Title	Comparative effectiveness of sotorasib versus docetaxel in second line and beyond (2L+) among patients with advanced non-small cell lung cancer (NSCLC) in the Flatiron Health (FH) Enhanced Datamart (EDM)
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Research Question and Objectives	**Primary objective:** • To compare overall survival in patients with KRAS p.G12C-mutated advanced NSCLC initiating sotorasib monotherapy versus docetaxel monotherapy or combination therapy in the 2L setting within the US FH EDM. **Secondary objective:** • To compare overall survival in patients with KRAS p.G12C-mutated advanced NSCLC initiating sotorasib monotherapy versus docetaxel monotherapy or combination therapy in the 2L+ setting within the US FH EDM.
Country of Study	US
Authors	PPD

Marketing Authorization Holder

Marketing Authorization Holder	Amgen Inc. Thousand Oaks, CA 91320
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1. ABSTRACT

● Title

Comparative effectiveness of sotorasib versus docetaxel in second line and beyond (2L+) among patients with advanced non-small cell lung cancer (NSCLC) in the Flatiron Health (FH) Enhanced Datamart (EDM)

● Keywords

Retrospective cohort study, KRAS p.G12C, advanced non-small cell lung cancer, Flatiron Health Enhanced Datamart, real-world comparative effectiveness, overall survival, propensity score overlap weighting, sotorasib, docetaxel

● Rationale and Background

Sotorasib is a KRAS G12C inhibitor used for previously treated KRAS G12C-mutated locally advanced or metastatic NSCLC. Docetaxel is a commonly used subsequent-line treatment and served as the active comparator in the phase 3 CodeBreaK 200 trial. Although CodeBreaK 200 found no difference in overall survival, interpretation of this endpoint was complicated by treatment crossover and the selected clinical-trial population. A real-world comparative study was therefore undertaken to characterize effectiveness in routine US oncology practice.

● Research Question and Objectives

Objectives	Endpoints
Primary	**Primary**
To compare overall survival in KRAS p.G12C-mutated advanced NSCLC patients initiating sotorasib monotherapy versus docetaxel monotherapy or combination therapy in the 2L setting within the US FH EDM.	Overall survival (OS)
Secondary	**Secondary**
To compare overall survival in KRAS p.G12C-mutated advanced NSCLC patients initiating sotorasib monotherapy versus docetaxel monotherapy or combination therapy in the 2L+ setting within the US FH EDM.	Overall survival (OS)

● Study Design

This was a retrospective, active-comparator, new-user cohort study using de-identified EHR-derived data from the Flatiron Health Enhanced Datamart. The primary analysis evaluated treatment initiation in 2L; the secondary analysis evaluated treatment initiation in 2L and beyond. Propensity score overlap weighting was used to balance measured baseline characteristics.

● Setting

The study included adults with KRAS G12C-mutated advanced NSCLC receiving care in the US Flatiron Health network. Advanced NSCLC diagnoses and treatment history were identified from 1 January 2011 through 30 September 2022, with outcome follow-up through 30 September 2023.

● Patients and Study Size, Including Dropouts

The 2L analysis included 102 patients initiating sotorasib monotherapy and 58 initiating docetaxel monotherapy or combination therapy. The 2L+ analysis included 164 sotorasib-treated and 116 docetaxel-treated patients. Patients were followed from treatment initiation until death, loss to follow-up, study end, clinical study drug initiation, or end of last activity date as applicable.

● Data Sources and Methods

The FH EDM includes structured and abstracted unstructured EHR data from community and academic oncology practices. Baseline characteristics were described before and after propensity score weighting. Propensity scores were estimated using logistic regression and overlap weights were applied to balance measured prognostic factors. Median OS and 95% confidence intervals were estimated using Kaplan–Meier methods; weighted Cox proportional hazards models estimated mortality hazard ratios. Prespecified subgroup, censoring sensitivity, outcome-model sensitivity, and quantitative bias analyses were conducted.

● Results

After propensity score weighting, variables included in the propensity score models were well balanced. In the 2L setting, weighted median OS was 10.2 months (95% CI, 7.6–16.3) with sotorasib and 6.0 months (95% CI, 4.2–11.0) with docetaxel; the weighted mortality HR was 0.62 (95% CI, 0.41–0.93). In the 2L+ setting, weighted median OS was 10.2 months (95% CI, 8.0–14.6) and 7.2 months (95% CI, 5.1–10.6), respectively; the weighted mortality HR was 0.65 (95% CI, 0.49–0.87). Across the four reported subgroup analyses, mortality HRs ranged from 0.61 to 0.65 in 2L and from 0.61 to 0.66 in 2L+, with all 95% CIs excluding 1.00. Most sensitivity analyses were consistent with the main analysis; the analysis censoring only at clinical study drug initiation or study-period end was attenuated to an HR of 0.80 in both settings, with 95% CIs including 1.00. Quantitative bias analysis G-values ranged from 3.75 to 6.45 across the evaluated confounder-prevalence assumptions.

● Discussion

- In this US real-world population of patients with previously treated KRAS G12C-mutated advanced NSCLC, sotorasib monotherapy was associated with longer median OS than docetaxel monotherapy or combination therapy in both 2L and 2L+ analyses after adjustment for measured baseline characteristics.
- The staging and clean-room framework approach, sensitivity analyses, and quantitative bias analysis enhanced the robustness of the comparative assessment.
- As a nonrandomized EHR-based study, the results remain subject to residual confounding, missing or incomplete clinical information, potential calendar-time differences, small sample size, and limited generalizability beyond the US Flatiron Health population.

● Marketing Authorization Holder

Amgen Inc.
Thousand Oaks, CA 91320

● Names and Affiliations of Principal Investigators

Not applicable.

2. LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
2L	Second line
2L+	Second line and beyond
ALK	Anaplastic lymphoma kinase
BMI	Body mass index
BRAF	B-Raf proto-oncogene, serine/threonine kinase
CI	Confidence interval
ECOG	Eastern Cooperative Oncology Group
EDM	Enhanced Datamart
EGFR	Epidermal growth factor receptor
EHR	Electronic health record
FDA	Food and Drug Administration
FH	Flatiron Health
HR	Hazard ratio
IPTW	Inverse probability of treatment weighting
KRAS *G12C*	Kirsten rat sarcoma protein with a G12C mutation at the protein level
LOT	Line of therapy
MAH	Marketing Authorization Holder
NDI	National Death Index
NICE	National Institute for Health and Care Excellence
NOS	Not otherwise specified
NSCLC	Non-small cell lung cancer
OS	Overall survival
PAS	Post-authorization study
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
PS	Propensity score
QBA	Quantitative bias analysis
SAP	Statistical analysis plan
SMD	Standardized mean difference
SSDI	Social Security Death Index
US	United States

3. INVESTIGATORS

Not applicable.

4. OTHER RESPONSIBLE PARTIES

Party	Roles and Responsibilities
Amgen Inc.	Sponsor; responsible for study design, data analysis, interpretation of results, report development, and funding.
Flatiron Health, Inc.	Source and curator of the de-identified EHR-derived FH EDM data used for the study.

5. MILESTONES

Milestone	Planned Date	Actual Date	Comments
Start of data collection	30 October 2023	30 December 2023	
End of data collection	30 May 2024	30 June 2024	Study data cut-off specified in the protocol and publication.
Final report on study results	December 2025	February 2026	final approval date.

6. RATIONALE AND BACKGROUND

Lung cancer remains a major cause of cancer morbidity and mortality. NSCLC comprises the majority of lung cancers, and KRAS is among the most frequently altered oncogenes in NSCLC. The KRAS G12C variant is the most common KRAS subtype and creates a therapeutically actionable target in a subset of patients with advanced disease (Biernacka et al, 2016; Judd et al, 2021).

For patients with advanced NSCLC whose disease progresses after platinum-based chemotherapy and/or immune checkpoint inhibition, subsequent-line treatment options historically included taxane-based chemotherapy such as docetaxel. Sotorasib is a first-in-class small molecule that specifically and irreversibly inhibits KRAS G12C. In the United States, sotorasib received accelerated approval for adults with KRAS G12C-mutated locally advanced or metastatic NSCLC who had received at least one prior systemic therapy (Skoulidis et al, 2021; Nakajima et al, 2022).

CodeBreaK 200 compared sotorasib with docetaxel in previously treated KRAS G12C-mutated advanced NSCLC. The trial demonstrated a progression-free survival benefit but did not detect a statistically significant difference in OS. Interpretation of OS was influenced by the trial design, including crossover and early treatment discontinuation, and clinical-trial populations may differ from patients treated in routine oncology practice (de Langen et al, 2023).

At the time of this study, no prior real-world study had directly compared sotorasib vs docetaxel in a real-world KRAS G12C-mutated population. Study 20230266 was therefore designed to estimate the comparative effectiveness of sotorasib monotherapy versus docetaxel monotherapy or combination therapy in 2L and 2L+ using the FH EDM.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 Primary

- To compare overall survival in KRAS p.G12C-mutated advanced NSCLC patients initiating treatment with sotorasib monotherapy versus docetaxel monotherapy or combination therapy in the 2L setting within the US FH EDM.

7.2 Secondary

- To compare overall survival in KRAS p.G12C-mutated advanced NSCLC patients initiating treatment with sotorasib monotherapy versus docetaxel monotherapy or combination therapy in the 2L+ setting within the US FH EDM.

8. AMENDMENTS AND UPDATES

No additional formal protocol amendment. Note: the use of propensity score overlap weighting in the final analysis was within the original protocol, which prespecified alternate weighting approaches to address non-overlap in the propensity score distribution.

9. RESEARCH METHODS

9.1 Study Design

This was a retrospective, active-comparator, new-user cohort study using the FH EDM. The study evaluated the comparative effectiveness of initiating sotorasib monotherapy versus docetaxel monotherapy or combination therapy on all-cause mortality. The primary analysis was restricted to 2L treatment initiation, and the secondary analysis included treatment initiation in 2L and beyond.

The analysis applied a staging and clean-room framework. Propensity score specifications and the selection of subgroup and sensitivity analyses were finalized and reviewed before outcome analyses were conducted, supporting transparent analytic decision-making and reducing the potential for outcome-informed model selection.

9.2 Setting

Patients were identified from the US-based de-identified FH EHR-derived database. The FH network included approximately 280 community cancer clinics and several academic centers, representing approximately 800 care sites. Data included longitudinal structured fields and unstructured information curated through technology-enabled abstraction.

Advanced NSCLC diagnoses were identified between 1 January 2011 and 30 September 2022. Sotorasib initiation was identified from 28 May 2021 through 30 September 2022, and docetaxel initiation was identified from 1 January 2019 through 30 September 2022. Outcome follow-up was available through 30 September 2023, providing at least a 12-month opportunity for follow-up for eligible patients.

9.3 Patients

Eligible patients had chart-confirmed advanced NSCLC, defined as locally advanced stage IIIB/IIIC or metastatic stage IV disease, or an earlier initial stage with subsequent recurrence or progression to advanced disease. Patients were required to be adults and to have a positive KRAS G12C molecular test result available on or before initiation of the treatment of interest.

- Sotorasib cohort: users of sotorasib monotherapy initiated in 2L or 2L+ between 28 May 2021 and 30 September 2022.
- Docetaxel cohort: users of docetaxel monotherapy or combination therapy initiated in 2L or 2L+ between 1 January 2019 and 30 September 2022.
- Patients were unexposed to the respective treatment of interest before 2L, and concurrent sotorasib and docetaxel use was excluded.
- Patients with a gap greater than 90 days from advanced NSCLC diagnosis to the start of structured EHR activity were excluded to reduce incomplete capture of the advanced-disease course.

9.4 Variables

9.4.1 Exposure Assessment

The exposures were initiation of sotorasib monotherapy and initiation of docetaxel monotherapy or combination therapy in 2L or 2L+. The index date was the start date of the relevant line of therapy. Treatment histories and oncology-defined, rule-based lines of therapy were derived from medication orders, administrations, and abstracted oral therapy information in the FH EDM.

9.4.2 Outcome Assessment

The outcome was overall survival, defined as time from treatment initiation to death from any cause. Death was identified using the FH composite mortality variable, which incorporates structured and unstructured EHR data, the Social Security Death Index, and a commercial mortality source. The composite endpoint has been validated against the National Death Index (Curtis et al, 2018; Zhang et al, 2021).

