Real-World Adherence Patterns of Comprehensive Genomic Profiling to Biomarker Recommended Therapies in Patients With Advanced Non–Small Cell Lung Cancer

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ABSTRACT

PURPOSE The National Comprehensive Cancer Network (NCCN) guidelines recommend comprehensive genomic profiling (CGP) for identifying advanced non–small cell lung cancer (NSCLC) patients eligible for targeted treatment, with frequent updates to incorporate new variant-targeted therapies. CGP panels can identify multiple actionable biomarkers from a single sample to match patients to targeted therapies. We assessed the adherence rate of NCCN recommendations to variant-specific matched therapy, the impact of timing of guideline updates on adherence rates, and time from sequencing to new targeted therapy adoption.

METHODS We conducted a retrospective cohort study of stage IV NSCLC patients, with Tempus xT tissue-based sequencing. Adherence to NCCN-recommended therapy was defined as the proportion of patients who initiated guideline-directed targeted therapy when the presence of an actionable variant was identified.

RESULTS Among the 1,407 evaluable patients, 233 patients had a NCCN-recommended targetable variant. The treatment adherence rate was 86.3% (N = 201) with median time from sequencing to targeted therapy initiation of 23 days. A subset of adherent patients (13.4%, n = 27) had targetable variants identified prior to guideline recommendation for testing, but received matched targeted therapy within a median of 96 days of new guidelines recommendations. The variant-specific adherence rate was correlated with the timing of guideline recommendation (P = .02, Wald test), with lower adherence rates for variant-matched therapies recently included into guidelines.

CONCLUSION In a large, real-world cohort of advanced NSCLC patients tested with CGP, the treatment adherence rate to matched NCCN-recommended targeted therapy was high. This study highlights the importance of CGP testing in identifying variants to provide timely matched targeted therapy in a rapidly evolving biomarker and therapeutic landscape.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

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INTRODUCTION

Patients with advanced non–small cell lung cancer (NSCLC) with targetable, oncogenic alterations achieve improved clinical outcomes when administered therapies targeting specific variants compared to standard chemotherapies.[1-5] However, not all patients with targetable variants receive clinical guideline-recommended targeted therapy.[1,6] Treatment guidelines from the National Comprehensive Cancer Network (NCCN)[6] and the ASCO[7] are updated regularly to match rapid advances in targeted therapy, with 24 therapies approved by the Food and Drug Administration targeting NSCLC-specific variants between 2020 and 2022.[8]

Comprehensive genomic profiling (CGP), defined as the use of next-generation sequencing to detect alterations in hundreds of genes simultaneously with one assay,[9] is a useful tool for molecular diagnostic testing and matching patients to appropriate targeted therapy. Retrospective CGP results can be utilized to match patients to newly approved therapies, as these panels often include emerging biomarkers in the early stages of clinical development. NCCN

CONTEXT

Key Objective
Do advanced non–small cell lung cancer patients receiving comprehensive genomic profiling (CGP) adhere to guideline-recommended, variant-specific matched therapy?

Knowledge Generated
In a large real-world study, adherence to guideline-recommended variant-specific matched therapy from CGP testing was 86.3%. Adherent patients received recommended targeted therapy quickly, with a median time from sequencing to start of therapy of 23 days.

Relevance
This study demonstrates that CGP testing can be used to identify actionable variants and facilitate timely, evidence-based treatment decisions.

guidelines for NSCLC recommend broad-panel based testing such as CGP to maximize diagnostic genomic information from a tissue biopsy to identify appropriate targeted therapy.[6] However, CGP testing is not always accessible due to lack of coverage from commercial payers.[10]

Rates of adherence to guideline-recommended therapy in advanced NSCLC patients with targetable variants range from 43.0% to 85.7%.[1,11–14] Adherence rates for well-known biomarkers such as *EGFR* variants and *ALK* fusions have increased over time, but adherence rates for newer biomarkers are not well characterized.[10] These variable rates may be due to inconsistency in reporting and lack of familiarity with emerging data.[10]

In this study, we evaluated the adherence to the NCCN guidelines through CGP testing in a large real-world (RW) cohort of advanced NSCLC patients sequenced from 2018 to 2022. We assessed variability in adherence rates by targetable variant, how adherence may be impacted by the timing of drug inclusion into the NCCN guidelines, and timing from sequencing to the start of matched targeted therapy in adherent patients.

METHODS

Study Design

We retrospectively analyzed deidentified patient records from the Tempus multimodal database, which includes longitudinal structured and unstructured deidentified data from geographically diverse oncology practices, including integrated delivery networks, academic institutions, and community practices across the United States. All patient-level data were deidentified in accordance with the Health Insurance Portability and Accountability Act. Tempus AI, Inc has been granted an Institutional Review Board exemption (Advarra Pro00072742) permitting the use of deidentified clinical, molecular, and multimodal data to derive or capture results, insights, or discoveries.

Cohort Inclusion and Exclusion Criteria

Study criteria included a diagnosis of stage IV NSCLC prior to or within 100 days of Tempus xT genomic sequencing of tumor tissue from 2018 to 2022 (Fig 1). If patients were sequenced multiple times, the earliest test after diagnosis of advanced stage was included. Patients were excluded from the study if they had histologies associated with small cell carcinoma, imprecise diagnosis date information, or unavailable staging information. Patients were included for analysis if they had at least 90 days of medication data after sequencing and received targeted therapy, immunotherapy, or chemotherapy within 2 years of the sequencing date. Patients who received targeted therapy prior to xT sequencing or received investigational therapies were excluded from our analysis as adherence to targeted therapy based on Tempus xT could not be evaluated.

CGP Assay

CGP was performed with the Tempus xT tissue-based assay (v2-4) as previously described.[15,16] Briefly, Tempus xT is a targeted, tumor-normal-matched DNA panel that detects single-nucleotide variants, insertions and/or deletions, and copy number variants in 596-648 genes, as well as chromosomal rearrangements in 22 genes with high sensitivity and specificity from tissue.

