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Original Article

Clinical Value of Timely Targeted Therapy for Patients With Advanced Non–Small Cell Lung Cancer With Actionable Driver Oncogenes

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Abstract

Background: A recent real-world study observed that 24% of patients with advanced non–small cell lung cancer (aNSCLC) with actionable driver oncogenes (ADOs) initiated nontargeted therapies before biomarker test results became available. This study assessed the clinical impact of the timing of first-line (1L) targeted therapies (TTs) in aNSCLC.

Materials and Methods: This retrospective analysis of a nationwide electronic health record–derived deidentified database included patients aged ≥18 years diagnosed with aNSCLC with ADOs (ALK, BRAF, EGFR, RET, MET, ROS-1, and NTRK) from January 1, 2015, to October 18, 2022, by biomarker testing within 90 days after advanced diagnosis and received 1L treatment. Cohorts were defined by treatment patterns ≤42 days after test results: "Upfront TT" received 1L TT ≤42 days; "Switchers" initiated 1L non-TT before or after testing but switched to TT ≤42 days; and "Non-switchers" initiated non-TT before or after testing and did not switch at any time. Adjusted multivariate Cox regression evaluated real-world progression-free survival, real-world time to next treatment or death, and real-world overall survival.

Results: A total of 3540 patients met the study criteria; 78% were treated in a community setting, and 50% underwent next-generation sequencing (NGS). There was no significant difference in outcomes between Switchers and Upfront TT; inferior outcomes were observed in Non-switchers versus Upfront TT.

Conclusion: Our findings demonstrated improved outcomes with upfront 1L TT versus non-TT in patients with aNSCLC with ADOs and observed timely switching to TT after biomarker test result had similar outcomes to Upfront TT. Opportunities remain to improve the use of NGS for early ADO identification and determination of 1L TT.

Key words: targeted therapy; NSCLC; real-world data; oncology.

Implications for Practice

This is the largest study to date to evaluate the clinical impact of different timing and treatment patterns of first-line (1L) targeted therapy (TT) in patients with advanced non–small cell lung cancer with an actionable driver oncogene (ADO) in a predominately community setting. The findings defined the appropriate timing to use biomarker testing results to inform treatment decisions and optimize patient outcomes. Opportunities remain to improve the use of next-generation sequencing for early identification of all ADOs and determination of appropriate 1L TT when indicated.

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Introduction

The treatment landscape for patients with advanced non–small cell lung cancer (aNSCLC) has evolved with numerous targeted therapies (TTs) approved by the US Food and Drug Administration (FDA). The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommends biomarker testing for patients with locally advanced and metastatic NSCLC to identify actionable biomarkers to inform the appropriate TT or immunotherapy.[1] The incremental effectiveness of biomarker-driven TT has been observed in routine clinical care; patients with an actionable driver oncogene (ADO) who received appropriate TT had significantly longer median overall survival compared with patients with the same ADO who did not receive TT.[2,3]

However, a recent real-world study observed that 24% of patients with aNSCLC with an ADO initiated non-TT before biomarker test results became available. Outcomes were significantly compromised in patients with aNSCLC who harbored an ADO and were treated with non-TT; this was also observed in patients who switched from non-TT to tyrosine kinase inhibitors ≤35 days.[4] The appropriate time to switch from non-TT to TT for optimal patient outcomes remains unclear. This study aims to evaluate the clinical impact of different timing and treatment patterns of first-line (1L) TT in patients with aNSCLC with an ADO.

Materials and Methods

This retrospective cohort study used the nationwide Flatiron Health electronic health record (EHR)–derived deidentified database. The Flatiron Health database is a longitudinal database that comprises deidentified patient-level structured and unstructured data, curated via technology-enabled abstraction.[5,6] During the study period, the deidentified data originated from approximately 280 US cancer clinics (≈800 sites of care), and the majority of patients in the database originated from a community oncology setting. The study was conducted in accordance with recognized ethical guidelines (eg, Declaration of Helsinki, Council for International Organizations of Medical Sciences, Belmont Report, and US Common Rule). Institutional review board approval of the study protocol was obtained from the WIRB-Copernicus Group prior to study conduct and included a waiver of informed consent.

Study Cohorts

Inclusion criteria were age ≥18 years; diagnosis of aNSCLC (stage IIIB, IIIC, IVA, or IVB at diagnosis and earlier-stage NSCLC with subsequent development of advanced disease) between January 1, 2015, and October 18, 2022; receipt of biomarker testing between initial diagnosis and up to 90 days after advanced diagnosis; presence of an ADO (ALK, BRAF, EGFR, RET, MET, ROS-1, or NTRK); receipt of 1L treatment; and evidence of ≥1 visit within 42 days after positive biomarker test result. Patients enrolled in clinical trials were excluded. Patients meeting the study criteria were followed up from the index date until death or last confirmed activity if no death event was observed. The study index date was 42 days after the advanced diagnosis date for patients who had a test result date prior to the advanced diagnosis date; the study index date was 42 days after the positive biomarker test result for patients who had a test result date on or after the advanced diagnosis date.

