Association of Timely Comprehensive Genomic Profiling With Precision Oncology Treatment Use and Patient Outcomes in Advanced Non–Small-Cell Lung Cancer

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ABSTRACT

PURPOSE Timely biomarker testing remains out of reach for many patients with advanced non–small-cell lung cancer (aNSCLC). Here, we studied the quality-of-care implications of closing the gap in timely receipt of comprehensive genomic profiling (CGP) to inform first-line (1L) decisions.

METHODS Using a real-world clinicogenomic database, we studied testing and 1L treatment patterns in aNSCLC after the approval of pembrolizumab in combination with pemetrexed and carboplatin (May 10, 2017). To estimate the association of timely CGP results with therapy selection and patient outcomes, we identified patients with no previous genomic testing beyond PD-L1 immunohistochemistry and dichotomized patients by whether CGP results were available before or after 1L therapy initiation.

RESULTS In total, 2,694 patients were included in the 1L therapy decision impact assessment. Timely CGP increased matched targeted therapy use by 14 percentage points (17% with CGP *v* 2.8% without) and precision immune checkpoint inhibitor (ICPI) use by 14 percentage points (18% with CGP *v* 3.9% without). Receipt of timely CGP resulted in an estimated 31 percentage point decrease in ICPI use among *ALK/EGFR/RET/ROS1*-positive patients at an expected per-patient reduction in ineffective ICPI therapy cost of $13,659.37 with timely CGP to inform 1L treatment selection. Patient benefit of CGP extended to real-world time to therapy discontinuation (median time to therapy discontinuation: 3.9 *v* 10 months [hazard ratio, HR, 0.54 [95% CI, 0.42 to 0.70]; P = 1.9E-06; adjusted hazard ratio [aHR], 0.50 [95% CI, 0.38 to 0.67]; P = 2.0E-06) in 1L driver-positive patients. This effect was not significant for real-world overall survival (median overall survival: 32 *v* 29 months [HR, 1.2 [95% CI, 0.84 to 1.67]; P = .33; aHR, 1.4 [95% CI, 0.92 to 1.99]; P = .12).

CONCLUSION Timely CGP is associated with the quality of patient care as measured by 1L matched targeted therapy use, time to therapy discontinuation, and avoidance of ineffective, costly ICPIs.

ACCOMPANYING CONTENT

Data Supplement

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INTRODUCTION

Our understanding of advanced non–small-cell lung cancer (aNSCLC) has expanded the role of biomarkers in treatment selection with direct impact on overall survival (OS) for patients.[1-3] Patient genomics are critical to first-line (1L) and second-line (2L) therapy selection in aNSCLC. For patients with oncogenic drivers including *EGFR* (common deletions/mutations in exon19/exon21), *BRAF* V600E, *MET*-exon14 skipping, as well as oncogenic fusions in *ALK*, *ROS1*, *RET*, and *NTRK* targeted therapies are approved 1L.[4,5] *KRAS* G12C, *EGFR* exon20 insertions, and *HER2* mutations are all additional actionable findings with 2L therapy approvals.[6] Timely, comprehensive biomarker testing is now critical to determine matched targeted therapy opportunities.

For patients whose tumors lack an actionable driver, immune checkpoint inhibitors (ICPIs), either as monotherapy, doublet-ICPI, or chemo-ICPI, are all 1L therapy options. However, predicting patient response to ICPIs remains challenging with durable responses limited to 20%-30% of ICPI-treated patients.[7,8] Currently, PD-L1 immunohistochemistry (IHC)

CONTEXT

Key Objective

We studied how the timing of comprehensive genomic profiling (CGP) relative to first-line (1L) initiation was associated with outcomes for patients with advanced non–small-cell lung cancer (aNSCLC) including 1L therapy selection, expenditure on immune checkpoint inhibitors (ICPIs) among *EGFR/ALK/RET/ROS1*-positive patients, and time-to-event outcomes.

Knowledge Generated

A total of 2,694 patients with aNSCLC pursuing 1L treatment were included in our study. Timely CGP before 1L initiation was associated with increased targeted therapy use, decreased expenditure on ICPIs among *ALK/EGFR/RET/ROS1* driver-positive patients, and longer time to therapy discontinuation. There was not a statistically significant difference in overall survival on the basis of CGP report timing. Eleven percent of patients initiating a chemotherapy-based 1L therapy before CGP result availability had a 1L actionable genomic finding.

Relevance

These findings support the importance of timely CGP to inform optimal 1L therapy selection in aNSCLC.

informs mono-ICPI use in the 1L with approval for patients with PD-L1 tumor proportion score (TPS) at or above 1%.[8,9] However, there remains significant uncertainty in ICPI response even when a patient's PD-L1 TPS is above 50%.[10] In addition, emerging evidence suggests tumor mutational burden (TMB) independently predicts ICPI treatment benefit beyond PD-L1, potentially expanding the relevance of comprehensive genomic profiling (CGP)–specific results for patients considering ICPI therapy options.[10] The choice to pursue mono-ICPI remains challenging and requires identifying both predictive biomarkers of ICPI benefit and concurrent presence of *ALK/EGFR/RET/ROS1* drivers, which suggest ICPI resistance and superior targeted therapy options.[11,12]

Recently, ASCO released a recommendation for multigene panel–based genomic testing among all advanced or metastatic patients with at least two applicable biomarker-linked regulatory agency–approved therapies.[13] Yet, many patients with aNSCLC still do not receive timely CGP testing.[14,15] There is a growing body of evidence that real-world comprehensive biomarker testing among patients with aNSCLC lags clinical guidelines. Recent studies have now further tied these testing delays to survival outcomes.[16,17]

Here, we studied the association of timely CGP with 1L therapy selection among patients with aNSCLC. We considered the decision impact of CGP testing by therapy class overall and among 1L driver-positive patients specifically. We further estimated the decision impact and cost implications of timely CGP on ineffective ICPI use among *ALK/EGFR/RET/ROS1* driver-positive patients. Finally, we studied the association between timely CGP and real-world time to therapy discontinuation (rwTTD) and real-world overall survival (rwOS).