NCCN Guidelines

The NCCN guidelines for NSCLC (v.3.2022)[17] support the medical necessity to test all advanced NSCLC patients for actionable variants and associated targeted therapies. We analyzed the evolution of NCCN guidelines from 2017 to 2023 by examining transparency documents from NSCLC NCCN Committee Meetings held during this period and

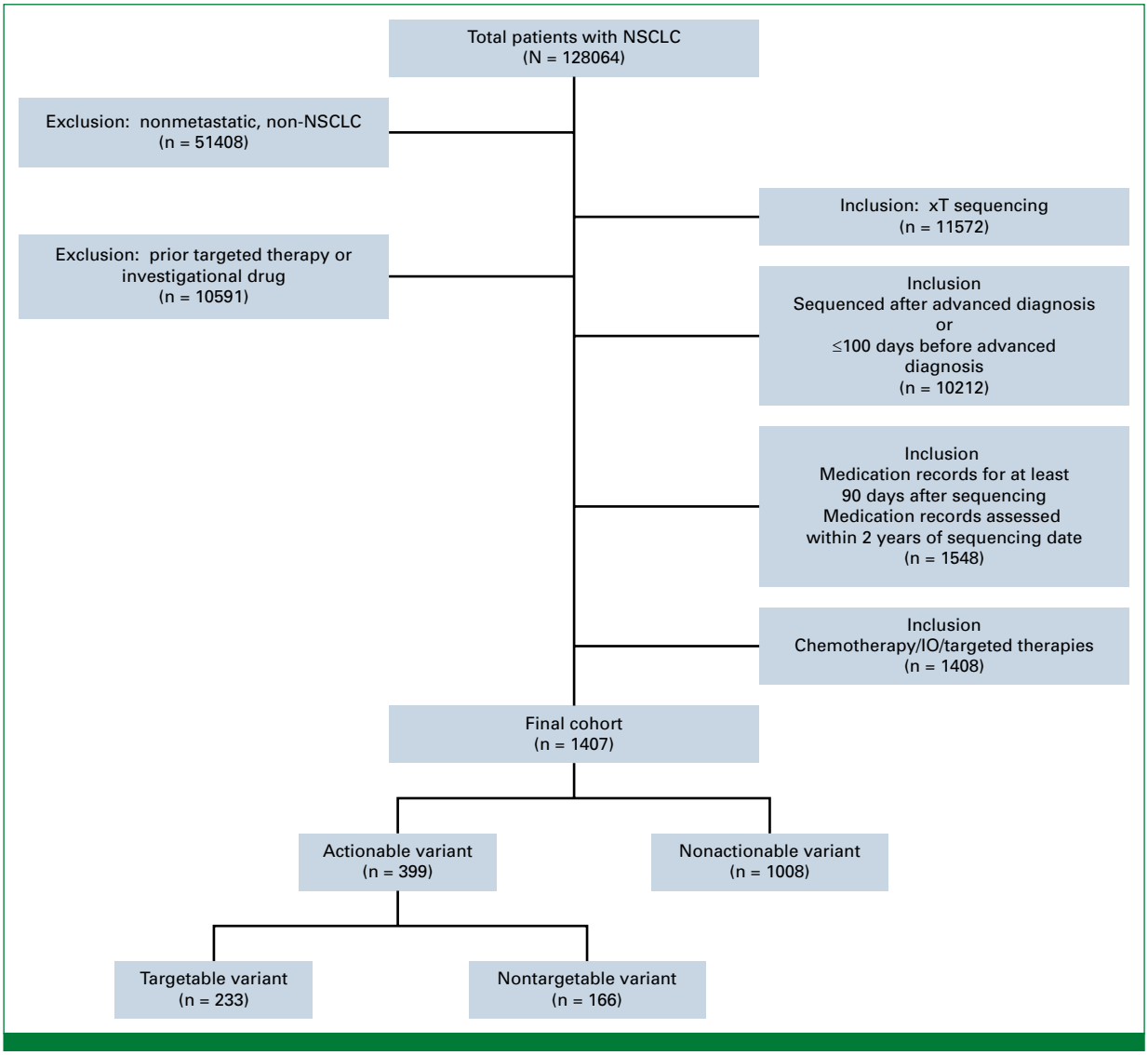

FIG 1. CONSORT diagram. IO, immunotherapy; NSCLC, non–small cell lung cancer.

documenting the dates when biomarkers and matched targeted therapy were included in guidelines. Prior to 2017, we evaluated changes in versions of NSCLC NCCN guidelines directly as Committee Meeting documentation was not available. This study includes the adherence profiles for all 15 NCCN-recommendation actionable variants with 25 matched targeted therapies and the timing of NCCN-inclusion of variant-matched therapy in guidelines (Fig 2).

Classification of Patient Population

Evaluable patients in this study were classified into four groups based on variant status (targetable variant or no targetable variant) and the postsequencing therapy received (targeted therapy or nontargeted therapy). Patients were classified as having a targetable variant if they had an NCCN-defined actionable variant and matched targeted therapy was recommended by NCCN guidelines when the patient received their first medication after sequencing.

Patients were classified as having a nontargetable variant if they had no actionable variant, or if they had an actionable variant but there was no matched targeted therapy recommended by NCCN guidelines when they received their first medication after sequencing. Nontargeted therapy was defined as immunotherapy agents and/or traditional chemotherapy.

For patients with variants where matched therapy is only recommended by guidelines during second-line therapy (*EGFR* Exon 20 insertions, *KRAS* G12C, and *ERBB2* variants), we classified these variants as targetable variants only if the medication within 1 year of sequencing that the patient received was in the second-line or beyond.

