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Original Article

Real-world treatment and outcomes for *EGFR* WT advanced/metastatic non-squamous non-small cell lung cancer: pooled analysis from project LUMINATE-101

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Abstract

Background: Lung cancer is the leading cause of cancer-related deaths in North America. Non-small cell lung cancer (NSCLC) is the most common type; most cases are advanced/metastatic at diagnosis. Available first and second lines of treatment include platinum-based chemotherapeutics, therapies targeting driver oncogene mutations, and immune checkpoint inhibitors, with limited options at later lines. Understanding the current treatment landscape to define unmet needs will benefit research and development of novel therapies for advanced/metastatic NSCLC.

Methods: The LUMINATE-101 retrospective cohort study evaluated real-world treatment patterns and outcomes for patients with non-squamous epidermal growth factor receptor (*EGFR*) wild type (WT) advanced/metastatic NSCLC diagnosed 1 January 2017 to 31 August 2022 that progressed on previous therapies. Patient data were pooled from US-based electronic health records-derived databases: Flatiron Health NSCLC real-world, ConcertAI Patient360 Lung Cancer, and ConcertAI RWD360NLP; redundant records were removed using tokenization.

Results: Overall, 620 patients were included; median age 67 years, >34% ECOG performance status ≥2, 19% had brain metastasis, 10% had liver metastasis, and 91% were current/ex-smokers. Most patients (54%) received a first-line platinum-based regimen ± immunotherapy and second-line docetaxel + ramucirumab/bevacizumab. Real-world outcomes included median overall survival (OS) = 6.4 months, median time to next treatment/death = 5.0 months, median time to treatment discontinuation = 2.3 months, and median progression-free survival = 3.5 months. ECOG performance status ≥2 correlated with poorer real-world outcomes overall; males had poorer survival and greater progression risk.

Conclusion: Real-world median OS of second-line patients on the current standard of care was < 7 months, highlighting an unmet need for more effective therapeutics in non-squamous *EGFR* WT advanced/metastatic NSCLC.

Key words: Real-world outcomes; tokenization; treatment patterns; *EGFR* WT; locally advanced/metastatic non-squamous non-small cell lung cancer; electronic health records.

Implications for practice

Patients with advanced/metastatic NSCLC have limited treatment options after progressing on front-line therapies. Understanding their real-world treatment landscape and outcomes will benefit ongoing research toward developing novel therapies.

The LUMINATE-101 retrospective cohort study evaluated real-world data for 620 patients with non-squamous *EGFR* WT advanced/metastatic NSCLC. Data were pooled from 3 large US-based Electronic Health Records-derived databases and redundant patient records were filtered using tokenization. The most common treatment regimen (54%) was first-line platinum-based ± immunotherapy and second-line docetaxel + ramucirumab/bevacizumab. The median overall survival of patients receiving second-line therapy was <7 months, highlighting an unmet need for more effective therapies.

Introduction

Lung cancer is the second most common cancer and the leading cause of cancer deaths in North America.[1] In early 2022, 654 620 individuals with a history of lung cancer were recorded in the United States, with a further 238 340 new diagnoses and 127 070 deaths predicted in 2023.[1] Non-small

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cell lung cancer (NSCLC) is the most frequent type of lung cancer (84%)[1] and non-squamous histology is the most common among NSCLC cases (70%-75%).[2] Most NSCLC cases are advanced or metastatic at diagnosis (an estimated 71% in 2020),[3] which negatively impacts prognosis. However, recent advances in early diagnosis and targeted therapies have begun to improve patient survival,[4] with the 2-year relative survival rate having increased in both men and women with NSCLC from 32% and 25% in 1975–1976 to 54% and 43% in 2017–2018, respectively.[1]

Platinum-based chemotherapeutics, including cisplatin and its less toxic derivatives such as carboplatin, have been used to treat NSCLC for decades; these continue to be used in the first-line treatment of lung cancer.[5] However, patients often develop resistance to these non-specific agents.[6] Over the past few decades, several targeted therapies have been developed against driver oncogene mutations in NSCLC, including activating mutations in the epidermal growth factor receptor (*EGFR*), which occur in 19% of patients.[7,8] Many generations of EGFR tyrosine kinase inhibitors (TKIs), including gefitinib,[9] erlotinib,[10] dacomitinib,[11] afatinib,[12] and osimertinib,[13] have been approved as first-line treatment for patients with mutated *EGFR* NSCLC by the US Food and Drug Administration (FDA). Second-line options for most of these patients usually involve platinum doublet chemotherapy. Significant advances have also been made in immunotherapy. Immune checkpoint inhibitors (ICIs), such as those targeting the programmed cell death protein-1 (PD-1)/PD-1 ligand-1 (PD-L1) signaling pathway, have been developed and approved for the treatment of NSCLC. The PD-1 inhibitor pembrolizumab and the PD-L1 inhibitor atezolizumab were approved by the FDA as first-line monotherapy for patients newly diagnosed with locally advanced or metastatic NSCLC with high PD-L1 expression and no known *EGFR* mutations or anaplastic lymphoma kinase (*ALK*) rearrangements.[14,15] In addition, ICIs have shown improved progression-free survival (PFS) and overall survival (OS) when combined with platinum-doublet chemotherapy for both squamous and non-squamous NSCLC across a range of PD-L1 levels, excluding those with known *EGFR* or *ALK* alterations.[16-18] A number of these combinations have been approved by the FDA, including neoadjuvant nivolumab plus chemotherapy for patients with operable NSCLC, pembrolizumab with pemetrexed and platinum chemotherapy as a first-line treatment for metastatic non-squamous NSCLC, and nivolumab, ipilimumab, and platinum-based chemotherapy for patients with metastatic NSCLC without EGFR or ALK alterations. However, most patients both with and without actionable genomic abnormalities experience progression after platinum doublet therapy either with or without concurrent ICI therapy, after which most patients are limited to docetaxel-based regimens without other treatment options, suggesting an urgent need for innovative therapies for later lines of treatment.[14]