METHODS

Cohort Selection

This study used real-world data from the Flatiron Health (FH)-Foundation Medicine (FMI) Clinico-Genomic Database (CGDB), a nationwide (US-based) deidentified electronic health record (EHR)–derived database that includes patients sequenced at FMI who received care within the FH network. The deidentified data originated from approximately 280 US cancer clinics (approximately 800 sites of care). Retrospective longitudinal clinical data were derived from electronic EHR data, comprising patient-level structured and unstructured data, curated via technology-enabled abstraction, and were linked to genomic data derived from FMI comprehensive CGP tests in the FH-FMI CGDB by deidentified, deterministic matching.[18] This study included 2,694 patients diagnosed with de novo aNSCLC who received FMI tissue CGP testing and were treated in the FH network between May 2017 and September 2022. Cohorts included in our analysis were limited to patients who had tissue CGP (FoundationOne or FoundationOne CDx). Patients who received their FMI report >60 days after their last FH network visit date were excluded to ensure that patients received CGP testing while they were receiving care in the FH network.

For FMI genomic analysis, approval for this study, including a waiver of informed consent and a Health Insurance Portability and Accountability Act waiver of authorization, was obtained from the Western Institutional Review Board Copernicus Group (WCG) Institutional Review Board (IRB; protocol No. 20152817). For FH-FMI CGDB analysis, IRB approval with waiver of informed consent was also obtained before study conduct from WCG IRB.

Comprehensive Genomic Profiling

For tissue specimens collected during routine clinical care, DNA was extracted from 40 microns of formalin-fixed paraffin-embedded (FFPE) sections and CGP was performed on hybridization-captured, adaptor ligation–based libraries to a mean coverage depth of >550X for 315 or 324 cancer-related genes plus selected introns from 28 or 36 genes frequently rearranged in cancer, as previously described.[19,20] The results were analyzed for base substitutions, short insertions/deletions, copy-number alterations, and rearrangements. TMB was calculated by counting the number of nondriver synonymous and nonsynonymous mutations across a 0.8-1.2 Mb region, with computational germline status filtering and reported as mutations/Mb, as previously described.[21]

PD-L1 IHC

PD-L1 expression was determined by IHC on FFPE tissue sections using the Dako 22C3 PD-L1 antibody, depending on the laboratory (both FMI PD-L1 testing and PD-L1 testing external to FMI available in the patient's EHRs). PD-L1 TPS was reported as a continuous variable with the percentage of positively stained tumor cells and summarized as negative (<1%), low positive (1%-49%), or high positive (≥50%).

1L Therapy Classification

1L therapies were classified as precision or empiric therapy according to both therapy type and the genomic status of the patient. Precision therapies required molecular or genomic findings, while empiric therapies did not. Precision therapies included two subcategories: matched targeted therapies and precision ICPIs. Matched targeted therapies include inhibitors of the respective oncogene for the following alterations as referred to in the National Comprehensive Cancer Network (NCCN) Guidelines (version 2.2023): *EGFR* mutations (exon 19 deletion, exon 20 insertion, L858R, G719X, S768I, L861Q), *BRAF* V600E, *KRAS* G12C, *MET* exon 14 skipping alterations, *MET* amplification, *ERBB2* mutations of known or likely functional significance, *ALK*-, *ROS1*-, or *RET*-activating rearrangements, and *NTRK* fusions. Designation of a patient's treatment regimen as a matched targeted therapy was restricted to only 1Ls initiated on or after the first oncogene-specific approval date (Data Supplement, Table S1). Precision ICPIs included mono- or doublet-ICPI given to *ALK/EGFR/RET/ROS1*-negative patients with either TMB ≥10 or PD-L1+ status. Mono-ICPI use when PD-L1 was missing/unobserved and TMB <10 was classified as other, given mono-ICPIs approvals are limited to PD-L1+ patients. Given doublet-ICPIs are approved for PD-L1 0%, these regimens were classified as precision ICPI regardless of PD-L1 or TMB status. Empiric therapies included any chemotherapy-containing regimen, including chemo-ICPI.

Clinical study drugs (masked) given alone were captured as their own category and clinical study drugs given in combination with another therapy were classified as other. Targeted therapies given to patients without an associated matched driver alteration (eg, osimertinib to a patient without an *EGFR*+ CGP result) are referred to as nonmatched targeted therapies and included in the other therapy classification group. Mono-ICPI regimens given to patients who do not meet the precision ICPI criteria (negative for *ALK/EGFR/RET/ROS1* and relevant TMB or PD-L1 status) were also classified as other. A full list of regimens classified as other is available in the Data Supplement (Table S2).

Statistical Considerations

rwOS was defined as the time from first therapy administration to date of death.[22] Patients without a death event were censored at their last date of known activity. rwTTD was defined as the time from the therapy start to therapy discontinuation for any reason. Patients with no evidence of treatment discontinuation, recorded date of death, or evidence of structured activity after their last therapy administration were censored. To account for left truncation, a patient's entry date into the CGDB was considered the later of the date of a patient's second visit in the FH network or their first eligible FMI CGP report. Risk set adjustment was used to ensure patients treated before entry date were not included in the at-risk population until they reached their entry date. Patients who received the entirety of their treatment line before entry date were excluded. The results from the clinical outcomes analysis were summarized with Kaplan-Meier plots of rwOS and rwTTD and corresponding Cox proportional hazards models.