Adherence

Patients with a targetable variant who received a targeted therapy were defined as adherent and patients with a

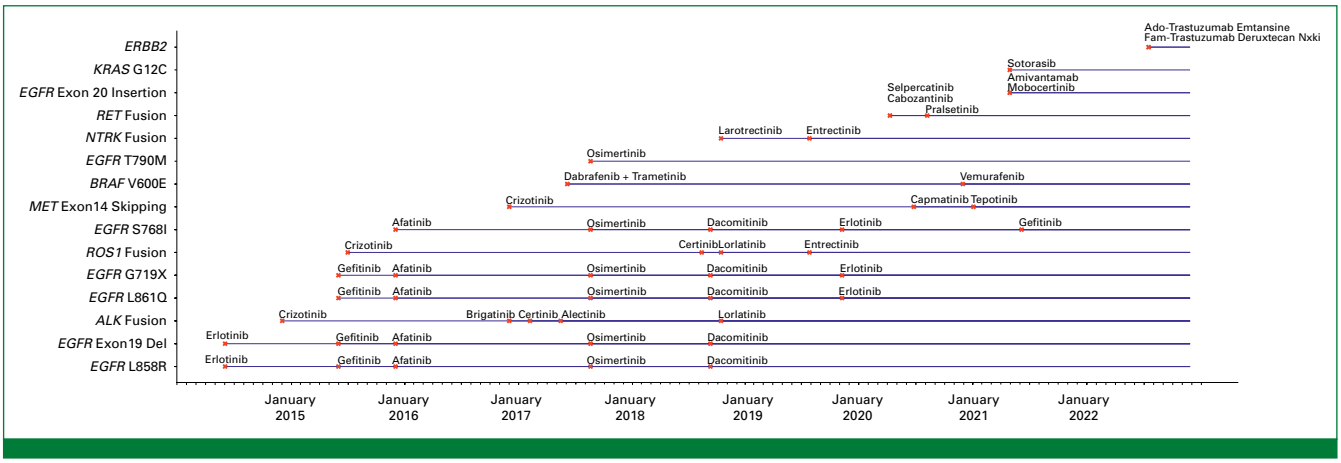

FIG 2. Timing of variant-therapy matched recommendations in NCCN guidelines.

targetable variant who did not receive a targeted therapy were defined as nonadherent.

Statistical Analysis

We evaluated differences in demographic and clinical characteristics using Chi-squared tests. Differences in the rates of targeted therapy for patients with targetable variants versus those without targetable variants was assessed using a Chi-squared test. Real-world overall survival (rwOS) was assessed for adherent versus nonadherent patients that received first-line medication after sequencing, to limit line of therapy as a potential confounder. A Cox proportional hazards model was fit from the start of first-line therapy after sequencing to death, with event-free patients censored at the earliest of the last known clinical record or 2 years following start of medication. Statistical significance of the hazards model was assessed via a two-sided Wald test.

The correlation between adherence rate and timing of matched therapy in NCCN guidelines was assessed via a Pearson correlation coefficient. Statistical significance was assessed via a Wald test with the null hypothesis that the Pearson correlation coefficient was not significantly different from zero. Time from sequencing or timing of NCCN guidelines to start of matched targeted therapy was assessed via cumulative incidence Kaplan Meier analysis.

RESULTS

Cohort Characteristics

The evaluable cohort consisted of 1,407 patients (Fig 1), of which 47.5% (n = 668) were female and the median age at the time of sequencing was 67 years old (Table 1). Most patients had adenocarcinomas (68.6%, n = 824/1,201 with known histology) and a history of smoking (86.4%, n = 1,161/1,343 with known smoking status). Approximately 16% of the cohort had a race or ethnicity other than White. The median time from diagnosis to sequencing was 27.0 days and the median time from sequencing to start of a new therapy was 24.0 days (Table 1). Three-hundred and ninety-nice patients (28.4%) harbored actionable variants detected by CGP (Fig 3A). Common variants detected in this cohort were *EGFR* (9.5%) and *KRAS* G12C (12.0%). The most prevalent targeted medications observed in the cohort were osimertinib (7.5%) and sotorasib (2.4%; Fig 3B).

Overall Treatment Adherence

A subset of patients with actionable variants (n = 233/399) were classified as targetable and evaluable for adherence analysis. Those not evaluable either received targeted therapy prior to NCCN guideline inclusion or were not evaluable due to line of therapy (Appendix Table A1, online only). The adherence rate in evaluable patients with targetable variants (n = 201) was 86.3% (Fig 4A). The therapies administered to adherent and nonadherent patients are described in Appendix Figure A1. There were no significant differences in patient characteristics when comparing adherent to nonadherent patients (Table 1). In the subset of patients with targetable variants who received first-line therapy after sequencing (n = 148), adherent patients had longer rwOS than nonadherent patients (Fig 4B; HR = 0.7, not significant). Median rwOS was not reached within 2 years of sequencing in adherent patients, whereas median rwOS was 17.2 months for nonadherent patients.

A minority of patients without targetable variants (4.9%, n = 57/1,174) received targeted therapy (Fig 4A). The rate of targeted therapy received in this population was significantly lower than in adherent patients ($P < .001$). Of these, 10 patients (17.5%) harbored an actionable variant and received matched targeted therapy but were considered to have an untargetable variant because they received therapy prior to guideline inclusion (Appendix Table A2). Of the remaining 47 patients, 26 patients (55.3%) had a pathogenic variant in the targetable gene which was not recommended for testing by NCCN guidelines, but for which there may be some clinical evidence that these therapies target these rare variants.