Research is ongoing toward developing novel therapeutics and identifying and targeting other biomarkers for NSCLC, such as c-Met protein (also known as MET protein) overexpression.[19,20] Antibody-drug conjugates (ADCs) are a promising class of therapeutics. These agents are composed of an antibody targeting a specific tumor biomarker that is chemically conjugated to a cytotoxin payload via a linker.[21] Several ADCs directed against different surface epitopes are under various stages of development for treating advanced solid tumors, including those targeting c-Met, such as telisotuzumab vedotin (Teliso-V),[22] RC108,[23] TR1801,[24] and SHR-A1403.[25] At the primary analysis of the phase 2 LUMINOSITY study, the response rate with Teliso-V monotherapy was 28.6% among previously treated patients with locally advanced/metastatic, c-Met protein–overexpressing, *EGFR* wild type (WT) non-squamous NSCLC (34.6% for patients with c-Met high overexpression, 22.9% for patients with c-Met intermediate overexpression).[26] In early 2022, it was announced that the FDA granted Breakthrough Therapy Designation to Teliso-V for the treatment of patients with advanced/metastatic *EGFR* WT, non-squamous NSCLC with high levels of c-Met overexpression whose disease has progressed on or after platinum-based therapy.[27] With the development of Teliso-V and other novel therapeutics, it is important to understand the current treatment landscape to define unmet needs and identify patient populations who would benefit most from these new treatment options. Herein, we report results from the LUMINATE-101 retrospective cohort study, which aimed to evaluate the real-world treatment patterns and outcomes of patients with non-squamous *EGFR* WT advanced or metastatic NSCLC that had progressed on previous therapies.

Methods

Study Design

This was a retrospective cohort study leveraging data from 3 large US-based, nationally representative electronic health records (EHR)-derived databases, Flatiron Health NSCLC real-world database, ConcertAI Patient360 Lung Cancer, and ConcertAI RWD360NLP, from 1 January 2011 to 30 September 2022. Flatiron Health has a nationwide network of community oncology practices and academic cancer centers, which comprises ~80% of patients from community practices and ~20% of patients from academic centers, roughly in line with where patients receive their cancer care in the United States. The nationwide Flatiron Health EHR-derived, de-identified NSCLC database is a longitudinal database comprising de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction, from its network.[28,29] During the study period, the de-identified data originated from approximately 280 US cancer clinics (approximately 800 sites of care) and included 83 008 patients diagnosed with NSCLC from 1 January 2011 to 30 September 2022. Lines of therapy in the Flatiron Health database were defined by expert oncology clinicians and based on a set of disease-specific rules that spanned 9 categories to summarize the sequence of antineoplastic, systemic therapies. The categories were: therapies eligible for inclusion in lines of therapy; index date; start of therapy; definition of a line of therapy; maintenance; gap in therapy; changes permitted within a line of therapy; changes not permitted within a line of therapy; and line of therapy end date. The ConcertAI Patient360 Lung Cancer and RWD360NLP are EHR databases where patients with lung cancer were first identified on the basis of International Classification of Diseases codes in electronic medical records (EMRs), aggregated by 400+ cancer centers from both academic and community settings and creating rapid learning systems for US oncology practice providers across all census regions to improve patient care. More than 37 000 adult patients with lung cancer who fulfilled record completeness screening had their EHRs abstracted and curated through natural language processing and standardized vocabulary mapping. Oncology practices were included

regardless of their EMR system, and 80% and 20% were from community and academic centers, respectively. These databases provided de-identified, curated, structured, and unstructured patient data recorded per standard documentation practices, including patient demographics, practice and provider information, diagnoses, clinical details such as biomarkers and pathology, cancer histology and staging, visits and telemedicine, laboratory values, vital signs, medication order and administration, drug episodes, treatment regimens and lines of therapy, Eastern Cooperative Oncology Group (ECOG) performance status, insurance payor types, mortality, and other clinical outcomes.

To reduce biases due to repeated inclusion of the same patients, overlap assessment was performed via tokenization by a third party (Datavant), redundant patient cases were removed, and patient cases from all 3 datasets were pooled for performance of the analysis. The tokenization process is depicted in **Figure 1**.

This study was conducted in accordance with the Health Insurance Portability and Accountability Act and all patient-level data were de-identified. Given the retrospective nature of the study design and de-identified data, the study was exempt from internal review board evaluation.

Patient eligibility criteria

Eligible patients needed to have a confirmed diagnosis of advanced or metastatic NSCLC on or after 1 January 2017 and before 31 August 2022 (index diagnosis event), with a histology code for non-squamous NSCLC. Patients were at least 18 years of age at the time of confirmed advanced or metastatic NSCLC diagnosis and had received at least 1 line of therapy (platinum agents with or without ICIs). Patients should not have tested positive for any oncogene prior to line 2 initiation + 28 days, or received targeted TKIs at first, second, or third line. Patients with unknown biomarker status may not be excluded. To ensure sufficient longitudinal data capture of patient journey, patients were included if they had at least 2 structured activities, which are defined as a recording of vital information, a medication administration, a non-canceled drug order, or a reported laboratory test/result in the EHR database, within 90 days after the confirmed advanced or metastatic NSCLC diagnosis.

Patients were excluded from the study if they had received at least 1 line of therapy through a clinical trial or had received targeted TKI therapy at first or later lines of treatment. Patients were also excluded if they had missing birth date or gender, or if their date of confirmed advanced or metastatic NSCLC diagnosis was within 30 days of the study end date.

Outcomes Analyses

This study assessed the real-world distribution of various standard-of-care first- and second-line systemic therapies for treating *EGFR* WT advanced or metastatic non-squamous NSCLC. Real-world time-to-event outcomes were also assessed, including time to next treatment or death (TTNT/D), time to treatment discontinuation (TTD), OS, and PFS. PFS, TTNT/D, and TTD were determined within-line for second- and third-line treatment, whereas OS was determined for the overall duration of treatment following second- or third-line initiation.

