ORIGINAL ARTICLE

Real-World Treatment Patterns and Outcomes of First-Line Immunotherapy Among Patients With Advanced Nonsquamous NSCLC Harboring *BRAF*, *MET*, or *HER2* Alterations

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ABSTRACT

Introduction: Data on utilization and clinical outcomes of programmed cell death protein or programmed death-ligand 1 (PD-[L]1) inhibitors in NSCLC with uncommon oncogenic alterations is limited.

Methods: This retrospective study used a deidentified U.S. nationwide clinicogenomic database to select patients with advanced nonsquamous NSCLC without *EGFR*, *ALK*, or *ROS1* alterations, diagnosed from January 1, 2016 to September 30, 2020, who initiated first-line therapy. Our objectives were to summarize characteristics and treatment patterns for patients with four little-studied genomic alterations or driver-negative NSCLC. We estimated Kaplan-Meier real-world time on treatment (rwTOT) and time to next treatment for patients receiving PD-(L)1 inhibitors. The data cutoff was September 30, 2021.

Results: Of the 3971 eligible patients, 84 (2%) had NSCLC with *BRAF* V600E mutation, 117 (3%) had *MET* exon 14 skipping mutation, 130 (3%) had *MET* amplification, 91 (2%) had *ERBB2* activation mutation, and 691 patients (17%) had driver-negative NSCLC. Patient characteristics differed among cohorts as expected. The most common first-line regimen in each cohort was a PD-(L)1 inhibitor as monotherapy or in combination with chemotherapy. The median rwTOT with anti–PD-(L)1 monotherapy was 4.6 months in the driver-negative cohort and ranged from 2.9 months (*ERBB2* mutation) to 7.6 months (*BRAF* V600E mutation). The median rwTOT with anti–PD-(L)1-chemotherapy combination was 5.2 months in the driver-negative cohort and 6 months in all but the *BRAF* V600E cohort (17.5 mo). The patterns of real-world time to next treatment results were similar.

Conclusions: Substantial use of anti–PD-(L)1 therapy and associated clinical outcomes are consistent with previous

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real-world findings and suggest no detriment from PD-(L)1 inhibitors for advanced nonsquamous NSCLC harboring one of these four genomic alterations relative to driver-negative NSCLC.

Keywords: Advanced non–small cell lung cancer; Genomic alterations; Immunotherapy; Real-world time on treatment; Real-world time to next treatment

Introduction

Mortality rates for NSCLC have improved in the past two decades in the United States, attributable to reduced incidence and treatment advances since 2013.[1] The identification of clinically relevant oncogenic driver alterations in NSCLC has improved the understanding of lung cancer pathogenesis and led to the introduction of novel treatment options, including targeted therapies directed against specific genomic alterations. In the past decade, multiple targeted agents have been approved by the U.S. Food and Drug Administration, in addition to immunotherapies, such as antibodies directed against the programmed cell death protein 1 (PD-1) axis.

The evolving therapeutic landscape has enabled more individualized treatment options (precision medicine), whereas many unanswered questions continue to drive active research.[2,3] The selection of optimal first-line and subsequent treatment regimens for patients according to specific NSCLC molecular profiles and biomarkers, the relative benefit of targeted therapy versus immunotherapy, and the optimal sequencing of systemic regimens constitute important clinical questions under study.[2–9]

Inhibitors of PD-1 and programmed death-ligand 1 (PD-L1) are often administered as first-line therapy for advanced NSCLC; however, evidence from both clinical trials and observational studies evaluating first-line PD-(L)1 inhibitors is limited for some of the less common genomic alterations in NSCLC, including alterations of *BRAF*, *MET*, and the *HER2* gene *ERBB2*.[9–12] Clinical trials may be conducted with small numbers of participants with oncogene-driven NSCLC, and long timelines are needed to understand outcomes.[13,14] Because NSCLC tumors with different genomic alterations are clinically and biologically diverse, the sensitivity of different alteration subtypes to immunotherapy can be heterogeneous.[5,14,15]

Comprehensive genomic profiling is now becoming routine practice for NSCLC;[16–18] therefore, the availability of tumor genomic data in real-world clinical data sets can be leveraged to understand clinical outcomes of PD-(L)1 inhibitor–based therapy for patients with NSCLC harboring genomic alterations.[19,20] The aims of this retrospective, descriptive study were to evaluate demographic and clinical characteristics, timing of comprehensive genomic profiling, and first-line systemic therapy administered in the setting of U.S. oncology clinics for patients with advanced nonsquamous NSCLC harboring at least one of four of the less-studied genomic alterations: *BRAF* V600E mutation, *MET* exon 14 skipping (*MET*ex14) mutation, *MET* amplification, and activation mutation of *ERBB2.* In addition, we evaluated two pragmatic, intermediate end points that can be estimated from routinely recorded clinical data, namely, real-world time on treatment (rwTOT) and real-world time to next treatment (rwTTNT) for first-line PD-(L)1 inhibitor–based therapy. These end points have been moderately to highly correlated with overall survival in previous real-world studies of immunotherapy.[21–23]

Materials and Methods

Data Source and Patients

The Flatiron Health-Foundation Medicine Clinico-Genomic Database (CGDB) contains electronic health record–derived, deidentified data from the Flatiron Health database linked with comprehensive genomic profiling data from Foundation Medicine, as previously described.[18] The nationwide Flatiron Health database includes retrospective, longitudinal patient-level structured and unstructured data, curated by means of technology-enabled abstraction from U.S. cancer clinics, including approximately 280 cancer clinics (~800 sites of care) at the time of this study. These data are linked by deidentified deterministic matching with next-generation sequencing test results for greater than 300 cancer-related genes determined using solid or liquid biopsy on Foundation Medicine platforms (FoundationOne CDx or FoundationOne Liquid CDx [Foundation Medicine, Cambridge, MA], respectively).

Patients in the CGDB who were eligible for this study were adults (≥18 y) with a confirmed diagnosis of advanced NSCLC (stages IIIB, IIIC, or IV) at initial presentation or on recurrence from January 1, 2016 to September 30, 2020 and who initiated a first line of systemic anticancer therapy after the advanced NSCLC diagnosis. We selected patients with nonsquamous NSCLC who had results of a single tissue or liquid gene panel with a sample date within 30 days before or at any time after the initial NSCLC diagnosis. Those with *EGFR* mutations, *ALK* rearrangements, or *ROS1* fusions were excluded, as were patients who received a clinical trial drug on or before first-line therapy initiation. The data cutoff date was September 30, 2021 to allow for at least

12 months of potential follow-up after the advanced NSCLC diagnosis.