Patients without a recorded death were censored at the earliest applicable date of loss to follow-up, end of the study period, initiation of a clinical study drug, or the maximum allowable follow-up of 855 days. Sensitivity analyses varied the censoring rules.

9.4.3 Covariate Assessment

Baseline covariates were assessed on or before the index date. Propensity score models included age, sex, race, oncology practice type, stage at initial diagnosis, ECOG performance status at treatment initiation, BMI, most recent baseline PD-L1 expression, time since advanced NSCLC diagnosis, time since initiation of first systemic therapy, time since the preceding line of therapy, and number of prior lines for the 2L+ analysis. Smoking history, histology, prior anti-PD-(L)1 therapy, prior chemotherapy, prior targeted therapy, and geographic region were described and evaluated in subgroup or sensitivity analyses when sparse cells or extreme weights limited inclusion in the propensity score model.

9.4.4 Validity and Reliability

The FH EDM combines structured data with technology-enabled abstraction of unstructured clinical documentation. Structured data are aligned to standard ontologies, and unstructured data are abstracted by trained personnel following standardized processes. Each delivered dataset undergoes data quality checks and statistical review. The validated composite mortality variable was used to improve death ascertainment beyond information recorded within the oncology EHR alone.

9.5 Data Sources and Measurement

Flatiron Health curates de-identified longitudinal oncology data from participating in the US community and academic practices. Structured information includes demographics, laboratory results, medication orders, and treatment administration. Unstructured information includes biomarker reports, physician notes, oral therapy use, confirmed diagnosis dates, and other data requiring abstraction. FH algorithmically derives oncology lines of therapy from structured and unstructured treatment records.

The de-identified FH EDM files were delivered to Amgen and loaded into the appropriate internal analytic environment. Patient-level data remained subject to contractual and legal restrictions designed to prevent re-identification and protect confidentiality.

9.6 Bias

Confounding by indication was addressed through an active-comparator, new-user design and propensity score weighting. Nevertheless, residual confounding cannot be excluded because some prognostic factors were unavailable or incompletely measured, including brain and liver metastases, selected molecular co-alterations, baseline organ function, and socioeconomic characteristics. Quantitative bias analyses were conducted

to evaluate the strength of imbalance in unmeasured organ metastases that would be required to explain the observed treatment association.

The docetaxel cohort included historical initiators beginning in 2019 to increase sample size. Secular changes in treatment availability, supportive care, and diagnostic practice could therefore introduce calendar-time bias. The start of the docetaxel window was selected to reflect the contemporary immunotherapy era, and a sensitivity analysis aligned the docetaxel treatment period with the sotorasib period.

Information recorded in EHRs may be incomplete or misclassified. ECOG performance status and PD-L1 expression were not available for all patients, and care received outside the FH network might not be fully captured. Missing categorical covariates were retained as explicit missing categories, and no imputation was performed. Censoring at last confirmed activity may underestimate time at risk among patients who leave the FH network. Conversely, allowing follow-up after last EHR activity may reduce death ascertainment because the composite mortality endpoint is more sensitive when EHR information remains available. The supplement therefore identified potential differential mortality capture as a limitation of the reduced-censoring sensitivity analysis.

In addition, selection into the FH EDM and the predominance of community oncology practices may limit generalizability to all US patients, academic centers, or health systems outside the United States.

9.7 Study Size

Protocol feasibility counts anticipated 102 sotorasib and 59 docetaxel patients in the 2L analysis and 179 sotorasib and 131 docetaxel patients in the 2L+ analysis. After application of the final analysis criteria, 102 sotorasib and 58 docetaxel patients were included in 2L, and 164 sotorasib and 116 docetaxel patients were included in 2L+. The final sample sizes and event counts were sufficient to estimate the planned comparative OS measures, although precision was limited in selected subgroups.

9.8 Data Transformation

FH delivered the EDM as de-identified data files to a dedicated secure environment. Amgen loaded the files into its internal analytic environment. No external patient-level linkage was required for this analysis. Derived variables included treatment line, index date, time-to-event outcomes, baseline covariates, and propensity scores.

9.9 Statistical Methods

9.9.1 Main Summary Measures

Categorical variables were summarized using frequencies and percentages. Continuous variables were described using means, standard deviations, medians, and ranges as appropriate. Baseline characteristics were presented before and after propensity weighting, and covariate balance was assessed using standardized mean differences. Median OS and corresponding 95% confidence intervals were estimated using Kaplan–Meier methods.

9.9.2 Main Statistical Methods

Propensity scores estimating the probability of initiating treatments were estimated using logistic regression. The original protocol specified IPTW as the initial approach and allowed alternate weighting methods, including overlap weighting, if non-overlap or

extreme weights were observed. The final analysis used overlap weights. This method emphasizes patients with a greater probability of receiving either treatment and achieved excellent balance for covariates included in the propensity score model.

Weighted Cox proportional hazards models estimated the association between sotorasib versus docetaxel initiation and all-cause mortality in the 2L and 2L+ analysis sets. Results were reported as mortality HRs with 95% confidence intervals. The analysis followed an intent-to-treat-like treatment assignment in the main analysis, subject to the specified censoring rules.

9.9.3 Missing Values

The extent of missing data was summarized by treatment cohort. Missing levels were included for categorical variables to retain patients in the analysis. No imputation was performed.

9.9.4 Sensitivity Analyses

- Re-estimation of weighted treatment effects in clinically relevant subgroups: patients with prior anti-PD-(L)1 therapy, patients with a smoking history, patients with non-squamous histology, and patients without prior targeted therapy or clinical study treatment.
- Alternative right-censoring approaches: censoring only at clinical study drug initiation or study-period end; censoring at comparator initiation, clinical study drug initiation, study-period end, or loss to follow-up (effectiveness without treatment switching); and NICE-informed censoring of docetaxel users at sotorasib initiation.
- An outcome model additionally including geographic region and prior anti-PD-(L)1 treatment.
- Quantitative bias analysis assessing unmeasured confounding by brain or liver metastases across assumed confounder prevalences of 15% to 35% in the sotorasib cohort.

9.9.5 Amendments to the Statistical Analysis Plan

No formal SAP amendment was identified from the original protocol.