The costing analysis focused on ICPI doses administered to *ALK/EGFR/RET/ROS1*-positive patients on chemo-ICPI or nonprecision ICPIs included in the other therapy category. Outcome measures included the time on and cost of ineffective ICPIs, and the expected ICPI expenditure change with timely CGP. The cost of ICPIs was based on doses administered in the patient medical records matched to the October 2022 Medicare Part B payment allowance limit (Data Supplement, Table S3). A per-infusion cost of $140.16 US dollars (USD) was applied on the basis of the 2022 Centers for Medicare and Medicaid Services physician fee schedule (CPT 96413). Since all patients in this analysis received CGP, the cost of CGP was equivalent between cohorts. Costs are reported in 2022 USD.

RESULTS

Cohort Characteristics

A total of 2,694 patients with aNSCLC filtered for data missingness with documented therapy use are shown in the flow diagram (Fig 1). Clinicopathologic characteristics differed between patients who received 1L treatment before versus after CGP report availability (Table 1). Patients with a 1L therapy start before CGP report availability had a higher prevalence of squamous cell histology, were more frequently treated at community practices, had higher prevalence of stage IIIB-C versus IV cancers, and had lower driver

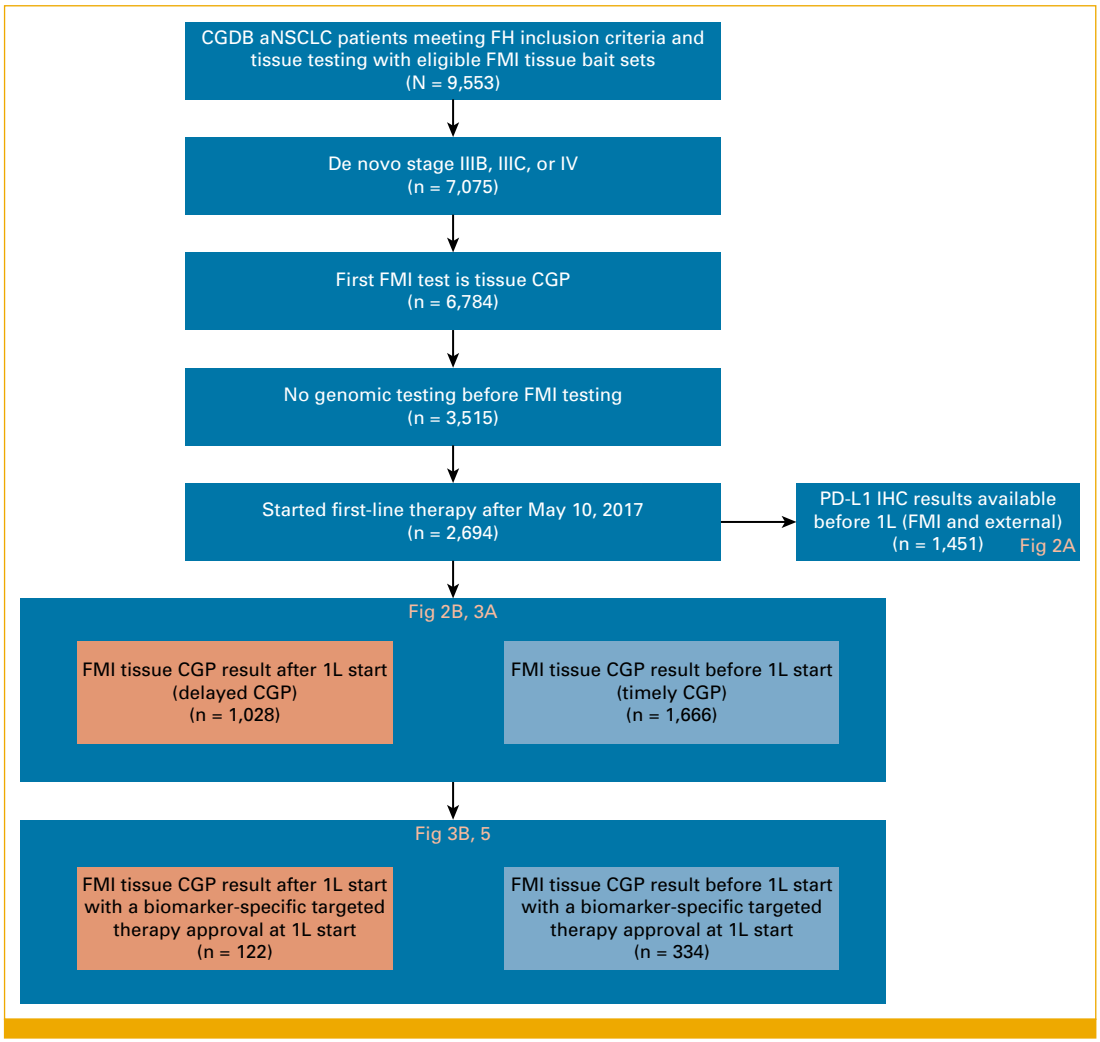

FIG 1. Flow diagram. 1L, first-line; aNSCLC, advanced non–small-cell lung cancer; CGDB, Clinico-Genomic Database; CGP, comprehensive genomic profiling; FH, Flatiron Health; FMI, Foundation Medicine; IHC, immunohistochemistry.

prevalence compared with patients who started 1L treatment with available CGP results (Table 1).