Institutional review board approval of the study protocol was obtained from the WCG Institutional Review Board,[24] with a waiver of informed consent granted for working with deidentified data. The deidentified data were subject to obligations to prevent reidentification and protect patient confidentiality.

Study Cohort Assignment

Patients with advanced nonsquamous NSCLC harboring at least one of four genomic alterations were identified on the basis of results of either tissue or liquid biopsy: (1) *BRAF* V600E mutation, (2) *MET*ex14 mutation, (3) *MET* amplification, or (4) activation mutation of *ERBB2*, including *ERBB2* exon 20 insertion (details in the Appendix). The fifth study cohort was the "driver-negative cohort," defined as NSCLC with no alteration of the following 13 genes as determined by tissue biopsy: *EGFR*, *ALK*, *ROS1*, *KRAS*, *BRAF*, *MET*, *RET*, *ERBB2/HER2*, *NTRK*, *PIK3CA*, *STK11*, *KEAP1*, and *NF1*.

Statistical Analyses

For the overall population and the five study cohorts, patient demographics and clinical characteristics were described using summary statistics, including Eastern Cooperative Oncology Group performance status (ECOG PS) closest to the start of first-line therapy, when available, and the Charlson comorbidity index score.[25] In addition, the timing of genomic profiling results relative to the advanced NSCLC diagnosis and to the start of first-line therapy was summarized overall. Treatment patterns were described, with first-line therapies assigned to five categories in a hierarchical fashion beginning with (1) PD-(L)1 inhibitor-based therapy (monotherapy and in combination with other agents), and then (2) targeted therapy, (3) anti–vascular endothelial growth factor (anti-VEGF) therapy, (4) chemotherapy (platinum-based and nonplatinum), and (5) other regimens. Thus, for example, a PD-(L)1 inhibitor-plus-chemotherapy combination regimen would be assigned to PD-(L)1 inhibitor–based therapy (not to the chemotherapy category). Subcategories were included for pembrolizumab monotherapy and pembrolizumab-pemetrexed-platinum combination therapy. We also summarized the number and percentage of patients who received second and third-line therapy.

Follow-up time was calculated from the date of first-line therapy initiation (index date) to the last recorded activity in the database, death, or data cutoff on September 30, 2021, whichever occurred first. The lines of systemic anticancer therapy were determined by oncologist-defined, rules-based methods, and dates of death were determined using the Flatiron Health validated real-world mortality end point.[26–29]

For the five study cohorts, rwTOT and rwTTNT were determined for PD-(L)1 inhibitor–based and pembrolizumab-based regimens, limited to patients initiating the first-line regimen on or before March 31, 2021, thus, with at least 6 months of potential follow-up after initiating first-line therapy. We used the Kaplan-Meier method to estimate rwTOT and rwTTNT from the date of PD-(L)1 inhibitor initiation, with data reported for subgroups of 10 patients or more. The rwTOT (also known as treatment duration or real-world time to treatment discontinuation) was defined as the time from initiation to discontinuation of first-line therapy for any reason. Discontinuation of therapy was defined at the last administration of first-line therapy when a patient continued to the next line of therapy, died, or had a gap of at least 120 days between the last therapy administration and last known activity in the data set; all other patients were censored at the last administration of first-line therapy, as previously described.[30–32]

The rwTTNT was defined as the time from first-line therapy initiation to initiation of a subsequent (second-line) therapy, thus, capturing both time on treatment and the treatment-free interval before initiation of second-line therapy.[32] Patients were censored at the last known activity when no subsequent systemic therapies were administered.

In sensitivity analyses, we determined rwTOT and rwTTNT for patients in the five study cohorts with ECOG PS of 0 or 1 who initiated the first-line regimen on or before March 31, 2021. The rwTOT and rwTTNT analyses were conducted also for patients with genomic alterations as determined only by means of tissue biopsy.

Statistical analyses were performed using Excel software (Microsoft Corp., Redmond, WA) and R statistical software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Population

A total of 6733 patients with advanced NSCLC and a single tissue or liquid gene panel test were selected in the CGDB (Fig. 1). We then excluded 1059 patients (16%) with *EGFR*, *ALK*, and *ROS1* genomic alterations. Of the remaining 5674 patients, 3971 (70%) had nonsquamous NSCLC and were included as the overall population in the present analysis.

Among patients in the overall population, 84 patients (2%) had tumors harboring *BRAF* V600E