9.10 Quality Control

FH applies predefined quality standards and statistical review to each delivered dataset. Structured data are standardized, and unstructured abstractions are completed by trained abstractors whose performance is monitored over time. The protocol specified independent quality control by a second programmer. In addition, the staging and clean-room framework provided external review checkpoints for propensity score balance, subgroup definitions, sensitivity analyses, and model specifications before the outcome results were unmasked or finalized.

9.11 Changes in Study Conduct

No changes in study conduct were identified from the source documents used to prepare this draft. Confirmation against the final SAP, programming specifications, and study audit trail is required before finalization.

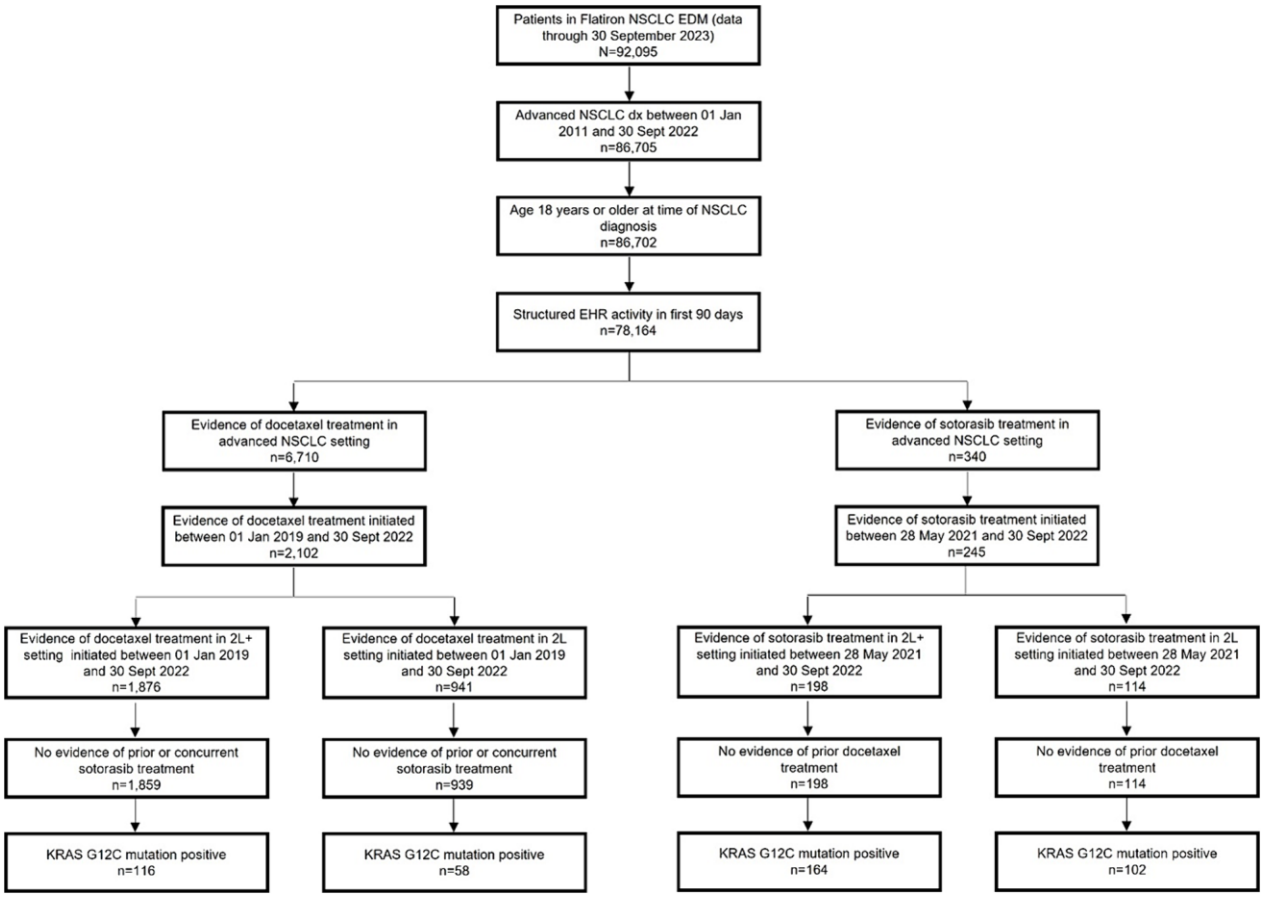
10. RESULTS

This report summarizes the results published for study 20230266, including patient disposition, baseline characteristics, treatment patterns, overall survival, subgroup analyses, sensitivity analyses, and quantitative bias analyses.

10.1 Participants

The FH NSCLC EDM included 92,095 patients through 30 September 2023. Among these, 86,705 had an advanced NSCLC diagnosis between 1 January 2011 and 30 September 2022, 86,702 were adults, and 78,164 had structured EHR activity within 90 days of advanced diagnosis. After treatment and eligibility criteria were applied, the final 2L analysis included 102 sotorasib and 58 docetaxel patients; the 2L+ analysis included 164 and 116 patients, respectively.

Figure 10-1. Patient Identification



2L, second line; 2L+, second line and beyond; EDM, Enhanced Datamart; EHR, electronic health record; NSCLC, non-small cell lung cancer. Figure reproduced from the published study results.

10.2 Descriptive Data

10.2.1 Baseline Demographics

Before propensity score weighting, patients in both treatment groups were predominantly aged 65 years or older, White, treated in community practices, and had a history of smoking. In the 2L analysis, mean age was 71 years in the sotorasib cohort and 67 years in the docetaxel cohort. In 2L+, mean age was 70 and 68 years,

respectively. Sex distributions were similar across treatment groups. Propensity score overlap weighting balanced the demographic variables included in the propensity score models.

10.2.2 Baseline Disease Characteristics

Most patients had advanced stage disease at initial diagnosis, non-squamous histology, ECOG performance status 0 or 1, and prior anti-PD-(L)1 and/or platinum-based chemotherapy. Approximately one fifth to one quarter of patients had no ECOG performance status available. PD-L1 expression was distributed across <1%, 1–49%, ≥50%, and no valid test categories. After propensity weighting, all variables included in the propensity score models had SMDs below 0.01; residual imbalances remained for selected characteristics not included in the models because of sparse cells or extreme weights.