Real-World Treatment and Testing Patterns

For the 2,694 patients with aNSCLC with no genomic testing before their FMI CGP test, we evaluated treatment patterns and biomarker test timing. For the 1,451 patients with a PD-L1 IHC result before 1L initiation, precision ICPI was the dominant therapy choice for patients with a TPS ≥ 50%. Chemo-ICPI was the most common choice among patients with a TPS <50% and of the 545 patients with PD-L1 TPS ≥50%, 122 (22%) also received 1L chemo-ICPI (Fig 2A). For a subset of 1,262 patients with FMI PD-L1 IHC results reported before 1L initiation and before receipt of their CGP report, 165 (13%) initiated 1L treatment after receipt of their PD-L1 IHC result but before their CGP report. CGP reporting shifted earlier over time, increasing result availability at 1L initiation from 36% in 2014 to 63% in 2022. However, 1L decision making persistently occurs without CGP results (Data Supplement, Fig S1). Focusing on the 2,204 patients who started 1L therapy within 60 days of their CGP report, CGP results were available before 1L therapy initiation for only 60% of patients (1,313/2,204; Fig 2B). Among patients with nonsquamous aNSCLC, we observed similar tension between 1L chemo-ICPI and precision ICPI, with 63% of patients having CGP results before 1L initiation (Data Supplement, Figs S2 and S3).

Decision Impact of CGP Report Availability for 1L Therapy Selection

We assessed the impact of timely CGP on 1L treatment selection in a cohort of 2,694 patients. Although we can observe the occurrence of previous genomic testing, the biomarker results are limited and do not include all biomarkers with actionability 1L or genomic results sufficient in all cases to determine actionability. Because of these limitations, we excluded 3,269 patients on the basis of previous genomic testing. We studied patients who initiated 1L therapy after May 10, 2017, the approval date for pembrolizumab in

TABLE 1. Clinicogenomic Characteristics of Patients Who Initiated 1L Treatment Before (n = 1,028) Versus After (n = 1,666) CGP Report Receipt

	1L Therapy Decision Context		
Characteristic	Before CGP Results Available	After CGP Results Available	*P*
Sample size, No.	1,028	1,666	
Sex (M:F), %	57:43	50:50	.001
Age at diagnosis, years, median (IQR)	68 (61-74)	68 (61-76)	.13
Ancestry, No. (%)			
European	834 (81.1)	1,349 (81.0)	.32
African	97 (9.4)	175 (10.5)	
Admixed American	56 (5.4)	74 (4.4)	
East Asian	40 (3.9)	60 (3.6)	
South Asian	1 (0.1)	8 (0.5)	
Practice type, No. (%)[a]			
Academic	42 (4.1)	151 (9.1)	<.001
Community	985 (95.8)	1,506 (90.6)	
Academic/community	1 (0.1)	6 (0.4)	
Histology, No. (%)			
Nonsquamous cell carcinoma	642 (62.5)	1,293 (77.6)	<.001
Squamous cell carcinoma	326 (31.7)	303 (18.2)	
NOS	60 (5.8)	70 (4.2)	
History of smoking, No. (%)[b]	931 (90.7)	1,398 (84.0)	<.001
Stage, No. (%)			
IIIB-C	247 (24.0)	238 (14.3)	<.001
IV	781 (76.0)	1,428 (85.7)	
ECOG, No. (%)[c]			
0	304 (34.0)	441 (30.1)	.13
1	395 (44.2)	669 (45.7)	
≥2	194 (21.7)	354 (24.2)	
TMB, mut/Mb, median	10.3	9.4	.03
PD-L1 status, No. (%)[d]			
≥50%	258 (50.6)	482 (51.1)	.13
1%-49%	239 (46.9)	418 (44.3)	
<1%	13 (2.5)	44 (4.7)	
Driver, No. (%)			
ALK rearrangement	24 (2.3)	50 (3.0)	<.001
BRAF V600E	13 (1.3)	31 (1.9)	
EGFR mut	73 (7.1)	240 (14.4)	
ERBB2 mut	16 (1.6)	25 (1.5)	
KRAS G12C	107 (10.4)	188 (11.3)	
METex14/amp	47 (4.6)	80 (4.8)	
NTRK fusion	1 (0.1)	0 (0.0)	
RET rearrangement	5 (0.5)	15 (0.9)	
ROS1 rearrangement	6 (0.6)	9 (0.5)	
Multiple	3 (0.3)	14 (0.8)	
Negative	733 (71.3)	1,014 (60.9)	

Abbreviations: 1L, first-line; CGP, comprehensive genomic profiling; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; TMB, tumor mutational burden.

[a]Practice type was available for 1,663 patients with available CGP results before 1L.

[b]Smoking history was available for 1,027 with delayed CGP and 1,665 with timely CGP 1L patients.

[c]ECOG was available for 893 with delayed CGP and 1,464 with timely CGP 1L patients.

[d]PD-L1 was available for 510 with delayed CGP and 944 with timely CGP 1L patients.