Three cohorts were defined by treatment patterns ≤42 days after biomarker test results were available to avoid immortal time bias; this is the time equivalent of two 3-week treatment cycles of chemotherapy alone or in combination with immunotherapy. The Upfront TT cohort received 1L TT ≤42 days after a biomarker test result or the index date. The Switchers cohort initiated 1L non-TT before or after testing but switched to TT ≤42 days after a biomarker test result or the index date. The Non-switchers cohort initiated non-TT before or after testing and did not switch to TT at any time after a biomarker test result or the index date.

Variables

A broad biomarker panel (eg, *ALK*, *BRAF*, *EGFR*, *RET*, *MET*, *ROS-1*, *NTRK*, *KRAS*, and PD-L1) was abstracted from EHR documentation. In this study, we defined TTs specific to ADOs in the 1L treatment setting per NCCN Guidelines®,[1] including *ALK*, *BRAF*, *EGFR*, *RET*, *MET*, *ROS-1*, and *NTRK*. Line of therapy was oncologist defined and rule based; the full list of TTs included in this study is available in Supplementary Table S1. Data on next-generation sequencing (NGS) testing and results were also abstracted from EHR documentation from reports by testing technology platforms (eg, Illumina HiSeq), specific FDA-approved tests (eg, FoundationOne CDx), and testing providers (eg, Caris Life Sciences). Other biomarker testing, including fluorescence in situ hybridization, immunohistochemistry, polymerase chain reaction, and other sequencing methods, were also abstracted from EHRs.

Outcomes

Real-world progression-free survival (rwPFS) was defined as the time from the index date to a progression event or death, with censoring at the last confirmed activity. A progression event was based on radiographic evidence, pathological evidence, or clinical assessment. Real-world time to next treatment or death (rwTTNTD) was defined as the time from the index date to next treatment initiation or death, with censoring at the last confirmed activity. Real-world overall survival (rwOS) was defined as the time from the index date to death, with censoring at the last confirmed activity. Death is a composite endpoint of structured and unstructured EHR-derived data, obituary data, and the social security death index.[7]

Statistical Analysis

Patient characteristics and treatment patterns were descriptively summarized. Study cohorts were compared using the Kruskal-Wallis rank sum test for continuous variables and Pearson chi-square test for categorical variables. The Fisher's exact test for count data with a simulated *P* value (based on 2000 replicates) was performed for variables with small cell counts (<5). Unadjusted Kaplan-Meier curves estimated the median time to event outcomes (rwPFS, rwOS, and rwTTNTD), and log-rank tests compared outcomes across cohorts. Multivariable Cox proportional hazards regression models were used to estimate the adjusted hazard ratio (HR) after accounting for age, sex, race/ethnicity, insurance, practice type, area-level socioeconomic status (SES), histology, presence of recurrent versus de novo disease, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and available biomarker mutations (*ALK*, *BRAF*, *EGFR*, *RET*, *MET*, *ROS-1*, PD-L1, *KRAS*, or *NTRK*). Proportional hazards assumption was examined

using the log-log survival curves and goodness-of-fit test. The statistical significance threshold was set a priori using 2-sided tests at $P < .05$. All analyses were conducted using R version 4.2.2.

Sensitivity analyses on treatment outcomes were conducted by varying treatment patterns within 42, 63, and 84 days after biomarker test result; these are time equivalents of two, three, and four 3-week treatment cycles, respectively.

Results

A total of 3540 patients with aNSCLC harboring an ADO met the study criteria, including 2737 patients (77%) in the Upfront TT cohort, 149 (4%) in the Switchers cohort, and 654 (18%) in the Non-switchers cohort (Figure 1).

Chemotherapy, followed by chemotherapy in combination with immunotherapy, were the most common non-TTs received before test results in the Switchers (46% and 31%, respectively) and Non-switchers (36% and 24%, respectively; Supplementary Fig. S1) cohorts.

Overall, the majority of the study population (78%) was treated in a community setting and had de novo metastatic lung cancer (81%). There were more patients with a history of smoking in the Non-Switchers cohort (68%) than in the Upfront TT (45%) and Switchers (48%) cohorts ($P < .001$). Statistically significant differences were observed in advanced diagnosis age, sex, race/ethnicity, practice type, histology, smoking history, SES, and recurrent versus de novo cancer across all cohorts (Table 1).

Biomarker testing was commonly conducted after advanced diagnosis: 91% Upfront TT, 100% Switchers, and 87% Non-switchers. The median time of gap between advanced diagnosis to biomarker testing result was 21 days for Upfront TT, 35 days for Switchers, and 32 days for Non-switchers. During the study period from the years of 2015 to 2022, 50% (1777 of 3540) of patients received NGS in combination with other biomarker testing. The majority of NGS testing (86%) was conducted through a third-party commercial lab (Supplementary Table S2). NGS testing rate was higher in the Non-switchers cohort at 60% and 58% in the Switchers cohort compared with 48% in the Upfront TT cohort (Fig. 2). An increase in the uptake on NGS testing was observed after the Centers for Medicare & Medicaid Services national coverage determination (NCD) on NGS testing in 2018 with the rates before versus after NCD being: 23% versus 61% in the Upfront TT cohort; 38% versus 68% in the Switchers cohort; and 40% versus 69% in the Non-switchers cohort, respectively.