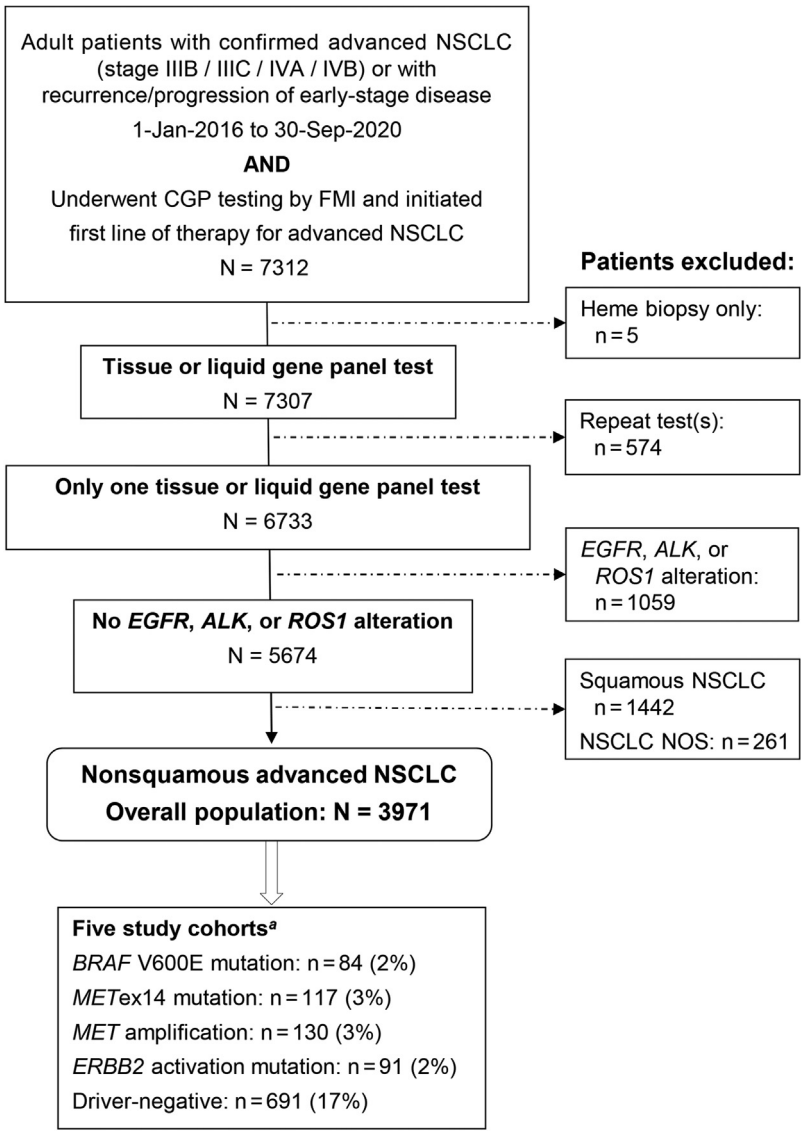

Figure 1. Flow diagram depicting selection of 3971 patients with advanced nonsquamous NSCLC from the database. [a]Study cohorts are further defined in the Methods section. CGP, comprehensive genomic profiling; FMI, Foundation Medicine, Inc.; *MET*ex14, *MET* exon 14 skipping mutation; NOS, not otherwise specified.

mutation, 117 (3%) had *MET*ex14 mutation, 130 (3%) had *MET* amplification, and 91 (2%) had *ERBB2* activation mutation, among them 65 with *ERBB2* exon 20 insertion. The fifth study cohort, driver-negative on the basis of tissue biopsy, included 691 patients (17%) with advanced nonsquamous NSCLC and no alteration of *KRAS*, *BRAF*, *MET*, *RET*, *ERBB2/HER2*, *NTRK*, *PIK3CA*, *STK11*, *KEAP1*, and *NF1*.

Overall, of the 3971 patients, the median age at the start of first-line therapy was 69 years, 1180 patients (30%) were 75 years or older, half were women (1978; 50%), and most (3546; 89%) had a history of smoking (Table 1). Three-quarters of patients (2730; 75%) with known race were White, 7% of patients were Black, and fewer than 2% were Asian.

Demographic characteristics exhibited differing trends across study cohorts (Table 1). Patients in the *BRAF* V600E mutation cohort tended to be older than the overall population (median, 72 years) and included more women (55%) than men (45%). The *MET*ex14 mutation cohort included the greatest percentage of patients 75 years and older (55%) of the five cohorts; in addition, this cohort included mostly women (61%) and a relatively low percentage of smokers (62%), whereas those with *MET* amplification tended to be younger (only 18% aged 75 years or older), less likely to be women (39%), and most had a history of smoking (95%). In the *ERBB2* mutation cohort, 62% of patients were women, and fewer than half (47%) had a history of smoking. In the driver-negative cohort, most patients were men (64%);

Table 1. Patient Demographic and Clinical Characteristics, Overall Population, and Five Study Cohorts Identified by Comprehensive Genomic Profiling

Characteristics	All Patients (N = 3971)	Five Study Cohorts				
		BRAF V600E Mutation (n = 84)	*MET*ex14 Mutation (n = 117)	*MET* Amplification (n = 130)	*ERBB2* Mutation (n = 91)	Driver-negative (n = 691)
Age at 1L start, median (range), y	69 (23-85)	72 (38-83)	76 (43-84)	67 (38-84)	68 (35-84)	68 (23-84)
Age <65	1355 (34.1)	23 (27.4)	14 (12.0)	49 (37.7)	37 (40.7)	266 (38.5)
Age 65-74	1436 (36.2)	28 (33.3)	39 (33.3)	58 (44.6)	32 (35.2)	235 (34.0)
Age ≥75	1180 (29.7)	33 (39.3)	64 (54.7)	23 (17.7)	22 (24.2)	190 (27.5)
Sex						
Female	1978 (49.8)	46 (54.8)	71 (60.7)	51 (39.2)	56 (61.5)	252 (36.5)
Male	1993 (50.2)	38 (45.2)	46 (39.3)	79 (60.8)	35 (38.5)	439 (63.5)
Race[a]						
White	2730 (74.9)	58 (77.3)	81 (75.0)	89 (74.8)	59 (70.2)	490 (77.8)
Black or African American	255 (7.0)	≤6	≤6	≤6	≤6	41 (6.5)
Asian	59 (1.6)	≤6	≤6	≤6	≤6	8 (1.3)
Other	602 (16.5)	12 (16.0)	19 (17.6)	23 (19.3)	16 (19.0)	91 (14.4)
Unknown	325	9	9	11	7	61
Smoking status[a,b]						
History of smoking	3546 (89.4)	62 (73.8)	72 (61.5)	123 (94.6)	43 (47.3)	606 (87.8)
No history of smoking	421 (10.6)	22 (26.2)	45 (38.5)	7 (5.4)	48 (52.7)	84 (12.2)
Practice type						
Community	3612 (91.0)	75 (89.3)	99 (84.6)	121 (93.1)	83 (91.2)	618 (89.4)
Academic	359 (9.0)	9 (10.7)	18 (15.4)	9 (6.9)	8 (8.8)	73 (10.6)
ECOG performance status[a]						
0-1	2755 (78.3)	59 (79.7)	78 (77.2)	94 (76.4)	59 (81.9)	485 (78.4)
≥2	763 (21.7)	15 (20.3)	23 (22.8)	29 (23.6)	13 (18.1)	134 (21.6)
Unknown	453	10	16	7	19	72
Charlson comorbidity index						
Mean (SD)	6.1 (3.3)	5.4 (3.3)	5.7 (3.4)	6.0 (3.4)	6.5 (3.2)	6.0 (3.4)
Median (range)	8 (2-20)	5 (2-14)	8 (2-14)	8 (2-13)	8 (2-13)	8 (2-17)
Advanced stage at initial diagnosis[a,c]	2929 (75.2)	66 (79.5)	92 (80.0)	109 (84.5)	72 (80.0)	515 (75.5)
PD-L1 expression[a,d]						
<1%	1027 (35.9)	5 (7.7)	12 (13.3)	15 (16.9)	37 (56.1)	221 (43.3)
1%-49%	893 (31.2)	17 (26.2)	24 (26.7)	11 (12.4)	16 (24.2)	171 (33.5)
≥50%	944 (33.0)	43 (66.2)	54 (60.0)	63 (70.8)	13 (19.7)	118 (23.1)
Unknown	1107	19	27	41	25	181
Biopsy type used for CGP						
Tissue biopsy	3119 (78.5)	74 (88.1)	104 (88.9)	127 (97.7)	73 (80.2)	691 (100)
Liquid biopsy	852 (21.5)	10 (11.9)	13 (11.1)	3 (2.3)	18 (19.8)	0
No. of metastatic sites						
0-1	1596 (40.2)	35 (41.7)	43 (36.8)	45 (34.6)	26 (28.6)	259 (37.5)
2	985 (24.8)	16 (19.1)	35 (29.9)	40 (30.8)	20 (22.0)	178 (25.8)
≥3	1390 (35.0)	33 (39.3)	39 (33.3)	45 (34.6)	45 (49.5)	254 (36.8)