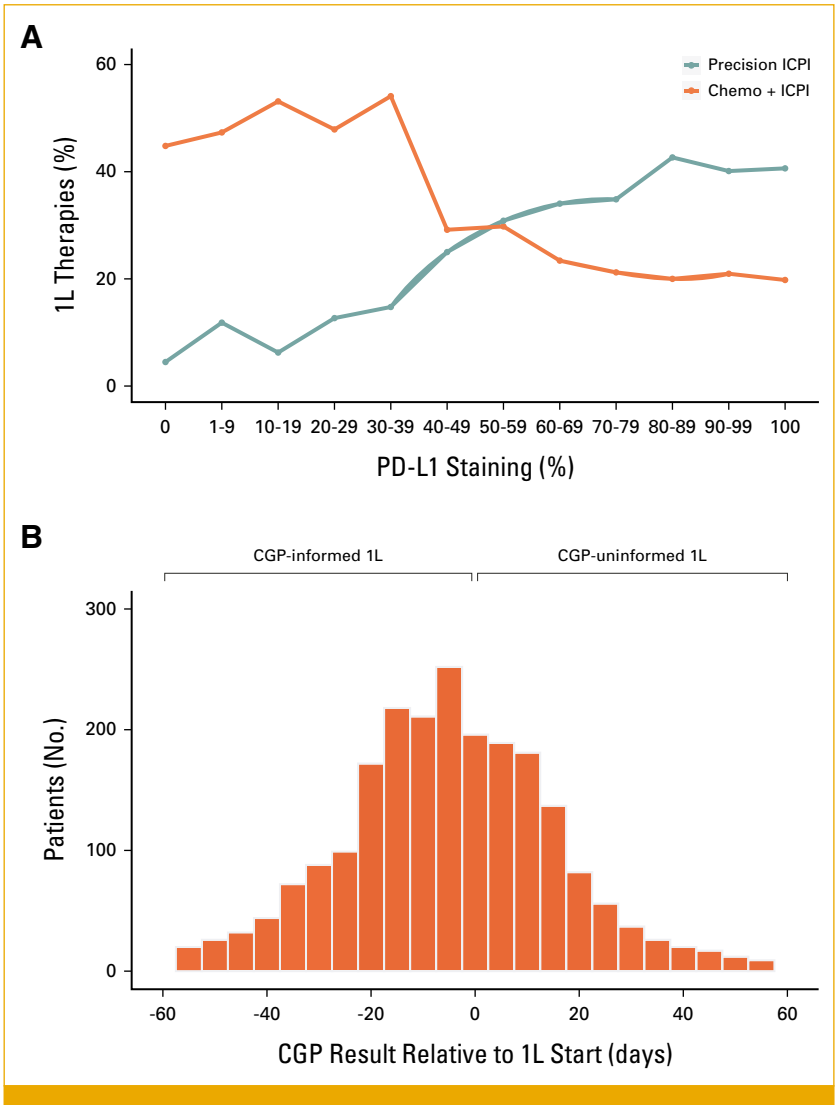

FIG 2. Biomarker testing patterns relative to initiation of 1L therapy. (A) Prevalence of 1L precision ICPI (n = 284) versus chemo-ICPI (n = 544) relative to PD-L1 staining percentage for the 1,451 patients with PD-L1 IHC results before 1L initiation. The percentage of 1L therapies shown is out of all 1L regimens observed, all other patients received other nonprecision ICPI or chemo-ICPI regimens. (B) Distribution of CGP report delivery among patients who received their CGP report within 60 days of 1L initiation. CGP report delivery was frequently either just before or just after initiation of 1L treatment. 1L, first-line; CGP, comprehensive genomic profiling; ICPI, immune checkpoint inhibitor; IHC, immunohistochemistry.

combination with pemetrexed and carboplatin.[23] Figure 3 plots 1L therapy class use by delayed versus timely CGP (Fig 3A) and among 1L driver-positive patients specifically (Fig 3B). The Data Supplement (Fig S4) plots the absolute percentage point change by therapy class when CGP results were available for 1L decision making.

For patients who received 1L therapy before receipt of their CGP results (delayed CGP; n = 1,028), 6.7% received a precision therapy, classified as a matched targeted therapy (2.8%) or precision ICPI (3.9%). Ninety percent of patients without available CGP results received an empiric therapy, most commonly chemotherapy alone (46%) or chemo-ICPI (44%). CGP result availability before 1L was associated with a 28 percentage point increase in precision therapy use (35% timely CGP *v* 6.7% delayed) and a 35 percentage point decrease in empiric therapy use (55% timely CGP *v* 90% delayed). Among precision therapy options, precision ICPI and matched targeted therapy use both increased by 14 percentage points.

CGP availability was associated with clinical study drug use (3 percentage point increase; 3.8% with timely CGP *v* 0.78% without). The remaining patients received either a nongenomically matched targeted therapy, a nonprecision