ALK and *EGFR* were the most common ADOs in the Upfront TT and Switchers cohorts; BRAF and rare mutations (eg, *MET*, *NTRK*, and RET) were more common in the Non-switchers cohort (Table 2). Beyond ADOs in the 1L setting, PD-L1 expression (staining ≥ 1%) was highest in the Non-switchers cohort (20%) compared with the Upfront TT (13%) and Switchers (9%) cohorts, $P < .001$. In addition, KRAS mutations (G12C, other mutation type [G12D, G12V]) were highest in the Non-switchers cohort (6%) compared with the Upfront TT (2%) and Switchers (<3%) cohorts, $P < .001$.

In our base case, where ≤42 days after biomarker test result was used as the threshold for timely TT, we observed the Non-switchers cohort, who had never received TT, had worse outcomes than Upfront TT (adjusted HR > 1), and comparable outcomes between the Switchers and Upfront TT cohorts (adjusted HR~1, Fig. 3). The regression analyses determined that treatment outcomes varied consistently: non-Hispanic Asian patients had better outcomes than non-Hispanic White patients; patients with recurrent aNSCLC had better outcomes than those with de novo aNSCLC; patients who received care in academic settings had better outcomes than those who received care in community settings; patients with nonsquamous aNSCLC had better outcomes than those with squamous aNSCLC; and patients with no history of smoking had better outcomes than those who smoked (Supplementary Fig. S2).

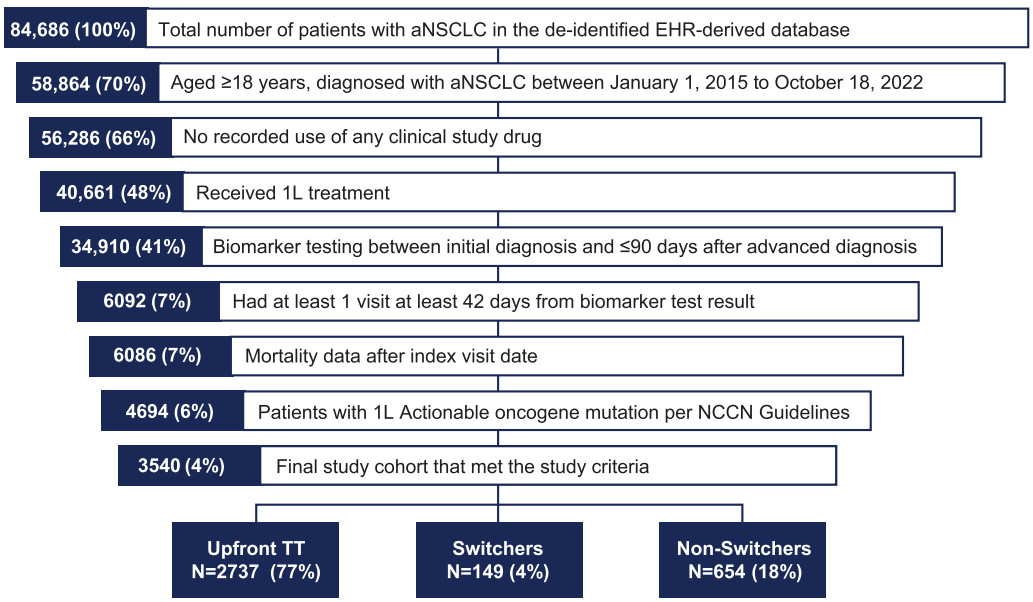


Figure 1. Patient Attrition. Abbreviations: 1L, first line; aNSCLC, advanced non–small cell lung cancer; EHR, electronic health record; NCCN, National Comprehensive Cancer Network; TT, targeted therapy.

Table 1. Patient demographics and clinical characteristics.