(continued)

Table 1. Continued

Characteristics	All Patients (N = 3971)	Five Study Cohorts				
		BRAF V600E Mutation (n = 84)	*MET*ex14 Mutation (n = 117)	*MET* Amplification (n = 130)	*ERBB2* Mutation (n = 91)	Driver-negative (n = 691)
Common metastatic sites[e]						
Bone	1818 (45.8)	29 (34.5)	59 (50.4)	49 (37.7)	56 (61.5)	300 (43.4)
Brain	1155 (29.1)	15 (17.9)	33 (28.2)	44 (33.9)	36 (39.6)	191 (27.6)
Liver	759 (19.1)	13 (15.5)	25 (21.4)	20 (15.4)	29 (31.9)	160 (23.2)

Note: Data are n (%) unless otherwise noted. Percentages may not add up to 100 because of rounding. Patients who were not included in the five cohorts were not separately evaluated.
[a]Percentages for race, smoking status, ECOG performance status, stage at initial diagnosis, and PD-L1 expression represent the percentages of patients with available data.
[b]Smoking status was missing for 4 patients overall, including one in the driver-negative cohort.
[c]Advanced stage at initial diagnosis included stages IIIB, IIIC, and IV. A total of 78 patients had no recorded stage at diagnosis, including from 1 to 2 in each genomic alteration cohort and nine in the driver-negative cohort.
[d]PD-L1 expression data were drawn from both the Foundation Medicine genomic profiling results and the clinical assays when available.
[e]Patients could have greater than 1 metastatic site.
1L, first-line therapy; CGP, comprehensive genomic profiling; ECOG PS, Eastern Cooperative Oncology Group performance status; *MET*ex14 mutation, *MET* exon 14 skipping mutation; PD-L1, programmed death-ligand 1.

otherwise, the distributions of age, race, and smoking history resembled those of the overall population (Table 1).

Performance status was recorded for 89% of patients overall, and the distribution of ECOG PS (when known) was similar among the five study cohorts, including 76% to 82% of patients with ECOG PS of 0 or 1, similar to the overall population (78%) (Table 1).

The pattern of tumor PD-L1 expression varied among the five study cohorts: PD-L1 expression was 50% or greater among 66%, 60%, and 71% of those in BRAF V600E, *MET*ex14 mutation, and *MET* amplification cohorts, respectively. Conversely, only 20% with *ERBB2* mutations and 23% in the driver-negative cohort had PD-L1 expression of 50% or greater, whereas 56% and 43%, respectively, had PD-L1-negative NSCLC (PD-L1 expression <1%) (Table 1). Immunohistochemistry assay types, when available, are reported in the Supplementary File.

Genomic profiling was conducted using tissue biopsy for 3119 patients (79%) and liquid biopsy for 853 (22%). In *BRAF* V600E, *MET*ex14 mutation, *MET* amplification, and *ERBB2* mutation cohorts, the percentages of tissue biopsies were 88%, 89%, 98%, and 80%, respectively (Table 1**)**. Patients with liquid biopsy tended to be older than those who had genomic profiling by means of tissue biopsy (37% versus 28% ≥75 years old, respectively [Supplementary Table 1]). Otherwise, the characteristics of patients with tissue biopsy were similar to those of the full cohorts and are summarized in Supplementary Tables 1 and 2.

Timing of Genomic Profiling Results

Genomic profiling results were available before first-line therapy initiation for 1747 patients (44%) and on or after first-line initiation for 2226 patients (56%). Further details regarding the timing of results are depicted in Figure 2.

First-Line Systemic Therapy

All 3971 patients in the overall population, per eligibility criteria, received first-line systemic therapy for advanced NSCLC. The most common first-line regimen was PD-(L)1 inhibitor–based therapy, administered as monotherapy or as PD-(L)1 inhibitor–based combination therapy to 2260 patients (57%), followed by chemotherapy (1156; 29%), including platinum-based chemotherapy for 1056 patients (27%) and nonplatinum chemotherapy for 100 patients (3%). Overall, 343 patients (9%) received anti-VEGF agents, 199 patients (5%) received targeted therapy, and 13 patients (<1%) received other therapies not included in the previous categories.