Within-line PFS was defined as the time from initiation of a line of treatment to the earlier of progression or death that occurred before the start of the subsequent line. Patients without a progression or death event during this assessment window were censored at their date of last clinical assessment within the same assessment window. The choice of the last clinical assessment date as the censoring date was based on established methodology[30] and was applied to a within-line assessment window. Within-line TTNT/D was defined as the time from treatment initiation within a line to the earliest initiation of the subsequent line or death. For patients who did not have an available date of death or initiation of subsequent line of therapy, the date of the last confirmed structured activity was considered for censoring. Within-line TTD was defined as the time from initiation of the line of treatment to discontinuation of that line, death, end of follow-up, or end of data availability, whichever came earlier. Patients who did not have a recorded date of death or treatment discontinuation were censored at their last known date of line-of-interest therapy usage. OS was assessed as the duration between the initiation of the line of therapy of interest and the death date, imputed as whichever is the latest of either the fifteenth of the death month or censored at the last confirmed structured activity of the death month.[30]

Disease progression was determined by a clinician on the basis of a radiographic scan or biopsy result or determined by the treating oncologist through clinical assessment. Death date was determined as the fifteenth of the death month or the date of last confirmed structured patient activity of the death month, whichever was recorded later in the pooled EHR database and was validated using the National Death Index (for cases from Flatiron database) or third-party death data (for cases from ConcertAI databases). Treatment discontinuation was defined as discontinuation of all agents in a line of interest therapy. The date of discontinuation was marked as the latest end date of all drug episodes (defined as the duration of treatment) and having a record of 1 of the following: subsequent systemic therapy regimen, a gap of 120 days since the last administration of line of interest therapy, or date of death while on the line of interest treatment. Since the last date of the therapy record could be driven by the loss of patient follow-up in the database, the discontinuation event was differentiated from the censoring date using additional qualifying criteria based on established methodology.[30]

Performance status was assessed within the window of 60-30 days prior to starting the corresponding line of treatment where outcomes were assessed. If multiple assessments were available, those prior to and closest to the start date of that line of treatment were selected. When Karnofsky performance scores were available, they were transformed to ECOG performance status using the Buccheri crosswalk.[31]

All time-to-event outcomes were analyzed using the Kaplan-Meier method, and the median time-to-event between groups was compared using the log-rank test. For each time-to-event outcome, multivariate Cox proportional hazard models were evaluated to determine the relative risk of the outcome due to several covariates. These covariates included patient demographics such as age, gender, and race, or provider characteristics like treatment setting and geographic location, or clinical characteristics including stage at initial diagnosis, line of therapy, ECOG performance status, smoking status, and presence of brain metastasis. A two-sided 95% confidence interval (CI) was calculated using the Clopper-Pearson exact method for binary variables[32] and multinomial proportions such as Sison and Glaz method for multinomial variables.[33]

Figure 1. Tokenization process, overlap assessment, and dataset stacking for pooled analysis. Abbreviations: aNSCLC, advanced non-small cell lung cancer; CAI, ConcertAI; DV, data vendor; EDM, enhanced datamart; NLP, natural language processing; PT, patient; RWD, real-world data.

Table 1. Patient characteristics.

	2L (*n* = 504)	**3L (*n* = 116)**	**Overall (*N* = 620)**
Line of therapy, % (*n*/*N*)	81.3 (504/620)	18.7 (116/620)	100.0
Treatment pattern, *n* (%)			
A: 1L platinum-based regimen (± IO); 2L docetaxel mono	170 (33.7)	0	170 (27.4)
B: 1L platinum-based regimen (± IO); 2L docetaxel combo (w ramucirumab/nintedanib/ bevacizumab)	334 (66.3)	0	334 (53.9)
C: 1L IO mono; 2L platinum-based regimen (± IO); 3L docetaxel mono or combo	0	37 (31.9)	37 (6.0)
D: 1L platinum-based regimen (± IO); 2L IO mono; 3L docetaxel mono or combo	0	79 (68.1)	79 (12.7)
Gender, *n* (%)			
Female	222 (44.0)	54 (46.6)	276 (44.5)
Male	282 (56.0)	62 (53.4)	344 (55.5)
Age at 2L/3L initiation, years			
Median	67.0	67.5	67.0
Min, max	35.0, 88.0	37.0, 85.0	35.0, 88.0
Age group at 2L/3L initiation, *n* (%)			
18-39	2 (0.4)	1 (0.9)	3 (0.5)
40-64	197 (39.1)	44 (37.9)	241 (38.9)
65-74	208 (41.3)	48 (41.4)	256 (41.3)
75+	97 (19.2)	23 (19.8)	120 (19.4)
Treatment setting, *n* (%)			
Academic	77 (15.3)	23 (19.8)	100 (16.1)
Community	414 (82.1)	87 (75.0)	501 (80.8)
Multiple	5 (1.0)	2 (1.7)	7 (1.1)
Unknown or missing	8 (1.6)	4 (3.4)	12 (1.9)
ECOG at 2L/3L initiation, *n* (%)			
0	63 (12.5)	12 (10.3)	75 (12.1)
1	194 (38.5)	41 (35.3)	235 (37.9)
2	122 (24.2)	32 (27.6)	154 (24.8)
3	45 (8.9)	9 (7.8)	54 (8.7)
4	2 (0.4)	0	2 (0.3)
Missing	78 (15.5)	22 (19.0)	100 (16.1)
Year of a/mNSCLC diagnosis, *n* (%)			
2017	65 (12.9)	52 (44.8)	117 (18.9)
2018	130 (25.8)	37 (31.9)	167 (26.9)
2019	133 (26.4)	15 (12.9)	148 (23.9)
2020	101 (20.0)	6 (5.2)	107 (17.3)
2021	65 (12.9)	5 (4.3)	70 (11.3)
2022	10 (2.0)	1 (0.9)	11 (1.8)
PD-L1 status, *n* (%)			
Positive	178 (35.3)	53 (45.7)	231 (37.3)
Negative	179 (35.5)	30 (25.9)	209 (33.7)
Unknown	147 (29.2)	33 (28.4)	180 (29.0)
Race, *n* (%)			
Asian	12 (2.4)	4 (3.4)	16 (2.6)
Black or African American	68 (13.5)	13 (11.2)	81 (13.1)
White	365 (72.4)	84 (72.4)	449 (72.4)
Other or Unknown	59 (11.7)	15 (12.9)	74 (11.9)
Ethnicity, *n* (%)			
Hispanic or Latino	10 (2.0)	4 (3.4)	14 (2.3)
Not Hispanic or Latino	271 (53.8)	68 (58.6)	339 (54.7)