	Overall (*N* = 3540)	Upfront TT cohort (*n* = 2737)	Switchers cohort (*n* = 149)	Non-switchers cohort (*n* = 654)	*P* value
Age at advanced diagnosis (years), mean (IQR)	69 (61, 77)	69 (60, 77)	68 (59, 73)	71 (64, 78)	<.001
Sex, *n* (%)					
Female	2236 (63%)	1764 (64%)	95 (64%)	377 (58%)	.005
Male	1304 (37%)	973 (36%)	54 (36%)	277 (42%)	
Race/ethnicity, *n* (%)					
Non-Latinx White	2015 (57%)	1517 (55%)	85 (57%)	413 (63%)	<.001
Non-Latinx Black	261 (7.4%)	204 (7.5%)	11 (7.4%)	46 (7.0%)	
Non-Latinx Asian	377 (11%)	334 (12%)	13 (8.7%)	30 (4.6%)	
Other	304 (8.6%)	225 (8.2%)	18 (12%)	61 (9.3%)	
Latinx	211 (6.0%)	172 (6.3%)	10 (6.7%)	29 (4.4%)	
Unknown	372 (11%)	285 (10%)	12 (8.1%)	75 (11%)	
Insurance type, *n* (%)					
Commercial	1977 (56%)	1534 (56%)	85 (57%)	358 (55%)	.5
Medicaid	131 (3.7%)	110 (4.0%)	2 (1.3%)	19 (2.9%)	
Medicare	423 (12%)	327 (12%)	14 (9.4%)	82 (13%)	
Other	438 (12%)	328 (12%)	23 (15%)	87 (13%)	
Unknown	571 (16%)	438 (16%)	25 (17%)	108 (17%)	
Practice type, *n* (%)					
Academic	769 (22%)	627 (23%)	26 (17%)	116 (18%)	.007
Community	2771 (78%)	2110 (77%)	123 (83%)	538 (82%)	
Histology, *n* (%)					
NSCC	3356 (95%)	2641 (96%)	137 (92%)	578 (88%)	<.001
NOS	67 (1.9%)	45 (1.6%)	5 (3.4%)	17 (2.6%)	
SCC	117 (3.3%)	51 (1.9%)	7 (4.7%)	59 (9.0%)	
Area-level socioeconomic status, *n* (%)					
1 (lowest)	401 (11%)	310 (11%)	13 (8.7%)	78 (12%)	.038
2	549 (16%)	412 (15%)	27 (18%)	110 (17%)	
3	634 (18%)	494 (18%)	20 (13%)	120 (18%)	
4	781 (22%)	599 (22%)	50 (34%)	132 (20%)	
5 (highest)	840 (24%)	665 (24%)	30 (20%)	145 (22%)	
Unknown	335 (9.5%)	257 (9.4%)	9 (6.0%)	69 (11%)	
Staging at initial diagnosis					
I	268 (7.7%)	197 (7.3%)	6(4%)	65(10%)	<.001
II	121 (3.5%)	82 (3.0%)	<5 (<3%)	36 (6%)	
III	381 (11%)	211 (7.8%)	7 (4.7%)	163 (26%)	
IV	2666 (77%)	2175 (81%)	130 (88%)	361 (57%)	
Unknown	32 (1%)	24 (1%)	2 (1%)	6 (1%)	
Recurrence, *n* (%)					
De novo	2880 (81%)	2265 (83%)	134 (90%)	481 (74%)	<.001
Recurrent	660 (19%)	472 (17%)	15 (10%)	173 (26%)	
History of smoking, *n* (%)					
Yes	1756 (50%)	1240 (45%)	72 (48%)	444 (68%)	<.001
No	1780 (50%)	1495 (55%)	77 (52%)	208 (32%)	
Unknown	<5 (<0.1%)	<5 (<0.2%)	0	<5 (<0.3%)	
ECOG performance status, *n* (%)					
0	1022 (29%)	808 (30%)	39 (26%)	175 (27%)	.6
1	1329 (38%)	997 (36%)	59 (40%)	273 (42%)	
2	417 (12%)	326 (12%)	19 (13%)	72 (11%)	
3-4	116 (3%)	91 (3%)	<5 (<3%)	21 (3%)	
Unknown	656 (19%)	515 (19%)	28 (19%)	113 (17%)	

Per the threshold accepted by the National Center for Health Statistics and the Agency for Healthcare Research and Quality and detailed in the Federal Committee's Statistical Policy, 2005, any category including <5 patients for a particular characteristic or variable has been described as such to eliminate potential patient reidentification. If it was possible to calculate <5 cell value using column total, the next higher number was used for both rows.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; NSCC, nonsquamous cell carcinoma; SCC, squamous cell carcinoma; TT, targeted therapy.

The comparable treatment outcomes between the Upfront TT cohort and Switchers observed in our base case were consistent across endpoints when the threshold for timely TT was changed to 63 days or 84 days from the 42 days used in the base case. Overall, those in the Non-switchers cohort had worse outcomes than those in the Upfront TT cohort, regardless of the time threshold used to define the cohorts (Fig. 4). The adjusted HR on rwPFS between Non-switchers and Upfront TT cohorts attenuated when varying the switching window to ≤63 and ≤84 days due to the crossover of the rwPFS curves at 24 months. As a result, we conducted a sensitivity analysis extending the Cox model by stratifying the follow-up period with respect to 24 months. The rwPFS within the 24-month index in Upfront TT versus Non-switchers were consistent with the base case finding of worse rwPFS in Non-switchers versus Upfront TT with an adjusted HR = 1.172, P = .029 for ≤63 days switching window, and an adjusted HR = 1.112, P = .159 for ≤84 days switching window (Supplementary Figs. 3, 4).

Since *EGFR* mutation was the most common ADO observed in both the Upfront TT (75%) and Switchers (64%) cohorts (Table 2), we conducted a subgroup analysis that focused on aNSCLC populations with EGFR mutations only.

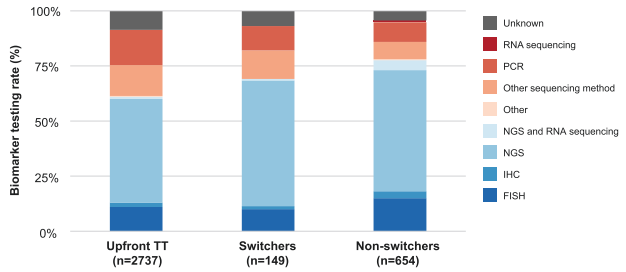


Figure 2. Testing Rate by Testing Type. Per the threshold accepted by the National Center for Health Statistics and the Agency for Healthcare Research and Quality and detailed in the Federal Committee's Statistical Policy, 2005, any category including <5 patients for a particular characteristic or variable has been described as such to eliminate potential patient reidentification. Abbreviations: FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; PCR, polymerase chain reaction; TT, targeted therapy.