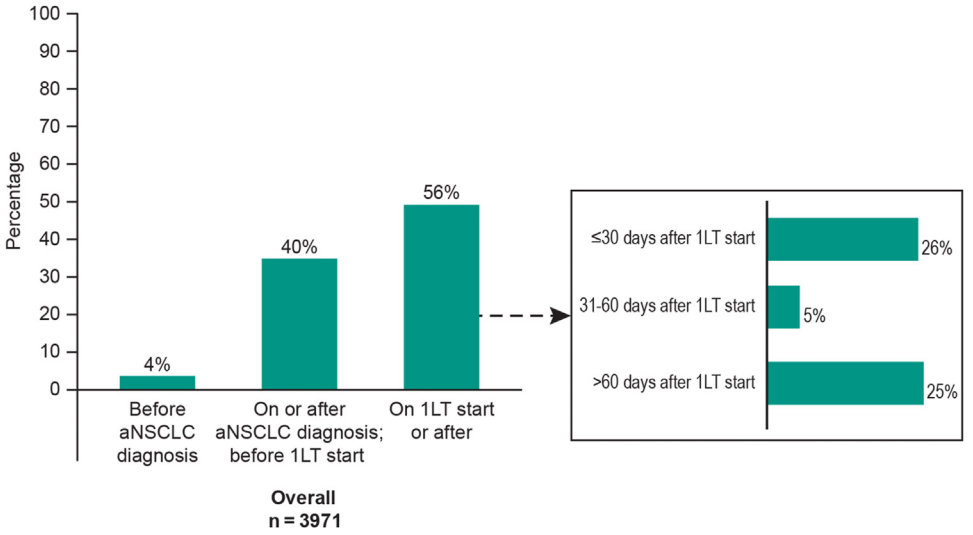

Figure 2. Timing of genomic profiling results relative to the advanced NSCLC diagnosis and the start of first-line therapy for the 3971 patients in the overall population. 1LT, first-line therapy; aNSCLC, advanced NSCLC.

For the five study cohorts, the most common first-line therapy was PD-(L)1 inhibitor-based, administered to 44% to 54% of patients in each cohort and most typically as pembrolizumab-containing therapy (Table 2). From 21% to 32% of patients in each study cohort, except the *ERBB2* mutation cohort (15%),

Table 2. First-Line Systemic Anticancer Regimens for Patients With Advanced Nonsquamous NSCLC in the Five Study Cohorts

First-Line Therapy Regimen[a]	*BRAF* V600E Mutation (n = 84)	*MET*ex14 Mutation (n = 117)	*MET* Amplification (n = 130)	*ERBB2* Mutation (n = 91)	Driver-negative (n = 691)
PD-(L)1 inhibitor-based therapy	40 (47.6)	52 (44.4)	70 (53.8)	44 (48.4)	369 (53.4)
PD-(L)1 inhibitor monotherapy	27 (32.1)	28 (23.9)	35 (26.9)	14 (15.4)	143 (20.7)
Pembrolizumab monotherapy	20 (23.8)	25 (21.4)	29 (22.3)	8 (8.8)	93 (13.5)
PD-(L)1 inhibitor + chemotherapy	13 (15.5)	24 (20.5)	35 (26.9)	30 (33.0)	222 (32.1)
Pembrolizumab + pemetrexed + carboplatin or cisplatin	12 (14.3)	21 (17.9)	28 (21.5)	27 (29.7)	185 (26.8)
IO + IO combination[b]	0	0	0	0	3 (0.4)
Targeted therapy	22 (26.2)	29 (24.8)	8 (6.2)	6 (6.6)	21 (3.0)
ALK inhibitor	0	22 (18.8)	6 (4.6)	1 (1.1)	4 (0.6)
EGFR TKI	0	0	2 (1.5)	5 (5.5)	14 (2.0)
BRAF/MEK inhibitor	20 (23.8)	0	0	0	1 (0.1)
BRAF inhibitor	2 (2.4)	0	0	0	0
MET inhibitor	0	6 (5.1)	0	0	0
RET inhibitor	0	0	0	0	0
Other targeted therapy	0	1 (0.9)	0	0	2 (0.3)
Anti-VEGF–based therapy	4 (4.8)	5 (4.3)	10 (7.7)	10 (11.0)	67 (9.7)
Chemotherapy	18 (21.4)	31 (26.5)	42 (32.3)	28 (30.8)	230 (33.3)
Platinum-based chemotherapy	18 (21.4)	27 (23.1)	40 (30.8)	25 (27.5)	210 (30.4)
Nonplatinum chemotherapy	0	4 (3.4)	2 (1.5)	3 (3.3)	20 (2.9)
Other therapy	0	0	0	3 (3.3)	4 (0.6)
Total no. lines of systemic therapy					
1	41 (48.8)	53 (45.3)	70 (53.9)	29 (31.9)	368 (53.3)
2	25 (29.8)	42 (35.9)	38 (29.2)	24 (26.4)	189 (27.4)
≥3	18 (21.4)	22 (18.8)	22 (16.9)	38 (41.8)	134 (19.4)

Note: Data are n (%). Percentages may not add up to 100 because of rounding.

[a]No patient in the genomic alteration or driver-negative NSCLC cohorts received IO + targeted therapy, an ERBB2 inhibitor, a KRAS inhibitor, a MEK inhibitor, or EGFR-antibody-based therapy.

[b]IO-IO combination includes combination of PD-(L)1 inhibitor with a CTLA4 inhibitor such as nivolumab plus ipilimumab with or without platinum-based chemotherapy.

IO, immuno-oncology agent; *MET*ex14 mutation, *MET* exon 14 skipping mutation; no., number; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Table 3. Real-World Time on Treatment With First-Line PD-(L)1 Inhibitor-Based Therapy for Patients Initiating First-Line On or Before 31 March 2021