Table 1. Continued

	2L (*n* = 504)	3L (*n* = 116)	Overall (*N* = 620)
Other or Unknown	223 (44.2)	44 (37.9)	267 (43.1)
Stage at initial NSCLC diagnosis, *n* (%)			
Stage IIIA or earlier	50 (9.9)	29 (25.0)	79 (12.7)
Stage IIIB or more advanced	449 (89.1)	87 (75.0)	536 (86.5)
Unknown or Missing	5 (1.0)	0	5 (0.8)
Brain metastasis, *n* (%)			
Yes	92 (18.3)	24 (20.7)	116 (18.7)
No	412 (81.7)	92 (79.3)	504 (81.3)
Liver metastasis, *n* (%)			
Yes	54 (10.7)	9 (7.8)	63 (10.2)
No	450 (89.3)	107 (92.2)	557 (89.8)
Smoking status, *n* (%)			
Current or ex-smoker	454 (90.1)	107 (92.2)	561 (90.5)
Non-smoker	48 (9.5)	9 (7.8)	57 (9.2)
Unknown or missing	2 (0.4)	0 (0)	2 (0.3)
Census region, *n* (%)			
Northeast	100 (19.8)	14 (12.1)	114 (18.4)
Midwest	77 (15.3)	22 (19.0)	99 (16.0)
West	50 (9.9)	10 (8.6)	60 (9.7)
South	226 (44.8)	49 (42.2)	275 (44.4)
Unknown or missing	51 (10.1)	21 (18.1)	72 (11.6)

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; a/mNSCLC, locally advanced or metastatic non-small cell lung cancer; combo, combination; ECOG, Eastern Cooperative Oncology Group; IO, immunotherapy; mono, monotherapy; PD-L1, programmed cell death protein 1 ligand 1; TKI, tyrosine kinase inhibitor.

Data harmonization and pooling were performed using SAS base edition (3.81 release; SAS Institute) and analyses were performed using R version 3.6.3.

Results

Patient characteristics and treatment patterns

Of the 61 031 patients initially considered, a total of 620 eligible patients with *EGFR* WT advanced or metastatic non-squamous NSCLC were included in the pooled database for this study (cohort attrition shown in Supplementary Table S1). Their characteristics, including stratification by line of therapy, are described in **Table 1**. Overall, the median age at initiation of second- or third-line treatment was 67 years. The patient pool was 56% male, 72% white, 13% Black, and 3% Asian; 81% of patients were from the community setting, and 91% were current or ex-smokers. Most patients had stage IIIB or later NSCLC (87%) at the time of initial NSCLC diagnosis, with 50%, 25%, and >9% having ECOG performance status ≤1, 2, and ≥3, respectively, at second- or third-line treatment initiation. Most patients (81%) were undergoing second-line therapy. About 19% had brain metastasis and 10% had liver metastasis; occurrence of metastases was comparable in second-line and third-line populations. Proportionally more patients in the third-line population were diagnosed in 2017-2018 (77%), whereas more patients in the second-line population were diagnosed later (61%). A greater proportion of patients in the third line were diagnosed at stage IIIA or earlier (25%) and were PD-L1 positive (46%) compared with those in the second-line population (10% and 35%, respectively).

Real-world treatment patterns for advanced NSCLC are shown in **Figures 2 and 3**. The most common treatment sequence following progression on or after a first-line platinum-based regimen with or without immunotherapy was second-line docetaxel combination therapy with ramucirumab or bevacizumab (54%), or second-line docetaxel monotherapy (27%), or second-line immunotherapy alone followed by third-line docetaxel mono- or combination therapy (13%). A less common treatment sequence included first-line immunotherapy alone followed by a second-line platinum-based regimen with or without immunotherapy, and third-line docetaxel mono- or combination therapy (6%). A list of the most common first-line regimens received by the study population is presented in Supplementary Table S2.

Real-world outcomes

The real-world time-to-event outcomes from this pooled analysis are presented in Figure 4. OS, TTD, and TTNT/D were assessed in all 620 patients, and PFS was evaluated in the 602 patients who had progression data available. Median OS was 6.4 months (95% CI: 6.01, 7.29) with median follow-up of 23.4 months, and median PFS within each line of therapy was 3.5 months (95% CI: 3.12, 3.88) with median follow-up of 17.8 months. For individual lines of treatment, patients reported a median of 5.0 months TTNT/D (95% CI: 4.37, 5.45) and 2.3 months TTD (95% CI: 2.10, 2.79); median duration of follow-up was 23.2 and 20.8 months, respectively.