Our findings were similar to those of the base case analysis: Upfront TT and Switchers within 42 days of the biomarker test result had comparable outcomes; while those in the Non-switchers cohort had poorer outcomes than Upfront TT (Fig. 5; Supplementary Fig. S5).

Discussion

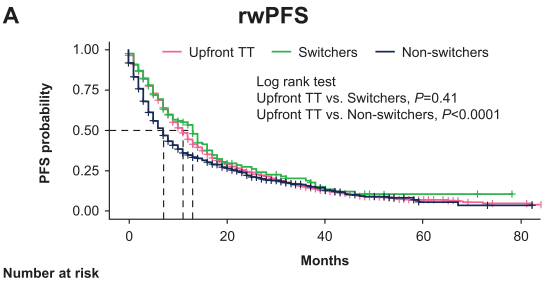
This study demonstrated the clinical value of TT in patients with aNSCLC; the findings observed in the routine clinical setting are consistent with those observed in clinical trials; better outcomes were seen with upfront TT compared with non-TT.[2,3] Our study also supports the body of recent literature that emphasizes the importance of leveraging biomarker testing results to determine appropriate TT options and avoid suboptimal patient outcomes.[8–10] We provided new insights on the most appropriate time period for using biomarker testing results to inform the decision to initiate TT and promote optimal patient outcomes. The comparable adjusted HRs observed between the Switchers and Upfront TT cohorts suggested comparable patient outcomes when timely switching from non-TT to ADO-specific TT up to 84 days after a biomarker test result. Findings from the subgroup analysis of patients with EGFR-mutated aNSCLC further validated the robustness of our base case findings; the Switchers cohort, which switched ≤42 days of the date of the biomarker test result, had comparable outcomes to the upfront TT cohort. The Upfront TT cohort had better outcomes compared to the Non-switchers cohort.

The biomarker testing pattern observed in this study is congruent with the types of ADOs that patients harbored. The higher NGS, with or without RNA sequencing, in Non-switchers reflects the higher proportion of rare mutations (*MET*, *RET*, and *NTRK*) detected in the Non-switchers cohort, especially considering rare mutations are most likely detected via NGS testing and not by single-gene testing. While we observed an increased uptake in NGS testing across the 3 studied cohorts after 2018, opportunities remain to further improve the use of NGS testing to reach universal testing, as observed in the current breast cancer care landscape.[11] In addition, the biomarker testing and treatment patterns observed in this study correspond to the different timing and line of

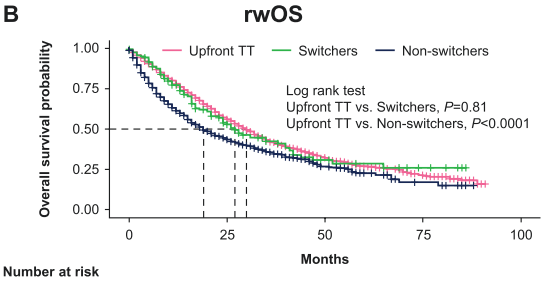
Table 2. Actionable driver oncogene mutation distribution by cohort in the 1L setting.

ADO mutation	Overall (N = 3540)	Upfront TT cohort (n = 2737)	Switchers cohort (n = 149)	Non-switchers cohort (n = 654)	Year first 1L TT approved
ALK	545 (15%)	416 (15%)	39 (26%)	90 (14%)	2011
BRAF	206 (5.8%)	79 (2.9%)	3 (2.0%)	124 (19%)	2017
EGFR	2330 (66%)	2059 (75%)	96 (64%)	175 (27%)	2013
MET	218 (6.2%)	62 (2.3%)	2 (1.3%)	154 (24%)	2020
NTRK	16 (0.5%)	0	0	12 (1.9%)	2018
RET	76 (2.1%)	21 (0.8%)	0	55 (8.4%)	2020
ROS-1	149 (4.2%)	100 (3.7%)	9 (6.0%)	40 (6.1%)	2016

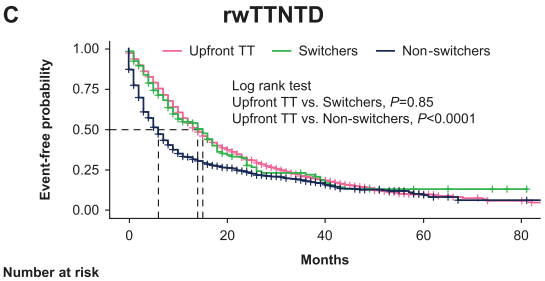
Per the threshold accepted by the National Center for Health Statistics and the Agency for Healthcare Research and Quality and detailed in the Federal Committee's Statistical Policy, 2005, any category including <5 patients for a particular characteristic or variable has been described as such to eliminate potential patient reidentification.
ADO were defined per NCCN Guidelines[1] and based on data available in the Flatiron database: *ALK* mutation included rearrangement present. *BRAF* mutation included V600E *BRAF* mutation. *EGFR* mutation included exon19 deletion, L858R point mutation in exon 21. *MET* mutation included *MET* exon 14 skipping. *NTRK* mutation included *NTRK* 1, 2, and 3 rearrangement positive. *RET* mutation included rearrangement present. *ROS-1* mutation included rearrangement present.
Abbreviations: 1L, first line; NCCN, National Comprehensive Cancer Network, TT, targeted therapy.