Outcomes from first-line therapy initiation[a]	*BRAF* V600E mutation (n = 83)	*MET*ex14 mutation (n = 117)	*MET* amplification (n = 130)	*ERBB2* mutation (n = 90)	Driver-negative (n = 687)
Follow-up Time[b]					
Study follow-up, median (range), mo	35.8 (6.6-66.6)	35.3 (9.3-66.3)	32.4 (9.6-66.9)	42.1 (11.2-65.5)	37.0 (7.1-68.0)
Patient follow-up, median (range, mo)	16.6 (0.4-59.1)	12.2 (0.2-61.5)	11.1 (<0.1-61.5)	14.5 (0.2-64.7)	11.6 (<0.1-66.2)
Real-world time on treatment (rwTOT)					
PD-(L)1 inhibitor monotherapy, n	26	28	35	14	140
Median rwTOT (95% CI), mo	7.6 (2.3-11.1)	5.6 (3.0-14.9)	4.9 (1.5-9.3)	2.9 (0.8-9.5)	4.6 (3.7-6.0)
On-treatment rate at 12 mo, % (95% CI)	21.6 (7.9-39.6)	37.9 (20.2-55.5)	22.7 (9.9-38.7)	10.7 (0.8-35.4)	24.0 (17.2-31.5)
Pembrolizumab monotherapy, n	19	25	29	8[c]	91
Median rwTOT (95% CI), mo	7.6 (0.7-11.1)	5.6 (2.8-17.3)	4.2 (1.2-9.9)	—	5.6 (4.1-6.9)
On-treatment rate at 12 mo, % (95% CI)	18.8 (4.7-40.1)	38.5 (19.7-57.1)	24.6 (10.0-42.6)	—	25.6 (17.0-35.0)
PD-(L)1 inhibitor + chemotherapy, n	13	24	35	30	221
Median rwTOT (95% CI), mo	17.5 (2.8-NR)	5.6 (3.5-6.5)	6.0 (2.8-10.4)	6.0 (3.9-7.8)	5.2 (4.4-6.5)
On-treatment rate at 12 mo, % (95% CI)	46.2 (19.2-69.6)	17.4 (5.4-35.0)	27.5 (13.4-43.7)	13.9 (4.4-28.8)	23.4 (17.8-29.4)
Pembrolizumab + pemetrexed + platinum, n	12	21	28	27	184
Median rwTOT (95% CI), mo	20.7 (2.8-NR)	5.6 (2.3-11.7)	7.6 (4.7-15.9)	5.7 (3.5-7.7)	5.1 (4.2-6.2)
On-treatment rate at 12 mo, % (95% CI)	50.0 (20.8-73.6)	20.0 (6.2-39.3)	35.1 (17.2-53.6)	7.8 (1.4-21.9)	20.5 (14.7-27.0)

[a]Analyses are reported for subgroups including 10 or more patients.
[b]Study follow-up was defined as the duration of follow-up from first-line therapy initiation to database cutoff (September 30, 2021). Patient follow-up was defined as time from first-line therapy initiation to the date of death, data cutoff, or last recorded activity in the database, whichever occurred first.
[c]Only one patient in each of the full *BRAF* V600E and *ERBB2* mutation cohorts, plus four in the driver-negative cohort, were excluded from these analyses because of first-line therapy start dates after 31 March 2021.
CI, confidence interval; *MET*ex14 mutation, *MET* exon 14 skipping mutation; NR, not reached; PD-(L)1, programmed cell death protein 1 and programmed death-ligand 1; platinum, carboplatin or cisplatin; rwTOT, real-world time on treatment.

Table 4. Real-World Time to Next Treatment after First-Line PD-(L)1 Inhibitor-Based Therapy for Patients Initiating First-Line On or Before 31 March 2021

Outcome by First-Line Regimen	*BRAF* V600E Mutation (n = 83)	*METex14* Mutation (n = 117)	*MET* Amplification (n = 130)	*ERBB2* Mutation (n = 90)	Driver-Negative (n = 687)
Real-world time to next treatment[a]					
PD-(L)1 inhibitor monotherapy, n	26	28	35	14	140
Median rwTTNT (95% CI), mo	10.5 (5.6-15.6)	7.1 (5.3-20.3)	8.0 (4.9-13.8)	4.2 (1.9-14.1)	11.3 (6.8-14.0)
No next treatment at 12 mo, % (95% CI)	37.7 (19.0-56.4)	42.2 (23.8-59.6)	32.4 (17.1-48.8)	19.0 (3.6-43.7)	46.7 (38.1-54.8)
Pembrolizumab monotherapy, n	19	25	29	8[a]	91
Median rwTTNT (95% CI), mo	8.3 (1.9-NR)	7.1 (4.1-20.3)	8.0 (4.5-16.7)	–	12.0 (7.6-16.0)
No next treatment at 12 mo, % (95% CI)	29.2 (10.1-51.6)	43.2 (23.5-61.5)	31.9 (15.2-50.2)	–	49.2 (38.3-59.1)
PD-(L)1 inhibitor + chemotherapy, n	13	24	35	30	221
Median rwTTNT (95% CI), mo	19.7 (3.4-NR)	7.0 (6.4-11.8)	7.0 (4.5-16.8)	7.1 (4.9-9.2)	7.6 (6.5-8.7)
No next treatment at 12 mo, % (95% CI)	46.2 (19.2-69.6)	26.1 (10.6-44.7)	37.0 (20.7-53.4)	17.4 (6.3-33.0)	33.7 (27.3-40.1)
Pembrolizumab + pemetrexed + platinum, n	12	21	28	27	184
Median rwTTNT (95% CI), mo	24.9 (3.4-NR)	7.2 (5.5-19.4)	12.5 (5.5-23.1)	6.7 (4.4-8.4)	7.4 (6.3-8.7)
No next treatment at 12 mo, % (95% CI)	50.0 (20.8-73.6)	30.0 (12.3-50.1)	47.4 (27.0-65.3)	15.6 (4.9-31.7)	31.9 (25.1-39.0)

[a]Analyses are reported for subgroups including 10 or more patients.

CI, confidence interval; *METex14* mutation, *MET* exon 14 skipping mutation; NR, not reached; PD-(L)1, programmed cell death protein 1 and programmed death-ligand 1; rwTTNT, real-world time to next treatment from first-line therapy initiation.

received PD-(L)1 inhibitor monotherapy. In the *ERBB2* mutation cohort, one-third of patients (33%) received combination PD-(L)1 inhibitor–chemotherapy, similar to the percentage in the driver-negative cohort (32%). Among the other three study cohorts, 16% to 27% of patients received PD-(L)1 inhibitor–chemotherapy.

Approximately one-quarter of patients in *BRAF* V600E and *MET*ex14 mutation cohorts received targeted therapy, most typically with a BRAF-MEK inhibitor and an ALK inhibitor, respectively (Table 2). In the *MET* amplification cohort, 5% of patients received an ALK inhibitor, and 8% of patients received anti-VEGF–based therapy. An anti-VEGF agent was administered to 11% and 10% of patients in the *ERBB2* mutation and driver-negative cohorts, respectively. Chemotherapy, most typically platinum-based, was administered in the first line to 21% to 33% of patients in each cohort (Table 2).

During the study, from 32% to 54% of patients in each cohort received one line of therapy, from 26% to 36% received two lines, and from 17% to 42% received three lines or more (Table 2). Patients in the *ERBB2* mutation cohort were most likely to receive multiple lines of therapy, with 42% receiving three lines or more. Treatment patterns for patients with tissue biopsy used for genomic profiling were similar, as summarized in Supplementary Table 3.