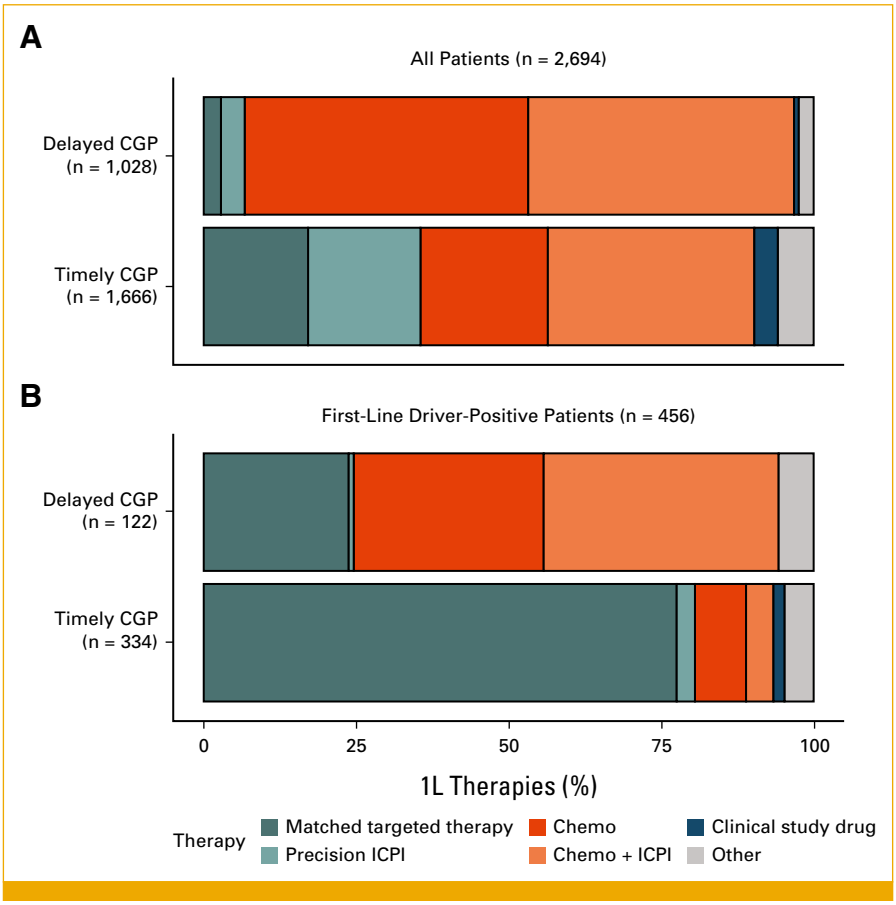

FIG 3. Decision impact of CGP on 1L treatment selection. Distribution of 1L therapy categories between patients who started 1L before (delayed CGP) versus after (timely CGP) report availability. (A) All patients without previous genomic testing who started 1L after May 10, 2017 (approval of 1L pembrolizumab + pemetrexed + carboplatin; n = 2,694), and (B) subanalysis for patients with a targetable driver alteration with an FDA-approved 1L targeted therapy available at the time of 1L initiation (n = 456). Therapy categories are defined in the Methods section. 1L, first-line; CGP, comprehensive genomic profiling; FDA, US Food and Drug Administration; ICPI, immune checkpoint inhibitor.

ICPI, or other rare therapy regimens, as shown collectively in gray on Figure 3. The Data Supplement (Table S4) includes the percentage share by therapy class as well as absolute and relative percentage point changes with timely CGP. The association between timely CGP and precision therapy use was amplified among patients with a 1L actionable driver, where CGP availability was associated with a 56 percentage point increase in precision therapy use and a 57 percentage point decrease in empiric therapy (Fig 3B; Data Supplement, Table S5). We observed analogous results among nonsquamous aNSCLC, with a 30 percentage point increase in precision therapy use (39% timely CGP *v* 8.6% delayed) and a 36 percentage point decrease in empiric therapy use (52% timely CGP *v* 88% delayed) associated with CGP report availability (Data Supplement, Fig S5).

Among the 1,028 patients who started 1L therapy before CGP, 926 (90%) received either chemotherapy alone (46%; 478/1,028) or chemo-ICPI (44%). Of these patients, 11% (99/926) had a targetable NCCN aNSCLC driver alteration with an approved 1L therapy. An additional 16% (145/926) of patients had 2L or off-label therapy options on the basis of their CGP results (primarily *KRAS* G12C). Patient results included *KRAS* G12C mutations (11%), canonical and uncommon EGFR driver mutations (5.4%), *ALK* rearrangements (1.8%), *MET* exon 14 (1.5%), and *BRAF* V600E (1.3%), among others. Elevated TMB (≥10 mut/Mb) comprised an additional 325 (35%) patient results (Fig 4). The Data Supplement (Table S6) disaggregates Figure 4 results by histology. Nonsquamous patients were enriched for driver-positive findings compared with squamous and not otherwise specified histologies (37% *v* 7.8% and 18%, respectively). Thirty percent of nonsquamous and 43% of squamous samples were driver-negative and had elevated TMB ≥10 mut/Mb.

Clinical Impact of Decision Making With CGP Results

The benefits of timely CGP extended to quantifiable and significant gains in real-world time to therapy discontinuation (median time to therapy discontinuation: 3.9 *v* 10 months

[hazard ratio, HR, 0.54 [95% CI, 0.42 to 0.70]; P = 1.9E-06; adjusted hazard ratio [aHR], 0.50 [95% CI, 0.38 to 0.67]; P = 2.0E-06) when comparing the cohort of 1L driver-positive patients with timely CGP versus delayed CGP (Fig 5). This same effect was not statistically significant for real-world OS (median overall survival: 32 *v* 29 months [HR, 1.2 [95% CI, 0.84 to 1.67]; P = .33; aHR, 1.35 [95% CI, 0.92 to 1.99]; P = .12) potentially because of use of precision therapies in later lines (Fig 5). We observed a similar association between timely CGP with rwTTD among patients with nonsquamous histology (Data Supplement, Fig S6).

Financial and Time Implications of Ineffective ICPI Use

Among *ALK/EGFR/RET/ROS1*-positive patients (n = 426), timely CGP increased use of matched targeted therapies by 52 percentage points (76% with CGP *v* 24% without), while simultaneously decreasing ineffective ICPI use by 31 percentage points (12% with CGP results *v* 43% without CGP; Data Supplement, Fig S7 and Table S7). *ALK/EGFR/RET/ROS1*-positive patients spent an average of 2.3 months with a range of 0-18.3 months corresponding to 1-27 ICPI infusions administered. The average estimated per-patient cost of ICPI treatment for these patients was $44,062.48. Patient-level cost of ICPI therapy ranged from $9,988.08 to $445,623.12. The expected expenditure reduction on ineffective ICPI therapy with timely CGP for all patients before 1L decision making was estimated as $13,659.37 per *ALK/EGFR/RET/ROS1*-positive patient (calculation details are available in the Data Supplement, Table S3).

DISCUSSION

The set of biomarkers informative for therapy selection in aNSCLC warrants CGP as standard of care to enable quality, precision oncology care. Yet, CGP remains underutilized despite coverage for advanced-stage Medicare beneficiaries since 2018 and subsequent coverage improvements in commercial and Medicaid beneficiary populations.[24,25] This study demonstrates the value of timely CGP testing to inform 1L therapy selection as measured by positive precision oncology decision impact, longer time to therapy discontinuation, and reduced time and expenditure on ineffective ICPIs among *ALK/EGFR/RET/ROS1*-positive patients.

