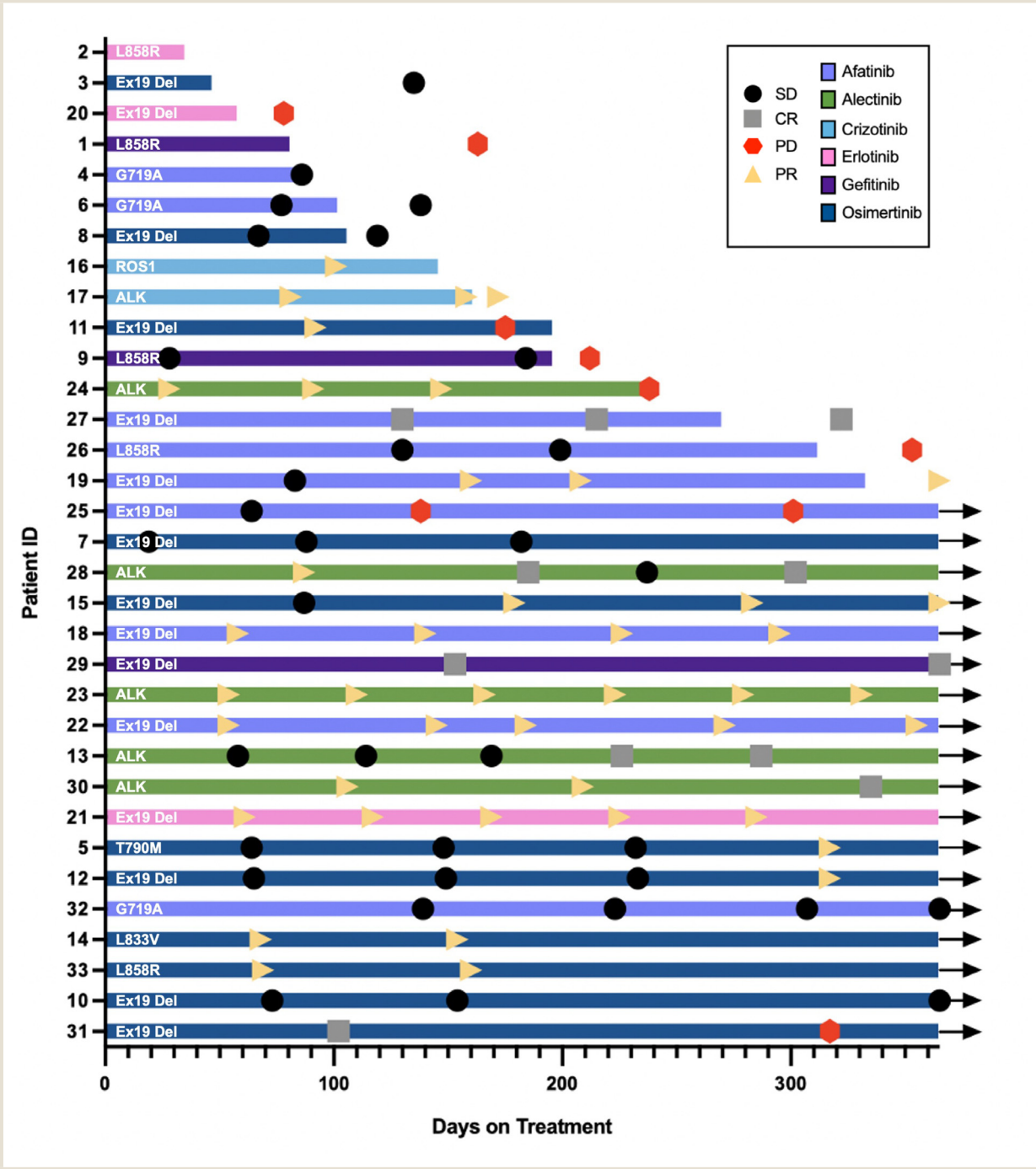
Figure 3 Swimmer's plot of the 33 evaluable patients treated with biomarker-guided targeted therapy. Colors of bars reflect first-line TKI, symbols represent outcome of CT scans. The variant identified in each patient is listed within the colored bar; ALK = *ALK* fusion; ROS1 = *ROS1* fusion; Ex19del/L858R/T790M/G719A/L833V = *EGFR* drivers.



and/or CGP by NGS, which have varying degrees of sensitivity and specificity for identifying genomic alterations.[14] Patients were followed for only 12-months after starting targeted therapy, and the median time on targeted therapy is typically greater than 12 months. Not all patients who were found to harbor an NCCN-guideline recommended biomarker received targeted therapy in the first line, and the reasons for choosing an alternate therapy were not provided. For the 28 patients treated with targeted therapy in the first line but not evaluable for RECIST response, these patients were lost to follow up, had lack of tumor reassessment during the