Table 10-1. Baseline and Disease Characteristics in the 2L Setting

Characteristic	Unweighted			Weighted		
	Sotorasib	**Docetaxel**	**SMD**	**Sotorasib**	**Docetaxel**	**SMD**
	n = 102	**n = 58**		**n = 102**	**n = 58**	
Mean age, years (SD)	71 (8.67)	67 (7.74)	− 0.41	68 (8.45)	68 (7.80)	<0.01
Age in years, n (%)			**0.37**			**0.1**
< 65	23 (23%)	21 (36%)		31 (30%)	19 (32%)	
65–74	44 (43%)	25 (43%)		48 (47%)	24 (42%)	
75–84	35 (34%)	12 (21%)		23 (23%)	15 (26%)	
Sex, n (%)			**0.01**			**<0.01**
Female	56 (55%)	32 (55%)		59 (58%)	33 (58%)	
Male	46 (45%)	26 (45%)		43 (43%)	25 (43%)	
Race, n (%)			**0.28**			**<0.01**
White	75 (74%)	41 (71%)		73 (71%)	41 (71%)	
Black or African American	6 (6%)	8 (14%)		11 (11%)	6 (11%)	
Other race or not available	21 (21%)	9 (16%)		18 (18%)	11 (18%)	
Geographic region, n (%)			**0.20**			**0.23**
Midwest	21 (21%)	8 (14%)		20 (19%)	8 (14%)	
Northeast	15 (15%)	9 (16%)		18 (18%)	9 (15%)	
South	32 (31%)	22 (38%)		36 (35%)	21 (36%)	
West	10 (10%)	6 (10%)		7 (7%)	7 (12%)	
Unknown/Missing	24 (24%)	13 (22%)		21 (21%)	13 (23%)	

Characteristic	Unweighted			Weighted		
	Sotorasib	**Docetaxel**	**SMD**	**Sotorasib**	**Docetaxel**	**SMD**
	n = 102	**n = 58**		**n = 102**	**n = 58**	
Smoking history, n (%)			**0.18**			**0.29**
History of smoking	97 (95%)	57 (98%)		95 (93%)	57 (99%)	
No history of smoking	5 (5%)	1 (2%)		7 (7%)	1 (1%)	
Practice type, n (%)			**0.09**			**<0.01**
Academic	23 (23%)	11 (19%)		20 (19%)	11 (19%)	
Community only	79 (77%)	47 (81%)		82 (81%)	47 (81%)	
Stage at initial diagnosis, n (%)			**0.06**			**<0.01**
Advanced stage (or not reported)	80 (78%)	47 (81%)		83 (81%)	47 (81%)	
Early stage	22 (22%)	11 (19%)		19 (19%)	11 (19%)	
ECOG performance status at index, n (%)			**0.30**			**<0.01**
0	10 (10%)	11 (19%)		16 (16%)	9 (16%)	
1	50 (49%)	23 (40%)		44 (43%)	25 (43%)	
2	15 (15%)	9 (16%)		15 (15%)	9 (15%)	
≥ 3	5 (5%)	4 (7%)		6 (6%)	3 (6%)	
Not available	22 (22%)	11 (19%)		21 (21%)	12 (21%)	
Histology, n (%)			**0.30**			**0.29**
Non-squamous cell carcinoma	100 (98%)	53 (91%)		100 (98%)	54 (93%)	

Characteristic	Unweighted			Weighted		
	Sotorasib	**Docetaxel**	**SMD**	**Sotorasib**	**Docetaxel**	**SMD**
	n = 102	**n = 58**		**n = 102**	**n = 58**	
Squamous cell carcinoma	1 (1%)	3 (5%)		2 (1%)	3 (6%)	
NSCLC histology NOS	1 (1%)	2 (3%)		0 (0%)	1 (1%)	
Most recent PD-L1 expression at baseline (tumor cell staining), n (%)			**0.36**			**<0.01**
< 1%	23 (23%)	21 (36%)		33 (33%)	19 (33%)	
1–49%	27 (26%)	13 (22%)		27 (26%)	15 (26%)	
≥ 50%	27 (26%)	9 (16%)		18 (18%)	11 (18%)	
No valid test	25 (25%)	15 (26%)		24 (23%)	13 (23%)	
Presence of actionable gene alterations (e.g., ALK, EGFR, ROS1, and BRAF), n (%)	0	1 (2%)	0.19	0 (0%)	0 (0%)	0.21
Prior treatment, n (%)						
Anti-PD-(L)1	77 (75%)	56 (97%)	0.64	78 (77%)	57 (98%)	0.64
Chemo	75 (74%)	51 (88%)	0.37	84 (83%)	49 (85%)	0.08
Platinum-based chemo and anti-PD-(L)1 combo	54 (53%)	49 (84%)	0.72	63 (62%)	48 (83%)	0.48

SMD, standardized mean difference. SMDs <0.1 indicate good balance, 0.1–0.2 moderate balance, and >0.2 inadequate balance. Percentages are based on the respective unweighted or weighted cohort.

Table 10-2. Baseline and Disease Characteristics in the 2L+ Setting

Characteristic	Unweighted			Weighted		
	Sotorasib	**Docetaxel**	**SMD**	**Sotorasib**	**Docetaxel**	**SMD**
	n = 164	**n = 116**		**n = 164**	**n = 116**	
Mean age, years (SD)	70 (8.48)	68 (7.95)	− 0.14	69 (8.13)	69 (7.81)	<0.01
Age in years, n (%)			**0.20**			**0.24**
< 65	48 (29%)	37 (32%)		54 (33%)	35 (30%)	
65–74	67 (41%)	52 (45%)		67 (41%)	54 (46%)	
75–84	48 (29%)	25 (22%)		43 (26%)	25 (22%)	
≥ 85	1 (1%)	2 (2%)		0	2 (2%)	
Gender, n (%)			**0.06**			**<0.01**
Female	91 (55%)	61 (53%)		90 (55%)	64 (55%)	
Male	73 (45%)	55 (47%)		74 (45%)	52 (45%)	
Race, n (%)			**0.21**			**<0.01**
White	122 (74%)	81 (70%)		115 (70%)	81 (70%)	
Black or African American	11 (7%)	15 (13%)		18 (11%)	13 (11%)	
Other race or not available	31 (19%)	20 (17%)		31 (19%)	22 (19%)	
Geographic region, n (%)			**0.22**			**0.21**
Midwest	29 (18%)	13 (11%)		29 (18%)	14 (12%)	
Northeast	21 (13%)	20 (17%)		20 (13%)	20 (18%)	
South	53 (32%)	42 (36%)		60 (37%)	39 (34%)	
Unknown/Missing	42 (26%)	27 (23%)		36 (22%)	28 (24%)	
West	19 (12%)	14 (12%)		18 (11%)	14 (12%)	