TABLE 1. Cohort Demographics of Patients With Targetable Variants

Characteristic	Overall (N = 1,407)	Adherent Patients (n = 201)	Non-Adherent Patients (n = 32)	*P*
Age at sequencing				
Median (IQR)	67.0 (60.0-74.5)	68.0 (58.0-76.0)	71.0 (63.0-78.3)	.13
Sex, n (%)				
Female	668 (47.5)	124 (61.7)	16 (50.0)	1.0
Male	739 (52.5)	77 (38.3)	16 (50.0)	
Race, n (%)				
Asian	30 (2.1)	15 (7.5)	NA	1.0
Black	145 (10.3)	20 (10.0)	1 (3.1)	
Other	56 (4.0)	7 (3.5)	2 (6.3)	
White	940 (66.8)	120 (59.7)	22 (68.8)	
Unknown	236 (16.8)	39 (19.4)	7 (21.9)	
Smoking status, n (%)				
Nonsmoker	182 (12.9)	76 (37.8)	6 (18.8)	.96
Smoker	1,161 (82.5)	118 (58.7)	24 (75.0)	
Unknown	64 (4.5)	7 (3.5)	2 (6.3)	
Histology, n (%)				
Adenocarcinoma	824 (58.6)	162 (80.6)	26 (81.3)	1.0
Non–small cell carcinoma	49 (3.5)	4 (2.0)	1 (3.1)	
Squamous cell carcinoma	183 (13.0)	8 (4.0)	1 (3.1)	
Unknown	206 (14.6)	17 (8.5)	3 (9.4)	
Other	145 (10.3)	10 (5.0)	1 (3.1)	
Diagnosis to sequencing				.86
Median days (IQR)	27.0 (18.0-47.0)	26.0 (17.0-42.0)	24.5 (18.8-42.3)	
Sequencing to medication start				.71
Median days (IQR)	24.0 (12.0-85.0)	23.0 (12.0-104.0)	33.0 (11.5-116.8)	
Sequencing date to last known date				.36
Median days (IQR)	323.0 (203.0-501.0)	375.0 (247.0-537.0)	295.0 (168.75-593.3)	

Abbreviation: NA, not applicable.

Treatment Adherence by Variant and NCCN Timing

Targeted therapy adherence rates varied by specific variant detected (Fig 4C). Among groups with at least 10 patients, the highest adherence rates were seen in *EGFR*-altered patients, with 100% adherence for patients with *EGFR* exon 19 deletions (n = 52/52). The lowest adherence rate was seen in *BRAF* V600E mutated patients (47.0%, n = 8/17). All other variant-specific adherence rates were ≥70.0%.

We hypothesized that the differences in adherence rates may be correlated to the timing of NCCN guideline therapy inclusion, with lower adherence rates for variants with matched therapies recently included in the NCCN guidelines. After excluding the outlier of *BRAF* V600E, there was a significant negative correlation between adherence rate and timing of targetable variant-matched therapy recommendation in NCCN guidelines ($r = -0.65$; $P = .02$), with lower adherence rates for patients with variants with more recent inclusion of biomarker testing and matched therapy included in the guidelines (Fig 4D).

Timing From Sequencing to Adoption of Targeted Therapy

We next evaluated the timing from sequencing to start of matched targeted therapy in adherent patients. The median time from sequencing to start of matched targeted therapy in all adherent patients was 23 days (Appendix Table A3). This timing was dependent on whether targeted therapies were included in the NCCN guidelines at the time of sequencing (Fig 5A). For the majority of patients (86.6%, n = 174), the matched targeted therapy was included in the NCCN guidelines at the time of sequencing (median time from sequencing to start of matched targeted therapy of 18 days). However, 27 adherent patients (13.4%) were sequenced prior to the inclusion of a matched targeted therapy in the NCCN guidelines. In this patient subset the median time from sequencing to start of matched targeted therapy was 304 days, while the median time from NCCN guideline inclusion to start of targeted therapy was 96 days.

These trends are further reflected in patients with common alterations for different timing of guideline recommendations for biomarker testing and matched therapy: patients with