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Table 2 RECIST Responses Across the Evaluable Patient Cohort

		Number (N = 33)	Percent
Overall response	CR	1	3
	PR	18	55
	SD	12	36
	PD	2	6
Best overall response (BOR)	CR + PR	19	58
Disease control rate (DCR)	CR + PR + SD	31	94
Durable response at 6 months	CR + PR + SD	25	76
Event-free survival at 12 months	CR + PR + SD	17	52
EGFR BOR	CR + PR	13	50
	Common EGFR (Exon19, L858R)	12	92
	EGFR rare (G719A, L833V)	1	8
	Germline EGFR T790M	0	0
ALK BOR	CR + PR	6	100
ROS1 BOR	CR + PR	0	0

study, or discontinued therapy due to toxicity. While limiting the depth of comparative analysis, this allowance reflects real-world testing practices in the community, a primary aim of this study. Study treatments were physicians' choice and not prescribed by study protocol, resulting in a variety of therapies being included in the outcomes analysis. The testing modality, plasma versus tissue, used to make a treatment decision for the patient was not identified by the treating oncologists and thus we could not determine which assay was used to guide therapy in every case. Although the sample size with completed outcomes in the NILE study is limited, this is typical of studies aiming to collect oncology research data from community-based sites.[36] It is important to understand why aNSCLC patients with actionable biomarkers did not receive approved targeted therapy as the treatment of choice in first line. A recent international survey of oncologists found that the majority of oncologists (60%) in North America did not base their treatment decision for aNSCLC patients on genomic information, and 21% of oncologists determined the treatment regimen for their patients before mutation results were available, despite clear evidence of the superior clinical efficacy and lower toxicity usually associated with molecularly matched therapy.[37]

In summary, this update of the NILE study demonstrates that a comprehensive cfDNA assay led to first-line treatment choice and subsequent targeted therapy outcomes similar to outcomes based on tissue-guided therapy, with a faster time to treatment initiation. Although the evaluable cohort is not large, this prospective North American, real-world practice study confirms findings from a similar prospective multicenter study of Spanish academic centers, and has the added value of demonstrating improved outcomes in real-world practice settings[27]. The addition of liquid biopsy to SOC tissue testing at diagnosis increases the number of patients found to have an oncogenic driver mutation and helps to overcome the limitations of tissue testing including insufficient material, the need to re-biopsy a patient's disease, and delays in time to treatment. The turnaround time for a liquid biopsy assay is significantly shorter than that of tissue testing, helping patients to get on therapy much faster. The complementarity of both assays in tandem has been acknowledged in numerous clinical studies, including the recently updated IASCL recommendations on liquid biopsy in aNSCLC,[12] and supports a "blood first" approach to comprehensive genomic profiling at diagnosis and subsequent treatment based on cfDNA result, with reflex to tissue testing if cfDNA testing is negative. This approach should be followed by tissue testing to assure that the search for targetable mutations is optimized in every patient with advanced NSCLC.[12]

Clinical Practice Points

- Somatic genotyping of advanced NSCLC is impertive to guide targeted therapy options for first-line treatment, proven to improve outcomes in patients who harbor an oncogenic driver as compared to chemotherapy regimens.
- Liquid biopsies have demonstrated high concordance with tissue genotyping and are a fast and reliable method to perform comprehensive genomic profiling to identify oncogenic drivers of NSCLC.
- Patients treated with targeted therapy guided by liquid biopsy results achieve clinical outcomes at rates similar to tissue genotyping, and are able to start therapy significantly faster due to the shorter turnaround time of the assay.

Statement of Translational Relevance

Expert guidelines recommend somatic genotyping for up to 8 molecular biomarkers to inform first-line targeted therapy options for patients with advanced nonsquamous, non–small cell lung carcinoma (NSCLC). However, challenges remain with collecting adequate tissue biopsies to successfully perform comprehensive genomic profiling. Plasma-based genotyping (liquid biopsy) has