Importantly, over half of the patients with delayed CGP received those results within 2 weeks of 1L therapy initiation. Our results suggest that waiting and incorporating CGP results into patient care matters. CGP availability before 1L was associated with increased clinical study drug, matched targeted therapy, and precision ICPI use. Encouragingly, CGP results are increasingly available before 1L. However, even in 2022, nearly half of all the CGP reports were delivered after 1L initiation. Patients are continuing to miss therapy options that account for their specific genomic profiles; we found that 11% of patients in the delayed CGP cohort had a US Food and Drug Administration–approved 1L actionable driver alteration. Although some patients may require urgent decisions without waiting for CGP results, many will benefit from waiting as demonstrated by both the increased precision therapy use and the time to therapy discontinuation findings.

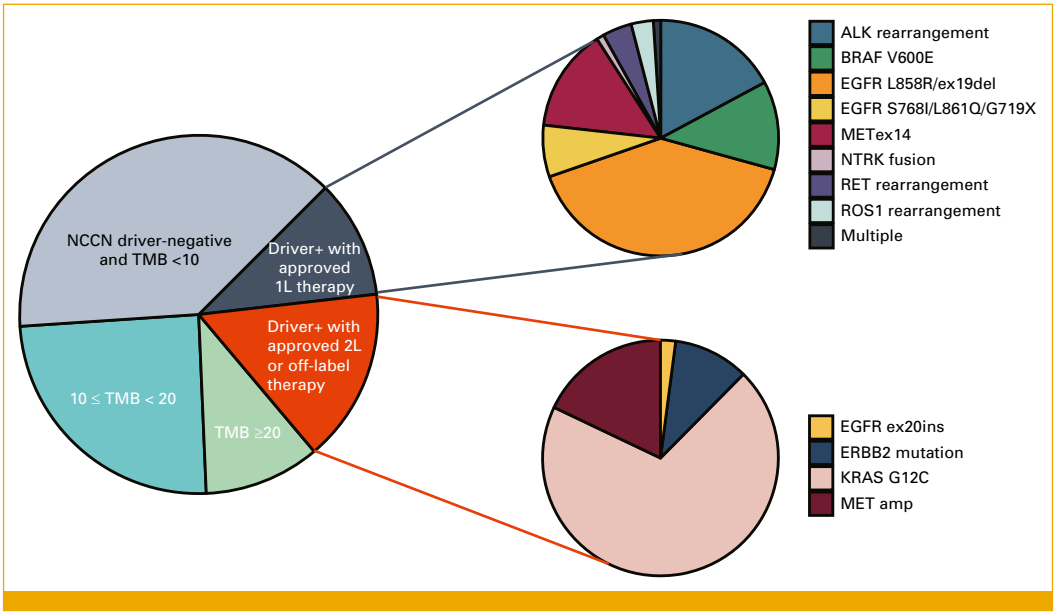

FIG 4. Targetable alterations identified in patients who received CGP results after starting 1L empiric chemotherapy or chemo-ICPI. Landscape of targetable drivers approved for 1L or 2L or off-label detected by CGP after initiation of 1L empiric chemo-ICPI (n = 448) or 1L empiric chemotherapy (n = 478) before known CGP results. Percentages specific to each result category as well as category breakdowns by histology are available in the Data Supplement (Table S6). 1L, first-line; 2L, second-line; CGP, comprehensive genomic profiling; ICPI, immune checkpoint inhibitor; NCCN, National Comprehensive Cancer Network; TMB, tumor mutational burden.