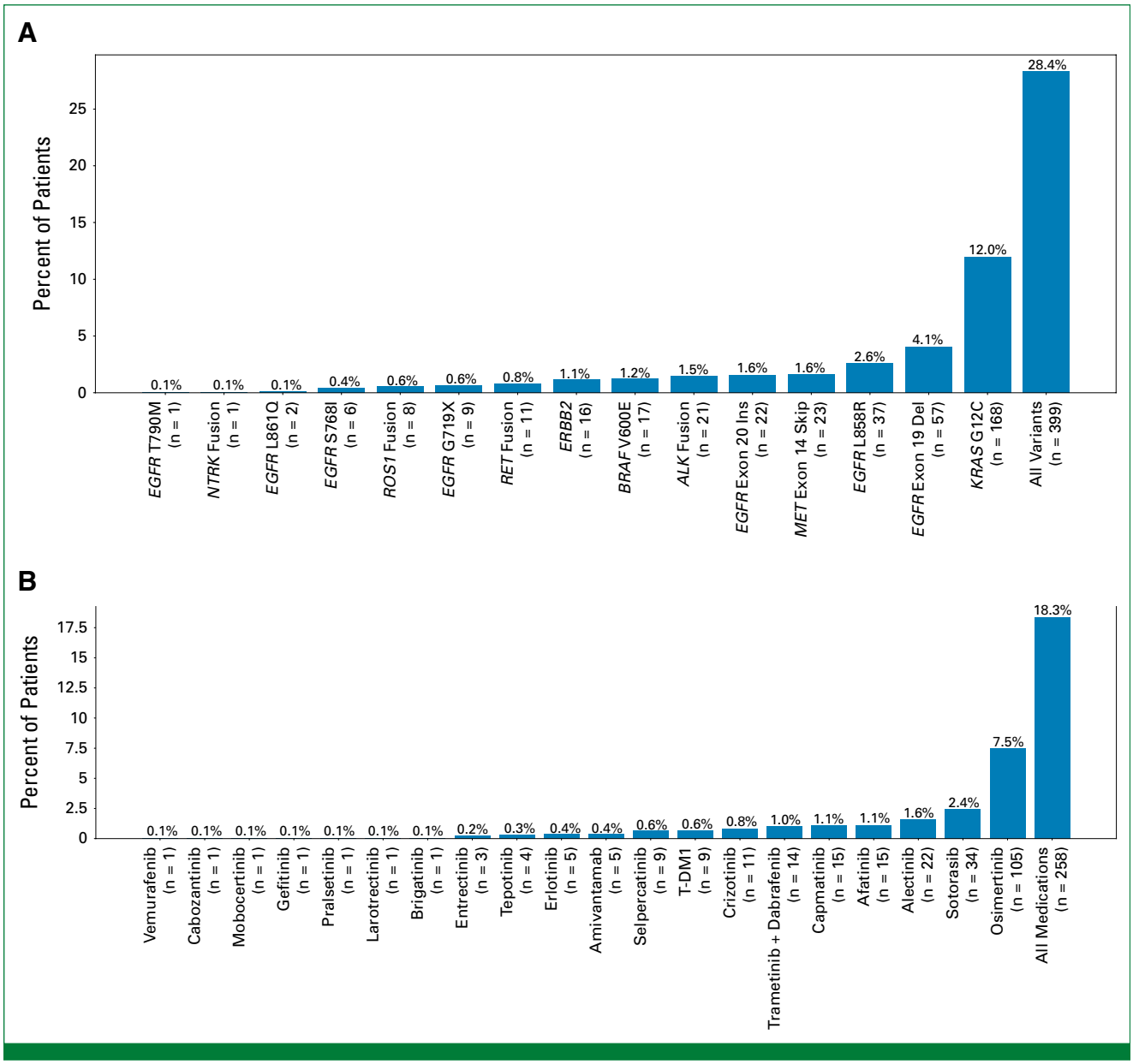

FIG 3. Prevalence of actionable variants and targeted therapies. (A) Prevalence of actionable variants. (B) Prevalence of targeted therapies.

EGFR L858R variants (n = 36), recommended in guidelines prior to 2018, compared to patients with *KRAS G12C* variants (n = 28), recommended in guidelines only in June, 2021 (Fig 5B). Timing of sequencing and start of targeted therapy in individual patients show that most *EGFR L858R*-altered patients receive therapy quickly (median, 17 days), regardless of year of sequencing or therapy received (Fig 5C). For *KRAS G12C*-altered patients, most patients sequenced prior to guideline recommendation for testing received matched therapy within 3 months of guideline recommendation (median of 95 days; Fig 5D).

DISCUSSION

In this large RW study of CGP tested, advanced NSCLC patients, the adherence rate of matched targeted therapy in patients with targetable variants was high (86.3%) and the time from sequencing to start of matched targeted therapy was 23 days. Notably, a subset of patients (n = 27) who were sequenced prior to inclusion of NCCN recommended biomarker testing received matched targeted therapy within 96 days. These results underline the importance of large panel CGP testing to retrospectively identify multiple biomarkers from a single sample, allowing patients to rapidly receive newly recommended targeted therapies.

Given the expansion of effective biomarker discovery, with multiple NCCN-recommended matched targeted therapies yearly, CGP is becoming an essential tool to identify actionable biomarkers for which matched targeted therapy can lead to improvement in patients' outcomes. CGP will become increasingly important as emerging evidence arises to