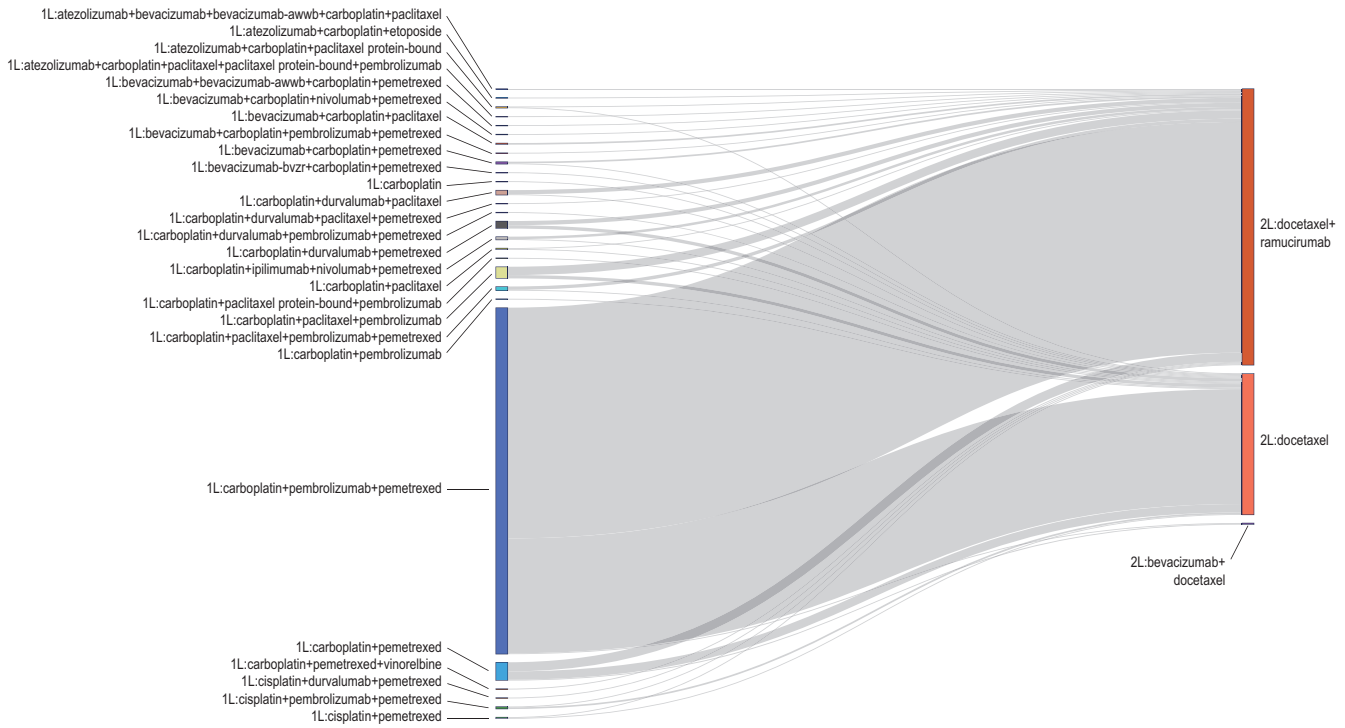

Figure 2. Sankey diagram on treatment pathway among patients receiving 2L docetaxel ± anti-VEGF therapy. Bevacizumab-awwb and bevacizumab-bvzr are biosimilars of bevacizumab. Abbreviations: 1L, first-line; 2L, second-line; VEGF, vascular endothelial growth factor.

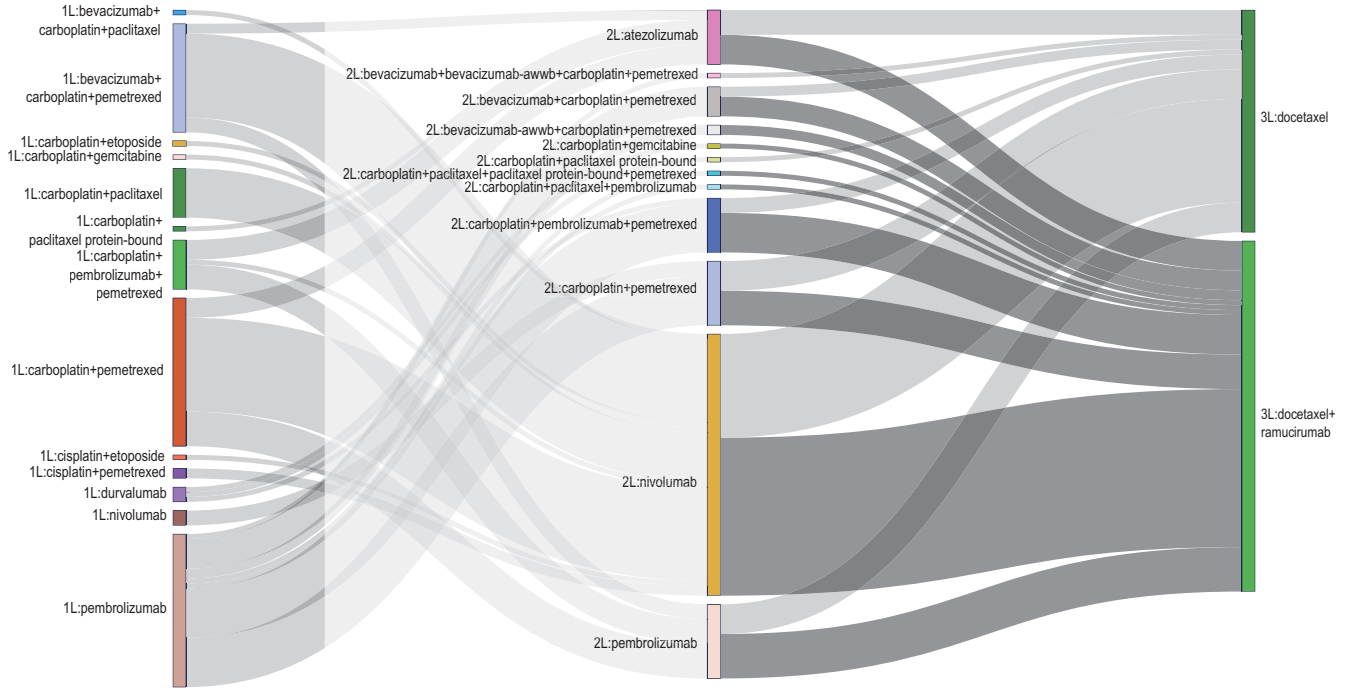

Figure 3. Sankey diagram on treatment pathway among patients receiving 3L docetaxel ± anti-VEGF therapy. Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; VEGF, vascular endothelial growth factor.

Outcomes were further stratified by line of therapy (Table 2), and patients receiving docetaxel-based regimens in the second line had comparable clinical outcomes to those receiving docetaxel-based regimens in the third line.

Multivariate analysis indicated that most factors tested for their prognostic value did not impact real-world outcomes, including patients' age, race, treatment setting or geographic location, cancer stage at initial diagnosis, current line of therapy, smoking status, PD-L1 expression status, or the presence of brain or liver metastasis. Conversely, higher ECOG performance status and male gender showed a statistically significant correlation with poor prognosis. When compared