Follow-Up Time

Follow-up times for the five study cohorts are summarized in Table 3 for patients who initiated first-line therapy on or before March 31, 2021 and were included in the rwTOT and rwTTNT analyses. The median study follow-up from initiation of first-line therapy to database cutoff (September 30, 2021) ranged from 32.4 months in the *MET* amplification cohort to 42.1 months in the *ERBB2* mutation cohort. The median patient follow-up from first-line therapy initiation to the date of death, data cutoff, or last recorded activity in the database, whichever occurred first, ranged from 11.1 months in the *MET* amplification cohort to 16.6 months in the *BRAF* V600E mutation cohort (Table 3).

Real-World Time On Treatment and Real-World Time To Next Treatment

The median rwTOT and 12-month on-treatment rates for PD-(L)1 inhibitor–based therapy are presented by study cohort in Table 3 for 10 patients or more. In the driver-negative cohort, the median rwTOT was 4.6 months (95% confidence interval [CI]: 3.7–6.0) with PD-(L)1 inhibitor monotherapy and 5.2 months (95% CI: 4.4–6.5) with PD-(L)1 inhibitor–chemotherapy; 12-month on-treatment rates were 24% and 23%, respectively. Among the four genomic alteration cohorts, the median rwTOT with PD-(L)1 inhibitor monotherapy ranged from 2.9

months (95% CI: 0.8–9.5) in the *ERBB2* mutation cohort to 7.6 months (95% CI: 2.3–11.1) in the *BRAF* V600E mutation cohort. For patients receiving PD-(L)1 inhibitor–chemotherapy, the median rwTOT was approximately 6 months in all but the *BRAF* V600E mutation cohort (median rwTOT, 17.5 months; 95% CI: 2.8–not reached). From 17% to 46% of patients remained on PD-(L)1 inhibitor monotherapy or combination with chemotherapy at 12 months, with the exception of those in the *ERBB2* mutation cohort (11% and 14%, respectively). Kaplan-Meier plots of rwTOT are depicted by study cohort in Supplementary Figures 1 and 2. Findings with pembrolizumab-based therapy were similar (Table 3).

The median rwTTNT in the driver-negative cohort, depicted in Table 4, was 11.3 months (95% CI: 6.8–14.0) for PD-(L)1 inhibitor monotherapy and 7.6 months (95% CI: 6.5–8.7) for PD-(L)1 inhibitor–chemotherapy; at 12 months, 47% and 34% of patients, respectively, had not initiated a second line of therapy. Among the four genomic alteration cohorts, median rwTTNT with PD-(L)1 inhibitor monotherapy ranged from 4.2 months (95% CI: 1.9–14.1) in the *ERBB2* mutation cohort to 10.5 months (95% CI: 5.6–15.6) in the *BRAF* V600E mutation cohort. For PD-(L)1 inhibitor-chemotherapy, the median rwTTNT was similar to that in the driver-negative cohort for all but the *BRAF* V600E cohort in which it was the longest (19.7 months; 95% CI: 3.4–NR). The 12-month rates of patients who had not initiated a second line of therapy were also aligned with those in the driver-negative cohort, except in the *ERBB2* mutation cohort, in which 12-month rates were 19% and 17% with PD-(L)1 inhibitor monotherapy and PD-(L)1 inhibitor-chemotherapy, respectively (Table 4). Kaplan-Meier plots of rwTTNT are depicted by study cohort in Supplementary Figures 3 and 4.

The results of sensitivity analyses of rwTOT and rwTTNT for patients with ECOG PS of 0 or 1 revealed similar trends and are reported in Supplementary Table 4. The rwTOT and rwTTNT analyses restricted to the study cohorts identified using tissue biopsy, including for ECOG PS of 0 or 1, are reported in Supplementary Tables 5 to 8.

Discussion

The use of immunotherapy alone or in combination with chemotherapy for patients with uncommon genomic alterations represents an area of discussion among clinicians, with no definitive answers. This analysis aims to add data to help clinicians in their daily decisions. In this retrospective study of patients with advanced nonsquamous NSCLC, we describe characteristics, treatment, and outcomes of patients with tumors harboring at least one of four different genomic alterations, *BRAF* V600E mutation, *MET*ex14 mutation, *MET* amplification, and *ERBB2* activation mutation, and for patients with driver-negative NSCLC. Patient characteristics differed among the study cohorts as expected. We observed that PD-(L)1 inhibitor-based therapies were more frequently administered among genomic alteration cohorts in the first line as monotherapy or in combination with chemotherapy or other agents, as compared with other systemic therapies. The rwTOT and rwTTNT findings for PD-(L)1 inhibitor-based therapies in the four cohorts with genomic alterations were mostly similar to those for the driver-negative cohort, although the median rwTOT and rwTTNT with PD-(L)1 inhibitor monotherapy for the *ERBB2* mutation cohort were shorter, and the median rwTOT and rwTTNT with PD-(L)1 inhibitor-chemotherapy for the *BRAF* V600E mutation cohort were longer (further discussed below).

Our findings regarding patient characteristics aligned with those of previous studies.[4,10,33] The patients with *MET*ex14-mutated NSCLC tended to be older, with a median age of 76 years, including more than half (55%) aged 75 years or older, as previously reported.[10] The percentages of women were lowest in the *MET* amplification cohort (39%) and greatest in the *MET*ex14 mutation and *ERBB2* mutation cohorts (61% and 62%).[4,10] The latter two cohorts (*MET*ex14 mutation and *ERBB2* mutation cohorts) also included the lowest percentages of patients with a smoking history, 62% and 47%, respectively, in contrast to 88% in the driver-negative cohort.[4,10] Patterns of PD-L1 expression levels among study cohorts also corresponded to those in previous reports.[15]

We observed frequent administration of PD-(L)1 inhibitor–based therapy as first-line therapy, even in the four genomic alteration cohorts, and targeted therapy administration in first-line was less common than expected for those alterations with available targeted therapies. There are several possible explanations for this finding. First, genomic profiling reports were available to guide therapy choices for only 44% of patients before the start of first-line therapy. Second, provider perception or clinical experience with the use of PD-(L)1 inhibitors could be driving their use given the lack of clinical trial data for PD-(L)1 inhibitor therapy for NSCLC with these genomic alterations. Finally, there were no targeted therapies approved for *MET* amplification or activation mutation of *ERBB2* during the time frame of the study. Relevant targeted therapies that received regulatory approval in the United States before or during the study period included dabrafenib-trametinib for NSCLC with *BRAF* V600E mutation and crizotinib, capmatinib, and tepotinib for NSCLC with *MET*ex14 mutation.