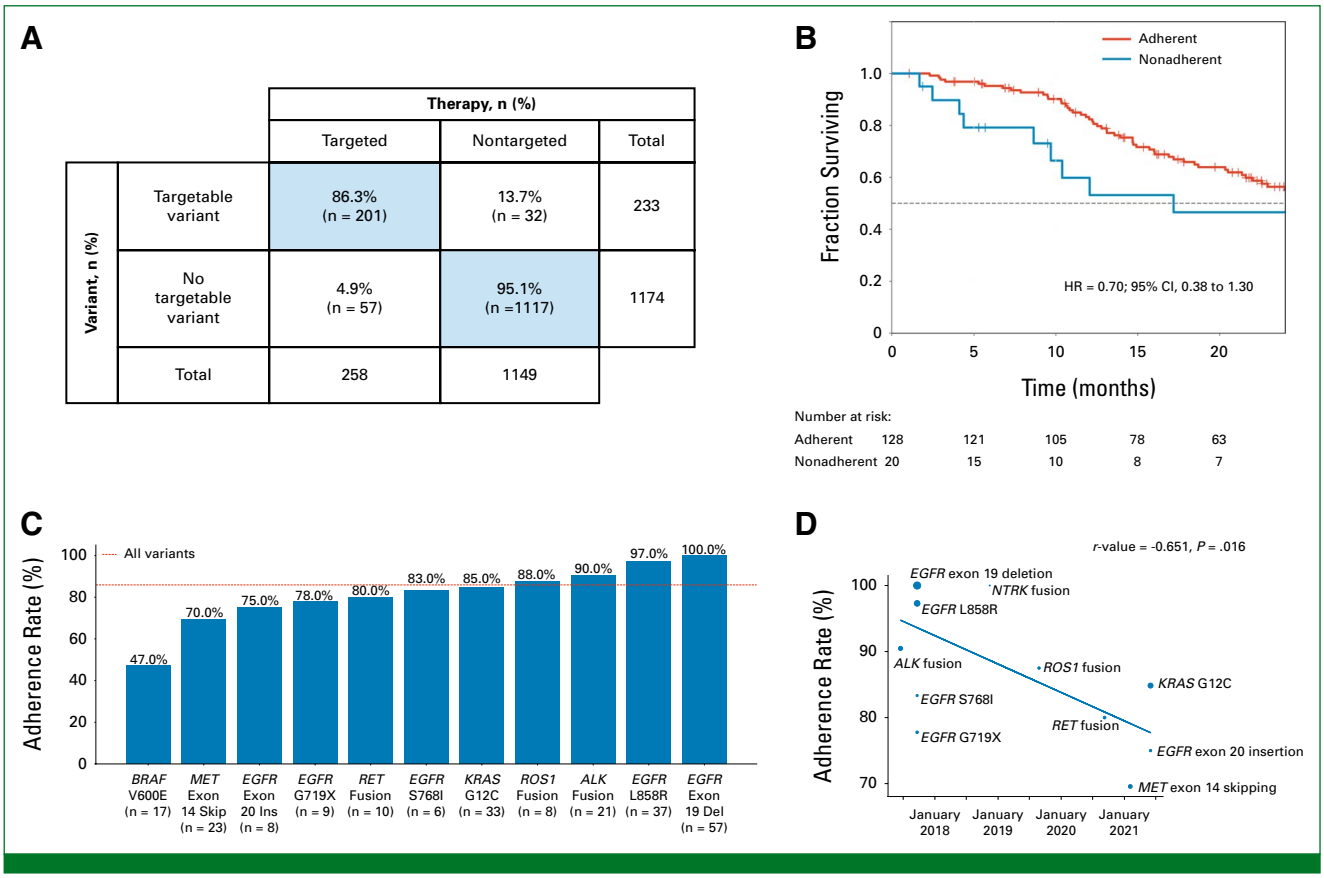

FIG 4. Rates of targeted therapy and adherence by variant. (A) Rates of targeted therapy in patients with and without targetable variants. (B) For patients with targetable variants that received a medication in the first-line setting, Kaplan Meier analysis comparing adherent and nonadherent patients. (C) Adherence rate by variant. Variant-level adherence is not shown for three variants for which fewer than five patients have this variant (*EGFR* L861Q, n = 2, adherence = 100%, *EGFR* T790, n = 1, adherence = 100%; *NTRK* fusion, n = 1, adherence = 100%, *ERBB2* variants, n = 1, adherence = 0%). (D) Relationship between adherence rate and timing of NCCN guideline inclusion for most recent variant-matched targeted therapy observed in the cohort. Each circle represents the number of evaluable patients with the variant of interest. Patients with *BRAF* V600E were excluded from this analysis. HR, hazard ratio; NCCN, National Comprehensive Cancer Network.

understand how co-occurrence of resistance and prognostic variants impact treatment efficacy both at diagnosis and at clinical progression.

Previous studies[1,12–14] have shown variable adherence rates in patients with actionable variants ranging from 43%[12] in a recent published study of approximately 4,000 advanced NSCLC patients, to 85.7% in a large retrospective analysis of claims and laboratory data from approximately 28,000 newly diagnosed advanced NSCLC patients that received biomarker testing with reported results.[14] This variation may be due to differences in definitions of actionable variants and matched therapy in addition to the timeframe that the study was conducted. Moreover, these studies did not incorporate changes in clinical guidelines over the study period, which can impact adherence rates, specifically lower adherence rates for biomarkers recently recommended for testing and matched therapy.

Timing of guideline inclusion is not the only factor influencing adherence rates. General clinical genomic literacy, ease of interpretability of a patient's next-generation sequencing variant report, strength of clinical evidence for the matched therapies, access to testing and comprehensive knowledge of appropriate treatment management of targeted therapies can impact CGP uptake in advanced cancer patients.[10] In our study patients with *BRAF* V600E variants had the lowest adherence rate (47.0%), although dabrafenib and trametinib were included in the NCCN guidelines in 2017. Low adherence to *BRAF*-related targeted therapies may be due to allowance in guidelines for nontargeted systemic therapy for BRAF-mutation patients, though targeted therapy is preferred, complex treatment management of combination targeted therapy, and a unique adverse event profile for *BRAF* regimens compared to other NSCLC-targeted therapies.[18]

Despite the merits of CGP testing, it is still not widely utilized in clinical settings.[10] A major barrier to CGP testing is commercial health insurance payer policies.[10] The Center for Medicare and Medicaid Services issued a National Coverage Decision in 2018.[19] Nevertheless, commercial health insurance payers often refuse coverage of CGP for two common reasons, the first being insufficient evidence