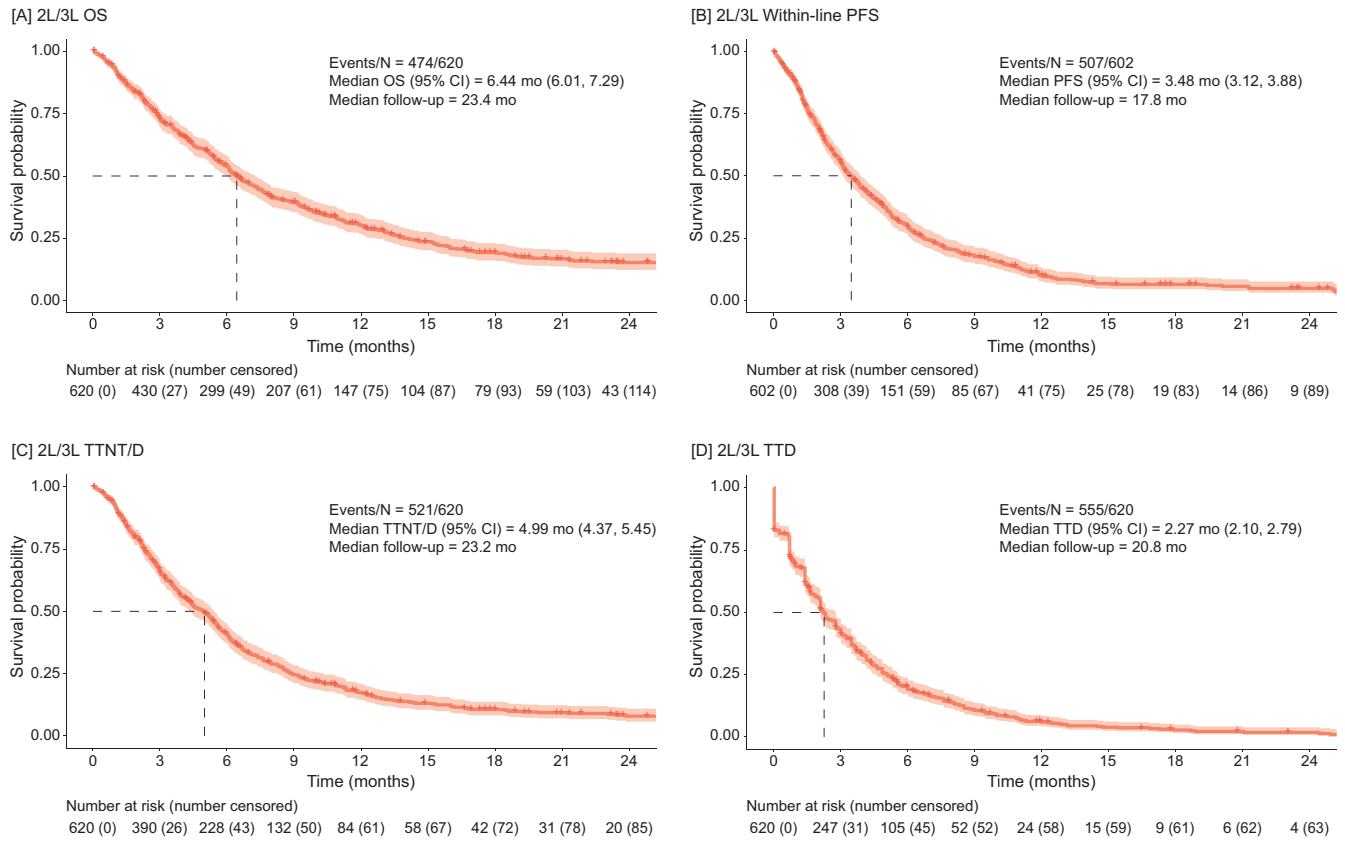

Figure 4. Real-world outcomes. Abbreviations: 2L, second-line; 3L, third-line; CI, confidence interval; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation; TTNT/D, time to next treatment or death

with patients having ECOG performance status 0-1, those with a score of 2 had 29% greater risk of death (OS hazard ratio [HR]: 1.29; 95% CI: 1.03, 1.62; $P = .03$), and patients with a score of 3-4 had 146% greater risk of death (OS HR: 2.46; 95% CI: 1.76, 3.44; $P < .001$) during second- or third-line therapies. Males had a 23% higher risk of death among patients (OS HR: 1.23; 95% CI: 1.00, 1.51; $P = .05$) when compared with females. For disease progression within a given line of therapy, ECOG performance status 3-4 was correlated with a 105% greater risk of progression (PFS HR: 2.05; 95% CI: 1.48, 2.84; $P < .001$) in patients receiving second or third line of therapy compared with a score of 0-1. Males had a 24% greater risk of progression (PFS HR: 1.24; 95% CI: 1.01, 1.52; $P < .04$) compared with females. For TTNT/D within each line of therapy, patients with ECOG performance status 3-4 had a 133% greater chance of progression to a subsequent line of therapy or death (HR: 2.33; 95% CI: 1.68, 3.24; $P < .001$) compared with patients having a score of 0-1. For the TTD outcome within each line of therapy, when compared with an ECOG performance status of 0-1, a score of 2 correlated with a 31% greater risk of discontinuation (HR: 1.31, 95% CI: 1.05, 1.62; $P = .01$), and a score of 3-4 correlated with a 120% increase in the risk of discontinuation (HR: 2.20, 95% CI: 1.60, 3.03; $P < .001$).

To further evaluate the association of ECOG performance status with real-world outcomes, subgroup analyses were performed in patients with a score of 0-1 and those with a score of 2-4, stratified by line of therapy (**Table 2**, **Figure 5**, **and Supplementary Figure S1**). Among patients with ECOG performance status 0-1 versus 2-4, the former had better outcomes; median OS was 7.7 versus 5.1 months, median PFS was 4.3 versus 2.7 months, median TTNT/D 5.6 versus 3.7 months, and median TTD 3.2 versus 1.4 months, respectively.

Discussion

Patients with advanced or metastatic *EGFR* WT non-squamous NSCLC have limited treatment options for second or later lines after progression on standard chemo- and/or immunotherapy. While next-line targeted therapies for some specific non-*EGFR* oncogenes are in development, most *EGFR* WT cases do not have a currently actionable genomic abnormality. Research is ongoing toward developing promising novel therapeutics for the bulk of the non-squamous *EGFR* WT population. As such, understanding the current standard of care in the real-world care setting and the resulting real-world outcomes is critical to define any unmet needs in this disease space. The LUMINATE-101 study, presented here, analyzed EHR-derived data for a large cohort of patients with *EGFR* WT advanced or metastatic non-squamous NSCLC, retrospectively pooled from 3 US-based real-world databases: Flatiron Health NSCLC real-world database, ConcertAI Patient360 Lung Cancer, and ConcertAI RWD360NLP. This study established that most patients who experienced progression on first-line platinum-based chemotherapy with or without immunotherapy received docetaxel in combination with ramucirumab or bevacizumab (54%) or docetaxel monotherapy (27%) as the second-line therapy. The next most common treatment sequence was second-line immunotherapy alone followed by third-line docetaxel mono- or combination

Table 2. Real-world outcomes.