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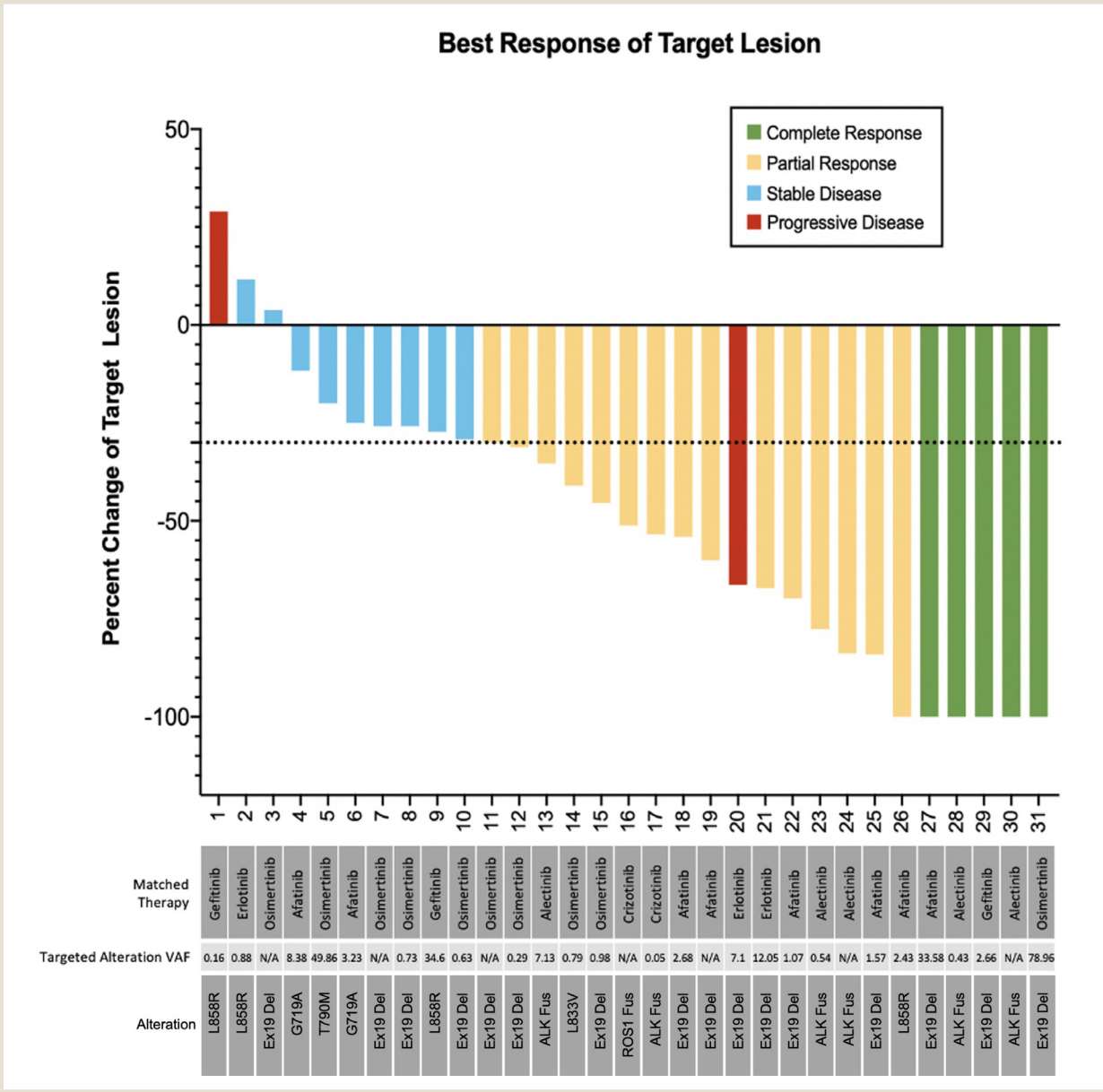
Figure 4 Waterfall plot measuring the change in target lesion volume as measured by CT scans. Dotted line represents a 30% decrease in target lesion volume consistent with partial response. Each color represents the best response of the target lesion while on targeted therapy. Treatment for each patient and the variant allele frequency (VAF) of the target gene alteration is listed below the table. The variant identified in each patient is listed under the target alteration VAF; ALK = *ALK* fusion; ROS1 = *ROS1* fusion; Ex19del/L858R/T790M/G719A/L833V = *EGFR* drivers.



previously demonstrated noninferiority to tissue biopsy for identifying targetable biomarkers in patients with NSCLC and achieves genotyping at a faster rate than tissue. This study analyzed clinical outcomes of patients who were treated with targeted therapy in the first-line setting based on liquid biopsy results and demonstrated that patients respond to therapy at rates similar to those treated based on tissue-genotyping results, while able to initiate targeted therapy significantly faster (18 vs. 31 days, respectively). These findings support the utility of liquid biopsy at diagnosis of advanced disease to inform targeted therapy options in a fast, noninvasive manner.

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Disclosure

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