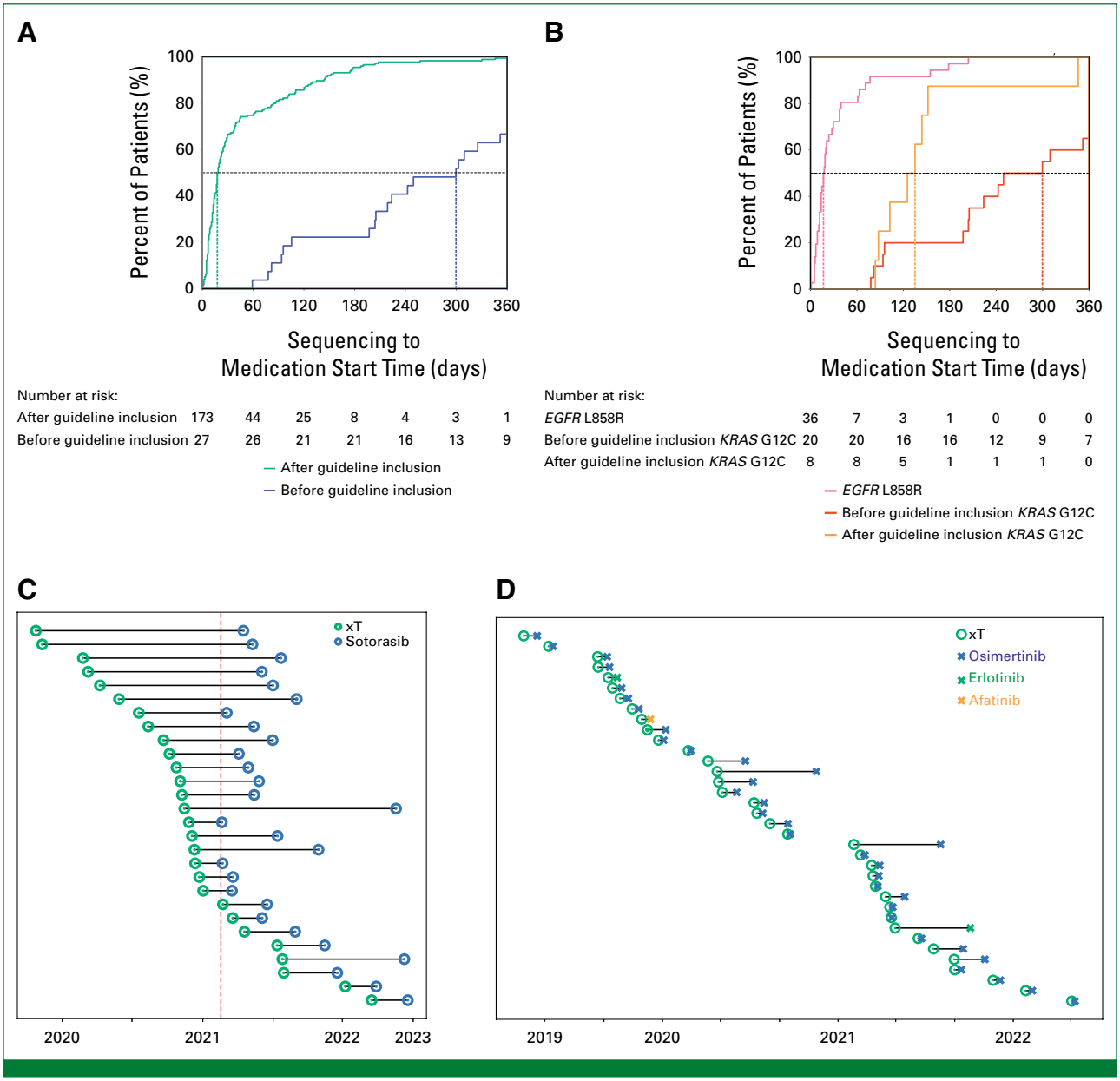

FIG 5. Timing from sequencing to start of targeted therapy. (A) Cumulative incidence plot of time from sequencing to start of targeted therapy for adherent patients, further stratified by adherent patients sequenced prior and post-NCCN guideline inclusion of matched targeted therapy. (B) Cumulative incidence plot of adherent patients with *EGFR* L858R and *KRAS* G12C variants, with *KRAS* G12C adherent patients further stratified by patients sequenced prior and post-NCCN guideline inclusion of sotorasib. (C) Swimmers plot of timing of sequencing and start of targeted therapy for adherent patients with *EGFR* L858R variants. (D) Swimmers plot of timing of sequencing and start of targeted therapy for adherent patients with *KRAS* G12C variants. NCCN, National Comprehensive Cancer Network.

of clinical utility to employ large panels over smaller panels (<50 genes).[20] However, smaller panels may not be able to detect ample targetable variants in the rapidly evolving NSCLC landscape. A recent study comparing testing with CGP to a smaller panel demonstrated a higher actionable variant detection rate with CGP (32.0% *v* 14.0%).[12] Commercial payers may also refuse coverage of CGP because of concerns that larger panel testing may result in high treatment variability outside of the guidelines.[21] Yet in our study, <5% (n = 57) of patients without actionable variants were given targeted therapies.

One of the main limitations of our analysis is the retrospective RW nature of the study, where the reasons for nonadherence were not specified and may not be fully captured. We could not control for confounders related to care access, including insurance coverage and time to prior authorization of testing that may lead to delays in treatment,[22,23] variability of clinical workflow, and differing electronic medical record environments of diverse practicing oncologists.[24] Finally, we were unable to stratify rwOS comparisons in adherent versus nonadherent patients by specific variant due to sample size limitations.

Nevertheless, this is a large study from a diverse patient population that provides insight into RW, clinical practice patterns of genomic testing and matched therapy adherence in an evolving landscape of new biomarker-matched therapy recommendations in NCCN guidelines. CGP test ordering and reporting were controlled as all providers ordered Tempus xT. Incorporation of timing of changes in oncology guidelines allowed for accurate calculation of adherence rates during the study period. Furthermore, our study's strict inclusion criteria for medication availability reduces potential data incompleteness seen in RW studies.

In a large, RW study of advanced NSCLC patients with CGP testing, most patients received NCCN-recommended targeted therapy. This is the first RW study illustrating that patients that received CGP results prior to NCCN guidelines inclusion of biomarker directed novel therapies received timely matched therapy once recommended in guidelines. These results demonstrate that CGP testing can provide valuable, genomic information from a single patient sample and be used to match patients efficiently to an ever increasing number of NCCN-recommended matched therapies.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/OP-24-00880. R.B., K.N., and R.P. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Deidentified data used in the research was collected in a real-world health care setting and is subject to controlled access for privacy and proprietary reasons. When possible, derived data supporting the findings of this study have been made available within the paper and its Appendix Tables A1-A3 and Figure A1.

AUTHOR CONTRIBUTIONS

Conception and design: Rotem Ben-Shachar, Kaveri Nadhamuni, Mark Carty, Rafi Pelossof, Daniel Morgensztern
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Real-World Adherence Patterns of Comprehensive Genomic Profiling to Biomarker Recommended Therapies in Patients With Advanced Non–Small Cell Lung Cancer

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APPENDIX

TABLE A1. Patients With Actionable Variants That Were Unevaluable for Adherence Analysis and Considered NonTargetable

Actionable Mutation	Received Therapy Prior to NCCN Guidelines Inclusion of Variant-Matched Therapy	Therapy Administered After Sequencing Was First-Line[a]	Total
KRAS G12C	89 (six received targeted therapy: four received sotorastib, two received afatinib)	46	135
EGFR exon 20 insertion	14 (four received osimertinib)	0	14
ERBB2 mutations	16 (six received ado-trastuzumab emtansine)	0	16
RET fusion	One (did not receive targeted therapy)	0	1
Total	120	46	166

Abbreviation: NCCN, National Comprehensive Cancer Network.
[a]Does not apply to RET fusions, where there is no line of therapy criteria.

TABLE A2. Variant Information for Patients With No Targetable Variants That Received Targeted Therapy

Medication Received	Targetable Gene	Number of Patients Receiving Medication	Number of Patients With Actionable But Non-Targetable Variant Due to Timing of Therapy	Number of Patients With Non-Targetable Pathogenic Variant(s) in Relevant Gene	No Pathogenic Variants in Targetable Gene
Afatinib	*EGFR*	10	0	3	7
Ado-trastuzumab emtansine	*ERBB2*	9	6	3	0
Osimertinib	*EGFR*	7	0	5	2
Trametinib + dabrafenib	*BRAF*	6	0	5	1
Sotorasib	*KRAS*	6	4	2	0
Capmatinib	*MET*	5	0	5	0
Crizotinib	*ALK*	4	0	0	4
Alectinib	*ALK*	3	0	0	3
Selpercatinib	*RET*	2	0	1	1
Vemurafenib	*BRAF*	1	0	1	0
Brigatinib	*ALK*	1	0	0	1
Cabozantinib	*RET*	1	0	0	1
Entrectinib	*ROS1*	1	0	0	1
Erlotinib	*EGFR*	1	0	1	0
All	NA	57	10 (17.5%)	26 (45.6%)	21 (36.8%)

Abbreviation: NA, not applicable.