Characteristic	Unweighted			Weighted		
	Sotorasib	**Docetaxel**	**SMD**	**Sotorasib**	**Docetaxel**	**SMD**
	n = 164	**n = 116**		**n = 164**	**n = 116**	
Smoking history, n (%)			**0.06**			**0.10**
History of smoking	158 (96%)	113 (97%)		157 (96%)	113 (98%)	
No history of smoking	6 (4%)	3 (3%)		7 (4%)	3 (3%)	
Practice type, n (%)			**0.10**			**<0.01**
Academic	41 (25%)	24 (21%)		35 (21%)	25 (21%)	
Community only	123 (75%)	92 (79%)		129 (79%)	91 (79%)	
Stage at initial diagnosis, n (%)			**0.08**			**<0.01**
Advanced stage (or not reported)	126 (77%)	93 (80%)		131 (80%)	93 (80%)	
Early stage	38 (23%)	23 (20%)		33 (20%)	23 (20%)	
ECOG performance status at index, n (%)			**0.22**			**<0.01**
0	17 (10%)	17 (15%)		22 (14%)	16 (14%)	
1	82 (50%)	47 (41%)		73 (44%)	51 (44%)	
2	25 (15%)	17 (15%)		25 (15%)	17 (15%)	
≥ 3	5 (3%)	5 (4%)		6 (4%)	5 (4%)	
Not available	35 (21%)	30 (26%)		38 (23%)	27 (23%)	
Histology, n (%)			**0.18**			**0.24**
Non-squamous cell carcinoma	158 (96%)	111 (96%)		157 (96%)	111 (96%)	

Characteristic	Unweighted			Weighted		
	Sotorasib	**Docetaxel**	**SMD**	**Sotorasib**	**Docetaxel**	**SMD**
	n = 164	**n = 116**		**n = 164**	**n = 116**	
Squamous cell carcinoma	1 (1%)	3 (3%)		2 (1%)	4 (4%)	
NSCLC histology NOS	5 (3%)	2 (2%)		5 (3%)	1 (1%)	
Most recent PD-L1 expression at baseline (tumor cell staining), n (%)			**0.14**			**<0.01**
< 1%	35 (21%)	31 (27%)		43 (26%)	30 (26%)	
1–49%	46 (28%)	29 (25%)		44 (27%)	31 (27%)	
≥ 50%	43 (26%)	27 (23%)		39 (24%)	28 (24%)	
No valid test	40 (24%)	29 (25%)		39 (24%)	27 (24%)	
Presence of actionable gene alterations (e.g., ALK, EGFR, ROS1, and BRAF), n (%)	2 (1%)	3 (3%)	0.10	3 (2%)	3 (3%)	0.05
Prior treatment, n (%)						
Anti-PD-(L)1	131 (80%)	110 (94%)	0.46	134 (81%)	112 (96%)	0.50
Chemo	132 (80%)	109 (94%)	0.41	139 (85%)	106 (92%)	0.23
Platinum-based chemo and anti-PD-(L)1 combo			**0.71**			**0.56**
Combined in same LOT	77 (47%)	67 (58%)		85 (52%)	72 (62%)	

Characteristic	Unweighted			Weighted		
	Sotorasib	**Docetaxel**	**SMD**	**Sotorasib**	**Docetaxel**	**SMD**
	n = 164	**n = 116**		**n = 164**	**n = 116**	
In separate LOTs with anti-PD-(L)1 first	5 (3%)	10 (9%)		5 (3%)	9 (8%)	
In separate LOTs with anti-PD-(L)1 Second	17 (10%)	25 (22%)		18 (11%)	22 (19%)	
Prior number of LOTs, n (%)			**0.25**			**<0.01**
1	102 (62%)	58 (50%)		94 (57%)	66 (57%)	
2	36 (22%)	35 (30%)		43 (26%)	31 (26%)	
≥ 3	26 (16%)	23 (20%)		27 (16%)	19 (16%)	

SMD, standardized mean difference. SMDs <0.1 indicate good balance, 0.1–0.2 moderate balance, and >0.2 inadequate balance. Percentages are based on the respective unweighted or weighted cohort.

10.2.3 Treatment Characteristics

Among patients initiating sotorasib in 2L, the most common frontline treatments were platinum-based chemotherapy combined with an anti-PD-(L)1 agent (53%), anti-PD-(L)1 monotherapy (20%), and platinum-based chemotherapy combination therapy (18%). Among 2L docetaxel initiators, the corresponding proportions were 85%, 12%, and 3%. Similar distributions were observed in the 2L+ analysis.

Docetaxel was administered as monotherapy in 19% of 2L patients and 23% of 2L+ patients. Most docetaxel patients received combination therapy, predominantly docetaxel plus ramucirumab. Subsequent treatment patterns were heterogeneous and included chemotherapy, sotorasib, docetaxel plus ramucirumab, other targeted therapies, immune checkpoint inhibitors, and clinical study drugs.

Treatment characteristic	2L	2L+
Docetaxel monotherapy	19%	23%
Docetaxel combination therapy	81%	77%
Docetaxel plus ramucirumab among all docetaxel initiators	69%	62%
Sotorasib patients receiving subsequent therapy	38 patients	67 patients
Docetaxel patients receiving subsequent therapy	18 patients	41 patients
Most common subsequent therapies	Chemotherapy; docetaxel + ramucirumab; targeted therapy	Chemotherapy; sotorasib; clinical study drug; other therapies

10.3 Outcome Data

In the 2L setting, 70 of 102 sotorasib patients and 45 of 58 docetaxel patients died during follow-up. Median follow-up was 10.2 months and 6.0 months, respectively. In the 2L+ setting, 109 of 164 sotorasib patients and 90 of 116 docetaxel patients died; median follow-up was 10.2 months and 7.1 months, respectively.