	Duration of follow-up, median (IQR) months	rwPFS, median (95% CI), months	Adjusted HRs
Upfront TT, n=2725	8 (3-17)	11 (10-12)	Reference group
Switchers, n=149	8 (3-17)	13 (9-16)	0.8977, *P*=0.3086
Non-switchers, n=647	5 (2-14)	7 (6-8)	1.1705, *P*=0.0204



	Duration of follow-up, median (IQR) months	rwOS, median (95% CI), months	Adjusted HRs
Upfront TT, n=2737	17 (8-32)	30 (28-32)	Reference group
Switchers, n=149	16 (8-33)	27 (21-40)	0.9697, *P*=0.8002
Non-switchers, n=654	11 (4-26.75)	19 (16-23)	1.3673, *P*=0.0000



	Duration of follow-up, median (IQR) months	rwTTNTD, median (95% CI), months	Adjusted HRs
Upfront TT, n=2737	10 (5-20)	14 (13-15)	Reference group
Switchers, n=149	10 (4-18)	15 (10-17)	0.9869, *P*=0.9008
Non-switchers, n=654	5 (1-13)	6 (5-7)	1.3308, *P*=0.0000

Figure 3. Outcomes by Treatment Patterns ≤ 42 Days of a Biomarker Test Result. Proportional hazards assumption was examined using the log-log survival curves and goodness-of-fit test. Patients with the last clinical note date prior to the index date were further excluded in the rwPFS analysis. Multivariable Cox proportional hazards regression models were used to estimate adjusted HR after accounting for age, sex, race/ethnicity, insurance, practice type, area-level socioeconomic status, histology, presence of recurrent versus de novo disease, smoking history, ECOG performance status, and biomarker mutation (*ALK*, *BRAF*, *EGFR*, *RET*, *MET*, *ROS-1*, PD-L1, *KRAS*, or *NTRK*). Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PFS, progression-free survival; rwOS, real-world overall survival; rwPFS, real-world progression-free survival; rwTTNTD, real-world time to next treatment or death; TT, targeted therapy.

TT approvals by the FDA for aNSCLC. Compared with the Non-switchers cohort, the Upfront TT and Switchers cohorts had a higher proportion of *EGFR* or *ALK* mutations; TT was approved for these mutations in 2011 and 2014, respectively. This contrasts with the recent (2017 and onward) approvals of TTs for rare mutations, such as *BRAF*, *MET*, and *NTRK*, which were observed mostly in the Non-switchers cohort. MET inhibitors are approved for both 1L and subsequent lines of treatment; therefore, physicians may have preferred MET inhibitors as later-line treatments as opposed to a 1L treatment. Since we did not evaluate treatment patterns beyond the 1L setting KRAS was not included in the list of 1L ADO due to its approval in the second-line setting only. However, information on KRAS positivity was considered to contextualize our findings because it serves as a prognostic biomarker of poor survival and perhaps resistance to tyrosine kinases inhibitors. Indeed, the higher proportion of *KRAS* mutations in the Non-switchers cohort (5% vs <3% in the Switchers cohort vs 3% in the Upfront TT cohort) suggests that physicians may factor KRAS as a resistance alteration in treatment decisions to delay the use of TT in the 1L setting. Our regression analysis output suggested that race/ethnicity, practice types, type of lung cancer recurrence, histology, and history of smoking are factors that impact treatment outcomes, in addition to timely treatment switching ≤42 days after a biomarker test result.

Findings from our study also suggest that several factors could have impacted timely treatment decisions in a routine clinical care setting. Physicians may have suspected that those in the Switchers cohort, which had a higher proportion of patients without a history of smoking, harbored ALK mutations; however, the initiation of TT may have been delayed due to a long time between the date of biomarker testing and the date on which a result was available. The observed longer median time from advanced diagnosis to test result at 32 days in Non-Switchers and 35 days in Switchers, compared with 21 days in Upfront TT, suggests that there might have been delays in treatment switching until disease progression and/or delays due to long testing turnaround time from biomarker testing order to results. Interventions to improve care coordination among health care professionals (including pulmonologists, interventional radiologists, surgeons, pathologists, and oncologists), promote better stewardship of limited tissue samples, and ensure earlier availability of test results would be beneficial. For example, universal data standards and applications that use application programming interfaces such as physician alerts embedded in EHR could be considered, along with a commitment by sequencing laboratories to consistently provide structured genomic data for clinical use.[12] Commitments from pathology groups to release blocks for testing in a timely manner in order to reduce testing turnaround times would be helpful. Additionally, pathologists and medical oncologists working together through diagnostic management teams to build testing algorithms that can then be initiated by pathologist upon diagnosis could streamline