	All patients			Patients with ECOG PS 0–1			Patients with ECOG PS 2–4		
	2L	3L	Overall	2L	3L	Overall	2L	3L	Overall
OS									
N	504	116	620	257	53	310	169	41	210
Events	385	89	474	186	42	228	138	30	168
Median (95% CI)	6.31 (5.75, 7.20)	7.00 (5.85, 10.40)	6.44 (6.01, 7.29)	7.59 (6.31, 9.33)	8.21 (6.08, 13.67)	7.72 (6.57, 9.26)	4.99 (3.91, 6.21)	6.11 (3.58, 12.16)	5.06 (4.24, 6.14)
Median follow-up, months	—	—	23.4	—	—	23.5	—	—	21.8
PFS									
N	490	112	602	246	51	297	168	40	208
Events	414	93	507	205	42	247	143	32	175
Median (95% CI)	3.55 (3.09, 4.04)	3.32 (2.89, 4.57)	3.48 (3.12, 3.88)	4.14 (3.55, 5.06)	4.57 (3.25, 7.20)	4.27 (3.61, 5.06)	2.56 (2.14, 3.42)	3.12 (2.27, 4.27)	2.69 (2.27, 3.25)
Median follow-up, months	—	—	17.8	—	—	18.7	—	—	17.3
TTNT/D									
N	504	116	620	257	53	310	169	41	210
Events	428	93	521	214	44	258	147	30	177
Median (95% CI)	4.90 (4.30, 5.42)	5.06 (3.71, 6.37)	4.99 (4.37, 5.45)	5.55 (4.90, 6.11)	6.08 (4.57, 8.77)	5.59 (5.19, 6.11)	3.58 (3.02, 4.96)	3.88 (3.15, 7.36)	3.71 (3.15, 4.67)
Median follow-up, months	—	—	23.2	—	—	23.5	—	—	21.3
TTD									
N	504	116	620	257	53	310	169	41	210
Events	453	102	555	229	47	276	153	35	188
Median (95% CI)	2.33 (2.10, 2.83)	2.10 (1.41, 2.79)	2.27 (2.10, 2.79)	3.25 (2.79, 3.71)	2.79 (1.64, 4.14)	3.15 (2.79, 3.71)	1.45 (1.05, 2.23)	0.85 (0.03, 2.33)	1.41 (0.95, 2.10)
Median follow-up, months	—	—	20.8	—	—	23.0	—	—	12.3

Abbreviations: 2L, second-line; 3L, third-line; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation; TTNT/D, time to next treatment or death.

therapy (13%). These real-world systemic treatment patterns are consistent with the recommendations from the National Comprehensive Cancer Network (NCCN).[34] The real-world outcomes of OS, PFS, TTD, and TTNT/D were at <7 months, indicating a poor prognosis when these patients received the current standard of care.

We also confirmed that ECOG performance status ≥2 was correlated with poorer outcomes overall and male gender was correlated with poorer survival and faster disease progression in this patient population.

Our survival results are not dissimilar to those reported by various retrospective studies and clinical trials. A recent literature review of clinical trials and real-world outcomes in patients with metastatic *EGFR* WT and mutated NSCLC who had experienced progression following platinum-based chemotherapy documented median OS and PFS rates ranging from 5.4 to 15.4 months and 1.9 to 5.2 months in clinical trials, and 8.3 to 18.0 months and 4.4 to 6.8 months in real-world studies, respectively.[35] Poor clinical outcomes (OS: 5.0 months [95% CI: 3.94, 6.50]; PFS: 1.8 months [95% CI: 1.7, 2.0]) were also observed in a retrospective real-world practice review at a single tertiary care center for patients with *EGFR* WT advanced or metastatic NSCLC following second-line docetaxel treatment.[36] Similarly, various clinical trials assessing outcomes with second-line docetaxel in patients with *EGFR* WT advanced NSCLC reported median OS rates ranging from 8.0 to 14 months and PFS from 2 to 11.9 months.[37-39] Taken together, these data underscore the unmet need for more effective therapies in patients with *EGFR* WT advanced NSCLC.

By studying EHR records of mostly community-based patients (n = 501, 81%), this study was able to assess real-world trends in treatments and outcomes within the community setting, where most patients with NSCLC (85%) are treated in the United States.[40] EHRs are also a critical source for data from certain subgroups of patients with NSCLC who are not well-represented in clinical trials, including elderly patients, patients with brain metastasis, patients with rare mutations, or those of racial backgrounds associated with biomarkers.[41] Further, pooling patient data from multiple