Analysis	Treatment	N	Deaths, n	Median follow-up, months
2L	Sotorasib	102	70	10.2
2L	Docetaxel	58	45	6.0
2L+	Sotorasib	164	109	10.2
2L+	Docetaxel	116	90	7.1

10.4 Main Results

10.4.1 Overall Survival

In the unweighted 2L analysis, median OS was 11.1 months (95% CI, 8.7–15.9) for sotorasib and 6.0 months (95% CI, 4.1–11.0) for docetaxel, with an unadjusted mortality

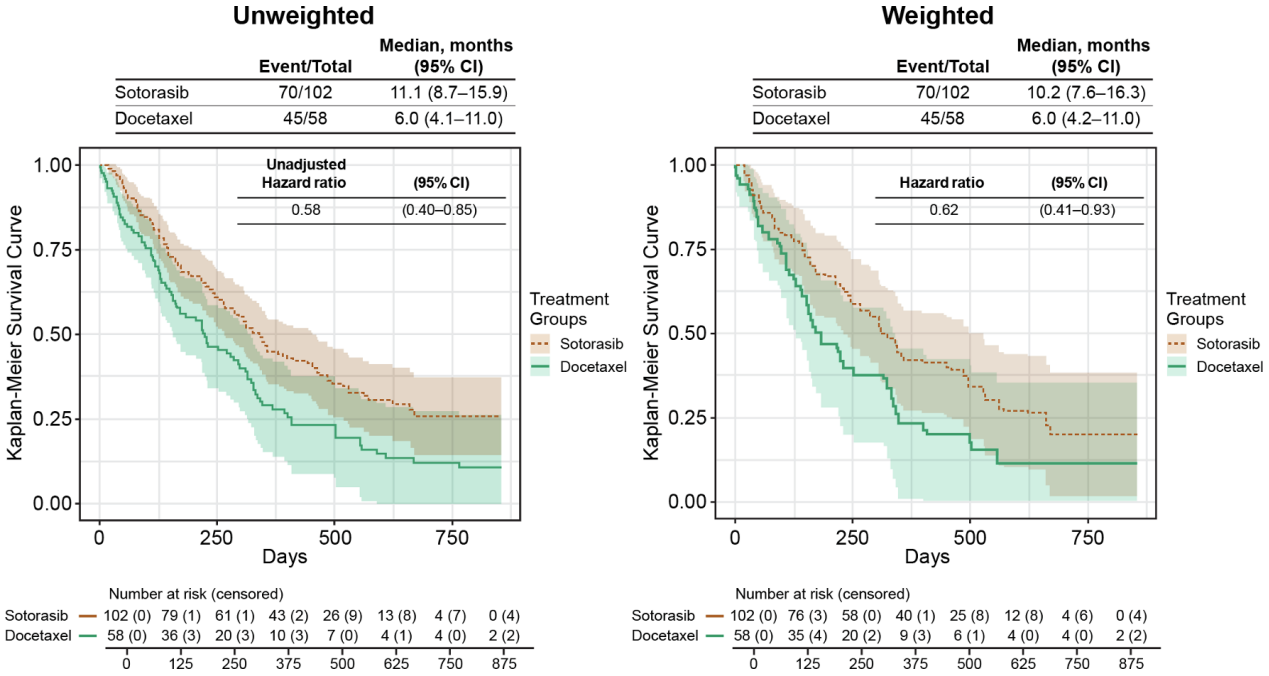
HR of 0.58 (95% CI, 0.40–0.85). After overlap weighting, median OS was 10.2 months (95% CI, 7.6–16.3) and 6.0 months (95% CI, 4.2–11.0), respectively; the weighted mortality HR was 0.62 (95% CI, 0.41–0.93).

In the unweighted 2L+ analysis, median OS was 11.1 months (95% CI, 8.7–14.8) for sotorasib and 7.4 months (95% CI, 5.3–10.6) for docetaxel, with an unadjusted mortality HR of 0.63 (95% CI, 0.48–0.84). After weighting, median OS was 10.2 months (95% CI, 8.0–14.6) and 7.2 months (95% CI, 5.1–10.6), respectively; the weighted mortality HR was 0.65 (95% CI, 0.49–0.87).

Analysis	Treatment	N	Deaths	Unweighted median OS (95% CI), months	Weighted median OS (95% CI), months	Mortality HR (95% CI)
2L	Sotorasib	102	70	11.1 (8.7–15.9)	10.2 (7.6–16.3)	0.62 (0.41–0.93)[1]
2L	Docetaxel	58	45	6.0 (4.1–11.0)	6.0 (4.2–11.0)	Reference
2L+	Sotorasib	164	109	11.1 (8.7–14.8)	10.2 (8.0–14.6)	0.65 (0.49–0.87)[1]
2L+	Docetaxel	116	90	7.4 (5.3–10.6)	7.2 (5.1–10.6)	Reference