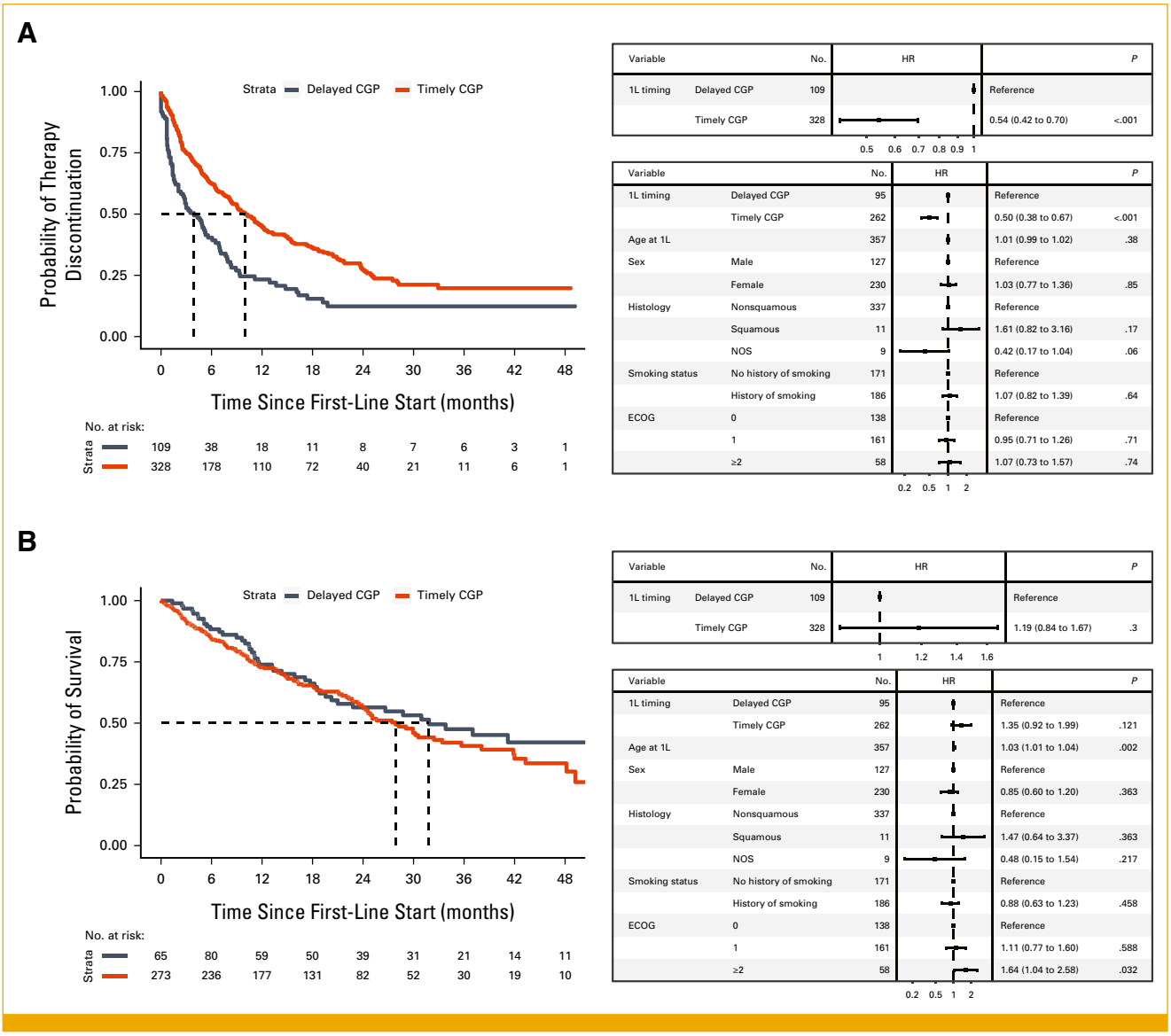

FIG 5. Receiving CGP reports before 1L therapy leads to longer rwTTD but not rwOS. Kaplan-Meier curve for real-world (A) time to treatment discontinuation and (B) overall survival for 437 patients with a targetable driver on their CGP report, an FDA-approved driver-matched targeted therapy available at the time of 1L initiation, and no previous genomic testing. Patients who initiated 1L therapy before CGP results (n = 109) were classified as delayed CGP versus those starting therapy after receipt of their CGP report (n = 328) were classified as timely CGP. Forest plots from univariate (top) and multivariable (bottom) Cox models are shown on the right. 1L, first-line; CGP, comprehensive genomic profiling; ECOG, Eastern Cooperative Oncology Group; FDA, US Food and Drug Administration; HR, hazard ratio; NOS, not otherwise specified; rwOS, real-world overall survival; rwTTD, real-world time to therapy discontinuation.

When PD-L1 IHC results are returned faster than CGP results, there may be specific pressure to act on the limited information available from patient PD-L1 status alone. This study highlights the potential pitfalls of relying solely on patient PD-L1 status. Acting on PD-L1 results alone misses clinical trial matches, patient-specific targeted therapy options, and chemosparing mono-ICPI treatment opportunities, and may lead to ineffective ICPI use among driver-positive patients. When driver status is unknown and driver-positive patients instead receive chemo-ICPI, patients face elevated risk of severe immune-related events on subsequent targeted therapy, making mistakes in 1L selection costly even after 1L discontinuation.[26]

Here, OS did not differ significantly between study cohorts. It is possible that patients with delayed CGP still benefited from those results in subsequent therapy lines. Furthermore, real-world observational treatment benefits, particularly when focused on testing as the interventional effect, are often attenuated compared with randomized controlled trials. Importantly, we did observe longer 1L time to therapy discontinuation for driver-positive patients when CGP

results were available before 1L. This study did not distinguish reasons for discontinuing therapy such as progression, the return of actionable biomarker information, or newly approved therapy options. From the patient, payer, and societal perspectives, the ability to avoid the use of ineffective therapies is another benefit of timely CGP. Overall, 19% (83 of 426) of *ALK/EGFR/RET/ROS1*-positive patients received 1L chemo-ICPI (n = 60) or nonprecision ICPIs classified as other (n = 23). We estimated that timely CGP could reduce expected expenditure on ineffective ICPIs by $13,659.37 per *ALK/EGFR/RET/ROS1*-positive patient.

Limitations of this study include our reliance on the FH-FMI CGDB, where all patients eventually receive CGP. Effect estimates from this population may be biased toward patients with a priori lower likelihoods of oncogenic drivers (patients with previous negative results then tested with CGP) or patient characteristics associated with CGP access such as insurance type or socioeconomic status. Patients in the timely CGP cohort were more often nonsmokers, diagnosed at stage IV, and received care at an academic center. We also observed some matched targeted therapy use among driver-positive patients before CGP result receipt, indicating potential missing genomic testing in our data set. Furthermore, this study only estimated the decision impact and patient outcomes comparing timely versus delayed CGP, not the full continuum of biomarker testing experiences. As liquid CGP is well suited to improve the timeliness of biomarker results for patients, further work assessing the decision impact of liquid CGP is needed.

In the coming years, therapy selection will continue to increase in complexity with consideration of oncogenic drivers, continuous biomarkers such as PD-L1 and TMB, prognostic genomics such as *STK11*, and patient ctDNA dynamics to monitor treatment response.[27] Furthermore, the US health system is under pressure to reduce health care spending and improve efficiency.[28] Closing the gap in timely CGP holds the possibility of not only improving patient care, but reducing ineffective, costly ICPI use in specific genomic subpopulations.

This study demonstrates that the lagging biomarker testing observed in aNSCLC is a quality-of-care barrier to precision oncology therapy access. With a comprehensive understanding of each patient's genomic profile, patients are more likely to receive matched targeted therapies, precision ICPIs, and clinical study drugs. That decision impact translates to longer time to therapy discontinuation among 1L driver-positive patients and reduced expenditure on ICPIs in *ALK/EGFR/RET/ROS1*-positive patients. Timely CGP is associated with improved 1L therapy selection and reduced health system ICPI expenditure inefficiencies.

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