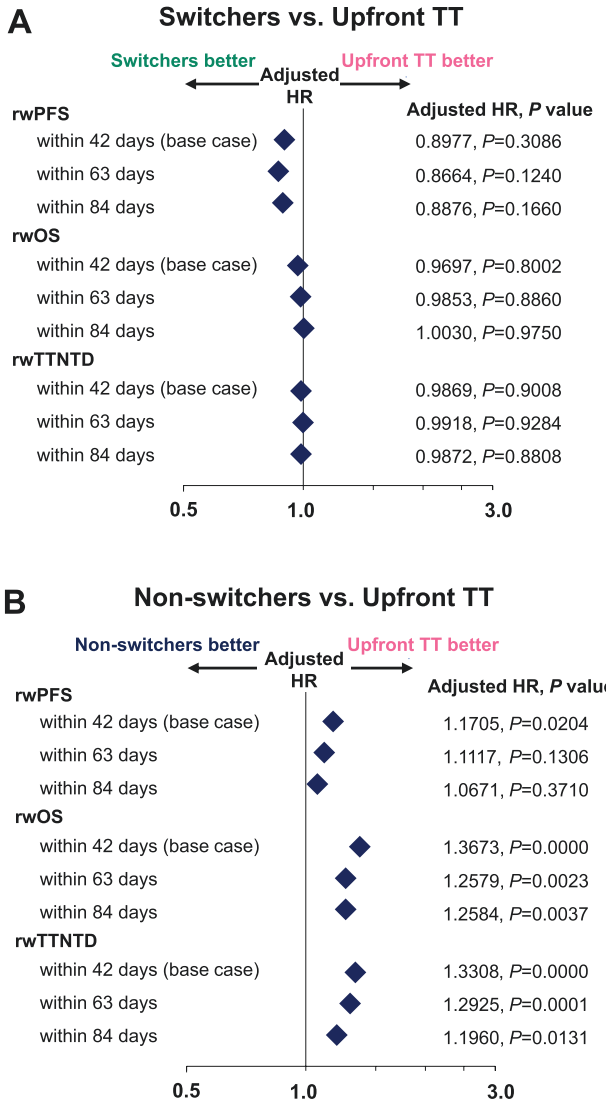


Figure 4. Outcomes by Treatment Patterns at Different Time Points From a Biomarker Test Result. Multivariable Cox proportional hazards regression models were used to estimate adjusted HRs after accounting for age, sex, race/ethnicity, insurance, practice type, area-level socioeconomic status, histology, presence of recurrent versus de novo disease, smoking history, ECOG performance status, and biomarker mutation (*ALK*, *BRAF*, *EGFR*, *RET*, *MET*, *ROS-1*, PD-L1, *KRAS*, or *NTRK*). Proportional hazards assumption was examined using the log-log survival curves and goodness-of-fit test. Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; rwOS, real-world overall survival; rwPFS, real-world progression-free survival; rwTTNTD, real-world time to next treatment or death; TT, targeted therapy.