The rwTOT findings for the driver-negative cohort in the present study generally aligned with those from

previous real-world studies of similar patient populations with advanced NSCLC and no known *EGFR* or *ALK* alteration.[34–37] For example, in a large study drawing on the Flatiron Health database, among patients with advanced nonsquamous NSCLC with varied ECOG PS and PD-L1 expression (as in the present study), the median rwTOT was 4.4 months (95% CI: 4.1–4.9) for 2166 patients treated with PD-(L)1 inhibitor monotherapy and 5.6 months (95% CI: 5.1–6.0) for 3457 patients treated with PD-(L)1 inhibitor–chemotherapy,[34] similar to our findings (median rwTOT of 4.6 months for PD-(L)1 inhibitor monotherapy and 5.2 months for PD-(L)1 inhibitor–chemotherapy).

The median rwTOT and rwTTNT in the four study cohorts with genomic alterations were generally similar to those in the driver-negative cohort with a couple of exceptions. Among patients with *BRAF* V600E-mutated NSCLC, the median rwTOT and rwTTNT were similar for those who received PD-(L)1 inhibitor monotherapy but markedly longer for those who received PD-(L)1 inhibitor–chemotherapy relative to the other cohorts, including the driver-negative cohort. For patients in the *ERBB2* mutation cohort who received PD-(L)1 inhibitor monotherapy, the median rwTOT, and rwTTNT were the shortest (2.9 and 4.2 months, respectively), consistent with previous reports of limited benefit of PD-(L)1 inhibitor monotherapy (albeit administered mostly in second-line or later in those studies) for *ERBB2*-mutated NSCLC.[5,15] Instead, with PD-(L)1 inhibitor–chemotherapy combination, the median rwTOT and rwTTNT in the *ERBB2* mutation cohort were similar to those outcomes in the other study cohorts, suggesting no detriment to first-line immunotherapy-chemotherapy combination, again, as previously reported in two real-world, noncomparative studies[38,39]—although the authors of one study noted that their findings suggested no advantage of PD-(L)1 inhibitor–chemotherapy over chemotherapy for this group of patients.[39]

The findings of our study address a gap in the literature by assessing the first-line treatment patterns at U.S. oncology clinics, and outcomes of PD-(L)1 inhibitor-based regimens as first-line therapy for NSCLC harboring the four genomic alterations. By linking genomic data with electronic health record–derived data, the CGDB enables these assessments for a larger patient population than those routinely enrolled in clinical trials. The present study included 84 to 130 patients in the four cohorts with genomic alterations, many of them older patients who are often excluded from clinical trials.[40] The median follow-up time from first-line therapy initiation to data cutoff was 32 to 42 months in the five study cohorts. Whereas the study was not designed to evaluate the timing of genomic testing in association with receipt of guideline-concordant therapy, a relatively limited number of regulatory-approved targeted therapies were available during the time frame of the study (January 2016 to September 2021).

The present study is not without limitations. Similar to most database studies, this study was conducted with clinical data that was not collected specifically for research purposes. Most patients were treated at community oncology practices that are part of the Flatiron Health network; therefore, the results may not be generalizable to patients treated at academic centers or outside the Flatiron Health network. Moreover, important clinical variables were missing for some patients, including ECOG PS for 11% of patients and PD-L1 expression level for 28%. The available data for PD-L1 expression level included the results of the different types of assays used in these real-world settings. The size of the genomic alteration cohorts was not large enough for stratified analysis of treatment-related outcomes by PD-L1 expression, a biomarker positively associated with clinical outcomes with PD-(L)1 inhibitor monotherapy.[41] In addition, the conclusions are limited by the small sizes of some of the treatment subgroups resulting in wide confidence intervals for the rwTOT and rwTTNT analyses. Finally, we note that the study did not use propensity score matching or any other statistical technique to balance cohorts with regard to prognostic factors.

Future research is needed using an enriched database with longer follow-up and more patients with advanced NSCLC harboring genomic alterations of interest to link biomarkers to other clinically relevant outcomes such as response to therapy, disease progression, and survival outcomes. In addition, as more data become available in the CGDB, research is needed regarding the genomic alterations that were too infrequent to warrant analysis in the present study (e.g., *RET* and *NTRK* fusions) or not yet available in the genomic profiling data in the CGDB (e.g., *NRG1* translocation). An updated time frame would also enable the capture of more recently approved targeted therapies and outcomes.

In conclusion, the findings of this study expand the limited knowledge regarding real-world patient characteristics and first-line treatment patterns for patients with advanced nonsquamous NSCLC harboring at least one of four genomic alterations: *BRAF* V600E mutation, *MET*ex14 mutation, *MET* amplification, or activation mutation of *ERBB2*. We observed that rwTOT and rwTTNT findings for PD-(L)1 inhibitor–based therapies administered in the first line to patients with these four genomic alterations were mostly similar to those observed for the patients with driver-negative NSCLC. The rwTOT findings were also in line with data reported in previous real-world studies. Substantial use of PD-(L)1 inhibitor–based therapy and associated clinical outcomes

suggest no detriment from PD-(L)1 inhibitors for patients with advanced nonsquamous NSCLC harboring one of these four genomic alterations.

CRediT Authorship Contribution Statement

Marina C. Garassino: Validation, Visualization, Writing - review & editing.

Sabine Oskar: Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Roles/Writing - original draft, Writing - review & editing.

Ashwini Arunachalam: Conceptualization, Funding acquisition, Investigation, Methodology, Validation, Visualization, Writing - review & editing.

Ke Zu: Conceptualization, Validation, Visualization, Writing - review & editing.

Yu-Han Kao: Data curation, Software, Validation, Writing - review & editing.

Cai Chen: Data curation, Formal analysis, Software, Validation, Writing - review & editing.

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Himani Aggarwal: Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Roles/Writing - original draft, Writing - review & editing.

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Data Sharing Statement

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 Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100568.

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