TABLE A3. Timing of Therapy From Sequencing or NCCN Inclusion

Patient Subcohort	Number of Patients	Median Time From Sequencing to Start of Targeted Therapy (days)	Median Time From NCCN Inclusion to Start of Targeted Therapy (days)
Patients with targetable variants	201	23	NA
Patients with targetable variants sequenced pre-NCCN drug inclusion	27	304	96
Patients with targetable variants sequenced post-NCCN drug inclusion	174	18	NA
Patients with *EGFR* L858R variants	36	17	NA
Patients with *KRAS* G12C variants sequenced pre-sotorasib inclusion in NCCN guidelines	20	304	95
Patients with *KRAS* G12C variants sequenced post sotorasib inclusion in NCCN guidelines	8	137	NA
Targetable mutation, no-targeted therapy	33	24	NA
No targetable mutation, targeted therapy	57	82	NA
No targetable mutation, no targeted therapy	1,116	24	NA

Abbreviations: NA, not applicable; NCCN, National Comprehensive Cancer Network.

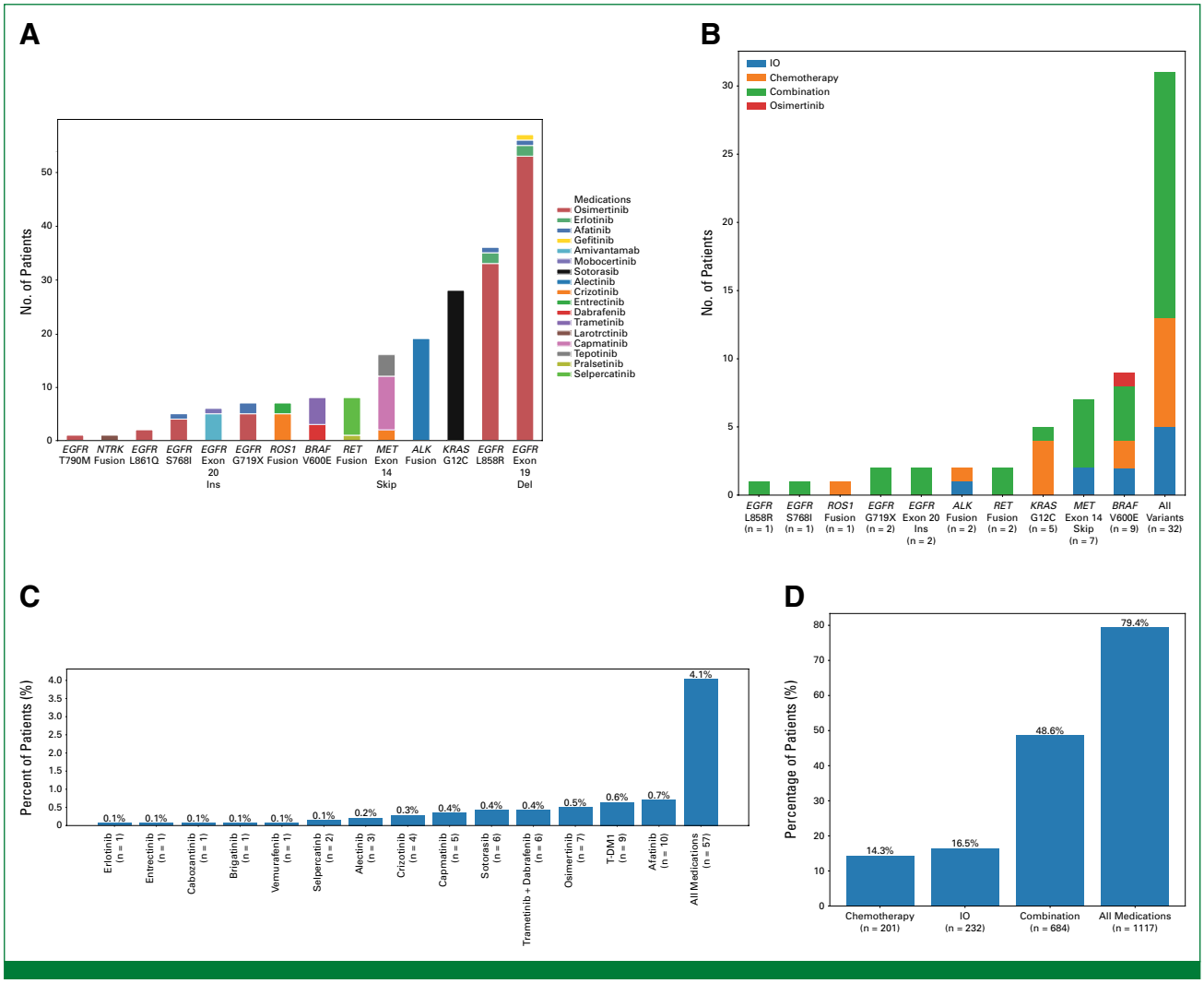

FIG A1. Medications received by patients in the full cohort. (A) Medications received by patients with targetable variants that received targeted therapy, that is, adherent patients (n = 201). (B) Medications received by patients with targetable variants that did not receive targeted therapy, that is, nonadherent patients (n = 32). (C) Medications received by patients with no targetable variants that received targeted therapy (n = 57). (D) Medications received by patients with no targetable variants that did not receive targeted therapy, that is, nonadherent patients (n = 1,117). chemo, chemotherapy; IO, immunotherapy.