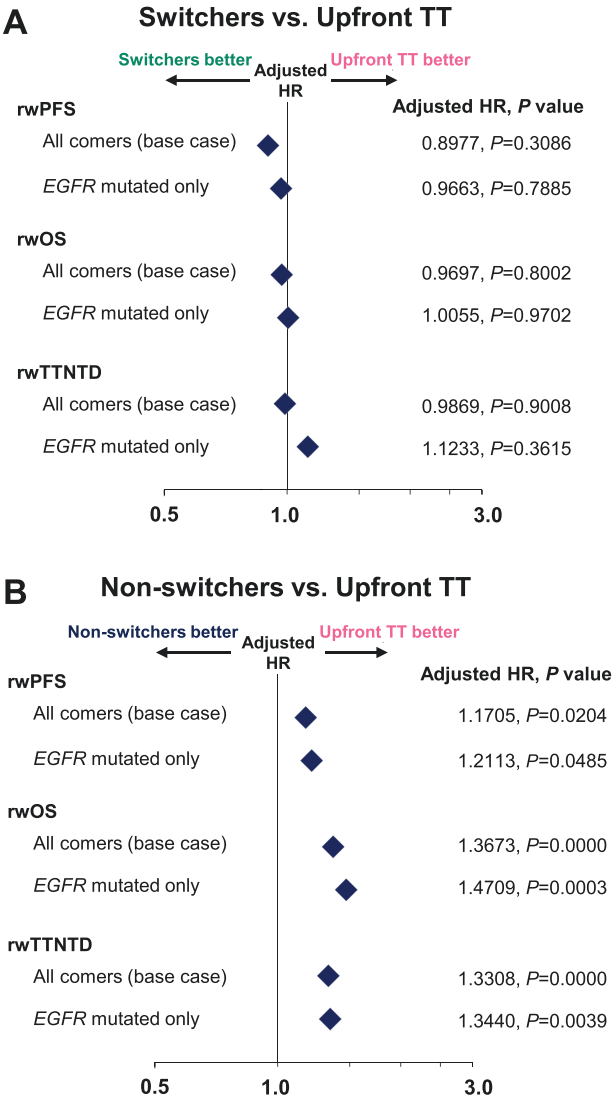


Figure 5. Outcomes in All-Comers and Those With EGFR Mutations by Treatment Patterns ≤ 42 Days of a Biomarker Test Result. All-comers defined as those with aNSCLC detected with 1 of the studied ADOs (*ALK*, *BRAF*, *EGFR*, *RET*, *MET*, *ROS-1*, or *NTRK*). Multivariable Cox proportional hazards regression models were used to estimate adjusted HRs after accounting for age, sex, race/ethnicity, insurance, practice type, area-level socioeconomic status, histology, presence of recurrent versus de novo disease, smoking history, ECOG performance status, and biomarker mutation (PD-L1, *KRAS*). Proportional hazards assumption was examined using the log-log survival curves and goodness-of-fit test. Abbreviations: ADO, actionable driver oncogene; aNSCLC, advanced non–small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; rwOS, real-world overall survival; rwPFS, real-world progression-free survival; rwTTNTD, real-world time to next treatment or death; TT, targeted therapy.

biomarker testing processes and improve testing turnaround times.[13]

There are several limitations to our study. Our study is reflective of practices in the Flatiron Health network, and the findings may not be generalizable to all practices in the US routine clinical setting. The study was evaluated based on information available in the database. While EGFR S768I, L861Q, and/or G719X were also listed as 1L actionable EGRF mutations in the guidelines, information on these biomarkers was not available in the database and these variants were not included in our analysis. Although we quantified the median time from advanced diagnosis to biomarker testing result, data on test order date were unavailable. Future studies are warranted to evaluate treatment patterns and outcomes factoring the median turnaround time from biomarker ordering to reporting date. While rwPFS outcomes were similar, they were consistently lower in magnitude than the rwTTNTD observed, this may be due to the fact that not all disease progression, tolerability, or consideration of patient frailty between progression and subsequent treatment initiation were documented in the database. We adjusted our analyses based on clinically relevant data available in the database; the analyses may not fully account for every factor that may impact outcomes, which limits the

validity of our findings. The reasons for treatment switching due to disease progression, tolerability, patient preference, delay in biomarker test results, and other rationales were not documented. Not all ADOs in the 1L treatment of aNSCLC were abstracted at the time of analysis, and this study was restricted to patients with only 1 ADO in the 1L treatment setting. Future studies are warranted to evaluate timely TT for possible co-mutations and oncogenes across different tumor types. Finally, we did not evaluate the impact of the different types of non-TT (chemotherapy vs immunotherapy) received prior to TT on the outcomes, where future research is needed.

Conclusion

To our knowledge, this is the largest study to date that evaluated the clinical impact of different timing and treatment patterns of 1L TT in patients with aNSCLC with an ADO in a predominately community setting. While guidelines recommend complete planned systematic therapy (including completing maintenance therapy) or interrupt and change to the recommended TT, our findings provide insights into the appropriate time period to make a timely treatment switch from non-TT to biomarker testing–informed TT for optimal patient outcomes. Opportunities remain to improve the use of NGS for early identification of all ADOs and determination of appropriate TT for 1L treatment when indicated.

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Conflict of Interest

Thomas Stricker: employee of Tennessee Oncology/One Oncology; honoraria from Illumina. Esprit Ma: employee of Genentech, Inc. and owns stock in Roche. Elaine Yu: employee of Genentech, Inc. and owns stock in Roche. Rongrong Wang: employee of Genentech, Inc. and owns stock in Roche. Robert Schuldt: employee of Genentech, Inc. and owns stock in Roche and United Health Group. Richard Price: employee of Genentech, Inc. and owns stock in Roche. Tania Szado: employee of Genentech, Inc. and owns stock in Roche. Jesse Sussell: employee of Genentech, Inc. and owns stock in Roche. Sarika Ogale: employee of Genentech, Inc. and owns stock in Roche. Victor Lin: board member of Taking Aim at Cancer in Louisiana (TACL). Dennis Slater: honoraria and speaker' bureau with Novartis. Daniel Vaena: consultant for Bristol Myers Squibb, Bayer, Genomic Health, Natera, SeaGen, Exelixis, EMD Serono, Immunomedics, and Eisai; received honoraria from HMP; received research funding from Bristol Myers Squibb, Novartis, AstraZeneca, Peloton, BioClin, Aeglea, Nektar, Calthera, Tizona, Compugen, TG, Merck, OBI, Incyte, SeaGen, and Roche/Genentech. Davey Daniel: has received research funding from AstraZeneca, Genentech, Guardant Health, Janssen, Bristol Myers Squibb, G1 Therapeutics, Merck, Novartis, AbbVie, ARMO, Immunomedics, Lilly, Merus NV, Daiichi Sankyo, F. Hoffmann-La Roche AG, Celgene, and Amgen. The other authors indicated no financial relationships.

Author Contributions

Conception/design: All authors. Provision of study material or patients: T.S., N.J., V.L., E.A., D.S., D.V., H.S., B.F., L.S., D.D. Collection and/or assembly of data: All authors. Data analysis and interpretation: All authors. Manuscript writing and final approval of manuscript: All authors.

Data Availability

The data that support the findings of this study have been originated by Flatiron Health, Inc. Requests for data sharing by license or by permission for the specific purpose of replicating results in this manuscript can be submitted to dataaccess@flatiron.com.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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