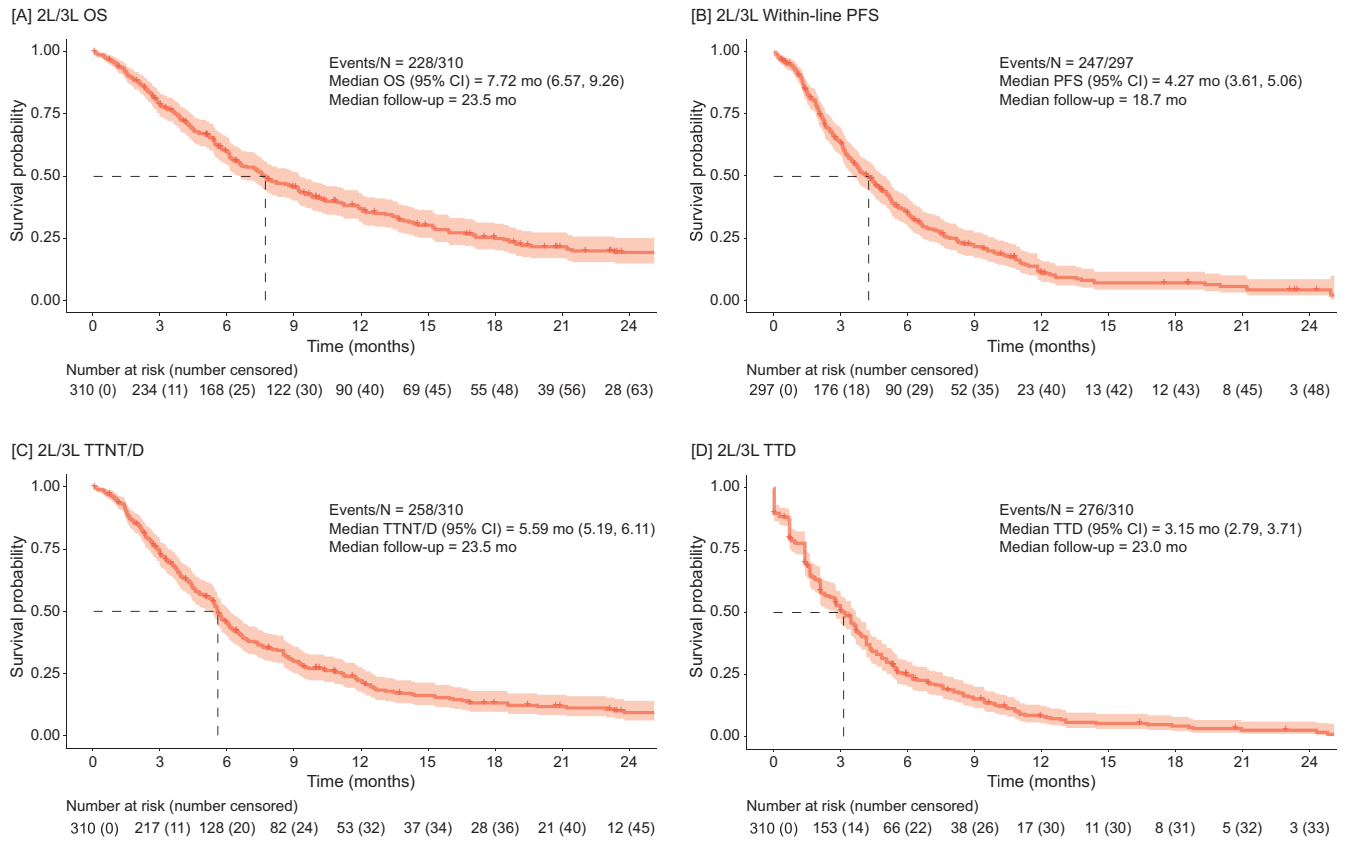

Figure 5. Real-world outcomes in patients with ECOG PS 0-1. Abbreviations: 2L, second-line; 3L, third-line; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation; TTNT/D, time to next treatment or death.

reliable EHR databases via a tokenization process minimized bias in our research where duplicate patient records existed in multiple data sources and resulted in an enhanced sample size of 620 unique eligible patients. This allowed the study to cover a broader US population, thus improving the generalizability of the results. However, the study excluded data on patients with early-stage III/IIIA NSCLC. Data on radiation or surgical procedures and neoadjuvant or adjuvant therapies could not be obtained from one of the data sources. In addition, real-world outcomes have their limitations; disease progression was not anchored on stringent Response Evaluation Criteria in Solid Tumors standards used in clinical trial settings, but instead based on physician notes/records in the included datasets. There were additional database limitations, including incomplete data on adverse events, cancer stage, race and ethnicity, underreported/detected comorbidity, brain and liver metastasis, and ECOG performance status at treatment initiation.

Proportionally more patients in the third-line setting were diagnosed earlier than those in the second-line setting, thus biasing the former subgroup of patients toward longer follow-ups. Further, a greater proportion of patients receiving third-line treatment were PD-L1 positive, which is associated with greater benefit from ICIs, thus biasing them toward better outcomes, as evident in the real-world outcomes (**Table 2**). This study aimed to evaluate treatment outcomes in an *EGFR* WT population. Per the eligibility criteria, included patients should have tested negative for *EGFR* mutation, without any positive *EGFR* test results prior to second-line treatment initiation. However, *EGFR* test results data could possibly be missing for some patients even if they were tested. The use of EGFR-targeting agents was incorporated in the patient exclusion criteria to mitigate this limitation. After screening based on these criteria, a few patients with other actionable genetic alterations remained, who were also excluded to further homogenize the study population, as these patients may benefit from targeted TKIs and have different clinical outcomes. However, there could be additional patients with actionable genetic alterations who had unknown data and were included in the final study population.

Despite the continuously evolving therapeutic landscape for advanced or metastatic NSCLC, effective treatment options are limited in the second line and beyond.[14] Further, chemotherapeutics, like docetaxel, are still commonly used in second or later lines of treatment, especially in patients whose disease progressed after immunotherapy.[15] The LUMINATE-101 real-world cohort study exposes a significant unmet need for novel therapeutics that are more effective in treating patients with non-squamous *EGFR* WT advanced or metastatic NSCLC.

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Conflicts of interest

N.G.: Employment: AstraZeneca (immediate family member); consulting or advisory role: AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, GlaxoSmithKline, Janssen; Lilly, MSD, Novartis, Pfizer, PharmaMar, Roche, Sanofi, Takeda; research funding: AstraZeneca (Inst), Boehringer Ingelheim (Inst), Roche (Inst); travel, accommodations, expenses: AstraZeneca, Bristol Myers Squibb, MSD Oncology, Roche. Q.X., S.N., R.K., C.R., H.A., S.C., S.K.: Employees at AbbVie Inc., and may own stock or options. D.R.C.: Consulting or advisory role: AbbVie, Apollomics, AstraZeneca, Daiichi Sankyo, Elevation, Kestrel, Nuvalent, Seattle Genetics, Takeda, Turning Point, Amgen, Anchiano, Bio-Thera, BMS, Eisai, EMD Serono, Eli Lilly, GSK, Helsinn, Janssen, OnKure, Mersana, Pfizer, Qilu, Roche, Sanofi, CBT Pharmaceuticals, G1 Therapeutics, Blueprint, Achilles, BeyondSpring, Archer, Medtronic, Ribon; Research funding: Inivata; Other relationships (company-sponsored trials at institution): AbbVie, AstraZeneca, Dizal, Inhibrx, Karyopharm, Pfizer, Phosplatin, PsiOxus, Rain, Roche/Genentech, Seattle Genetics, Takeda, Turning Point. S.B.: Honoraria: AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chugai, Daiichi Sankyo, FoundationOne, Gilead, GlaxoSmithKline, Janssen, Lilly, Merck Serono, Merck Sharp & Dohme, Novartis, Pierre Fabre, Pfizer, Roche, Servier, Sanofi, Takeda. S.L.: Research funding: AstraZeneca, Hutchison MediPharma, BMS, Hengrui Therapeutics, BeiGene, Roche, Hansoh; other relationships (speaker fees): AstraZeneca, Roche, Hansoh, Hengrui Therapeutics; consulting or advisory role: AstraZeneca, Pfizer, Boehringer Ingelheim, Hutchison MediPharma, Simcere, Zai Lab, GenomiCare, Yuhan Corporation, prIME Oncology, Menarini, Roche.

Ethics and data sharing

This was a retrospective real-world study leveraging deidentified patient data from electronic medical records of patients with NSCLC in the US. Only aggregated data were reported. The analysis was performed in accordance with the most recent ISPOR (International Society for Pharmacoeconomics and Outcomes Research) Good Practices for Outcomes Research for guidance.

Data availability

The authors confirm that the aggregate data supporting the findings of this study are available within the article and/or its supplementary materials. Restrictions apply to the availability of patient-level data, which were used under license for this study. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvieclinicaltrials.com/hcp/data-sharing/.

Supplementary material

Supplementary material is available at *The Oncologist* online.

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