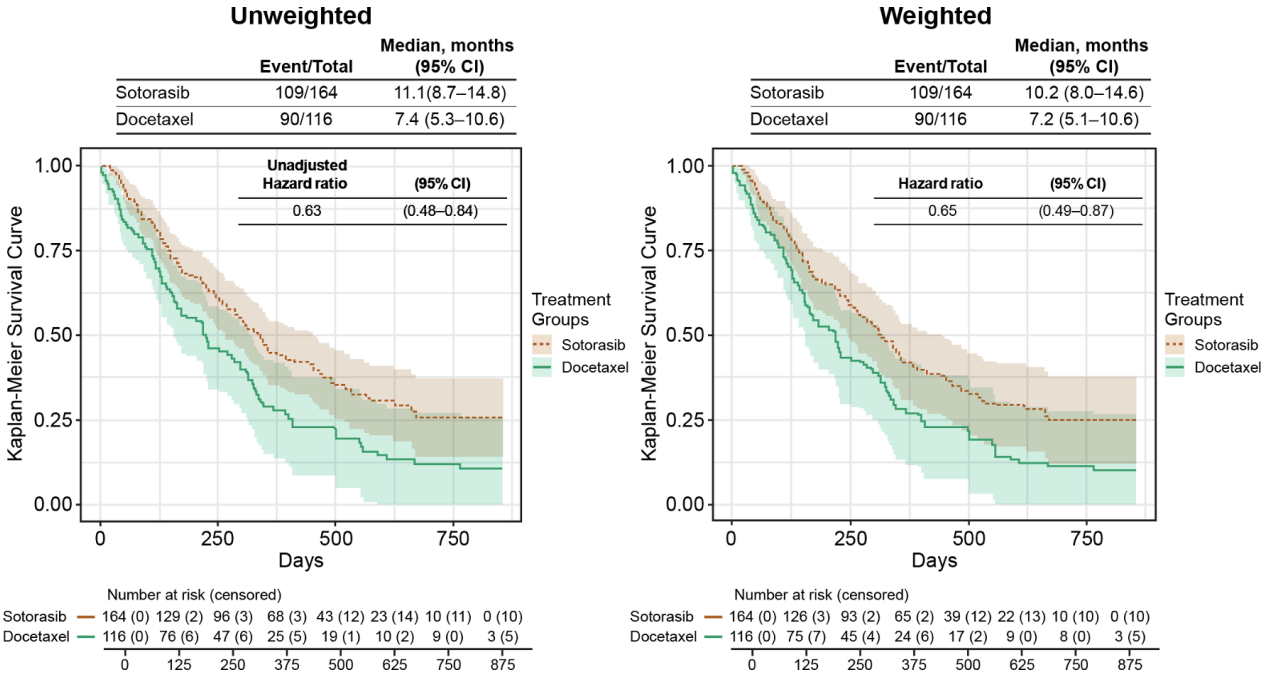
[1] Weighted Cox proportional hazards model comparing sotorasib with docetaxel. CI, confidence interval; HR, hazard ratio; OS, overall survival.

Figure 10-2. Overall Survival in the 2L Setting, Unweighted and Weighted Analyses



CI, confidence interval; OS, overall survival. Figure reproduced from the published study results.

Figure 10-3. Overall Survival in the 2L+ Setting, Unweighted and Weighted Analyses



2L+, second line and beyond; CI, confidence interval; OS, overall survival. Figure reproduced from the published study results.

10.5 Other Analyses

All four reported subgroup analyses favored sotorasib. In the 2L setting, mortality HRs ranged from 0.61 to 0.65, and in the 2L+ setting they ranged from 0.61 to 0.66. The 95% CIs excluded 1.00 for each subgroup. Detailed median OS and mortality HR estimates are shown in Table 10-3.

Table 10-3. Subgroup Analyses of Overall Survival

Subgroup	2L: mOS (95% CI), months; HR (95% CI), N	2L+: mOS (95% CI), months; HR (95% CI), N
Prior anti-PD-(L)1 treatment	10.67 (7.37–18.37) HR 0.61 (0.39–0.94); N=133	10.38 (7.93–16.03) HR 0.65 (0.48–0.89); N=241
History of smoking	10.14 (7.57–17.35) HR 0.65 (0.43–0.98); N=154	10.47 (8.22–14.84) HR 0.66 (0.48–0.89); N=271
Non-squamous cell carcinoma	10.14 (7.36–16.32) HR 0.64 (0.42–0.98); N=154	10.66 (8.24–14.85) HR 0.65 (0.48–0.88); N=269
No prior targeted therapy or clinical study treatment	10.13 (7.37–17.42) HR 0.61 (0.41–0.93); N=149	10.14 (7.89–17.06) HR 0.61 (0.44–0.85); N=216

2L, second line; 2L+, second line and beyond; CI, confidence interval; HR, hazard ratio; mOS, median overall survival; N, total subgroup sample size; S/D, sotorasib/docetaxel. mOS values are presented as sotorasib/docetaxel.

Sensitivity analyses that added census region and prior anti-PD-(L)1 treatment to the outcome model, censored at treatment switching, or applied NICE-informed switching rules produced estimates consistent with the main analysis. The analysis that censored only at clinical study drug initiation or study-period end was attenuated (HR, 0.80 in both settings) and had 95% CIs that included 1.00 (Table 10-4).

Table 10-4. Sensitivity Analyses of Overall Survival

Sensitivity analysis	2L: mOS (95% CI), months; HR (95% CI), N	2L+: mOS (95% CI), months; HR (95% CI), N
Census region and prior anti-PD-(L)1 treatment added to the outcome model	10.18 (7.57–16.32) HR 0.62 (0.41–0.93); N=160	10.20 (8.03–14.57) HR 0.65 (0.49–0.87); N=280
Censor only at clinical study drug initiation or study-period end [a]	10.47 (7.89–17.37) HR 0.80 (0.53–1.21); N=160	10.65 (8.07–15.14) HR 0.80 (0.59–1.07); N=280
Effectiveness without treatment switching: censor at comparator initiation, clinical study drug initiation, study end, or loss to follow-up	11.16 (7.58–18.77) HR 0.56 (0.36–0.86); N=160	11.16 (8.54–16.31) HR 0.60 (0.44–0.82); N=280
NICE-informed treatment-switching censoring: censor docetaxel users at sotorasib initiation, clinical study drug initiation, study end, or loss to follow-up	10.19 (7.57–16.32) HR 0.60 (0.39–0.91); N=160	10.20 (8.03–14.57) HR 0.64 (0.47–0.85); N=280

2L, second line; 2L+, second line and beyond; CI, confidence interval; EHR, electronic health record; HR, hazard ratio; mOS, median overall survival; N, total analysis sample size; NICE, National Institute for Health and Care Excellence; S/D, sotorasib/docetaxel. mOS values are presented as S/D. [a] The supplement notes possible bias toward the null because docetaxel patients had more post-EHR follow-up when mortality capture was less complete (mean [SD], 121.5 [233.7] versus 59.0 [117.5] days).

Across assumed confounder prevalences of 15% to 35% in the sotorasib cohort, supplemental quantitative bias analysis G-values ranged from 3.96 to 6.45 in 2L and from 3.75 to 6.05 in 2L+ (Table 10-5). At 25% prevalence, joint associations with treatment and mortality of 4.72 in 2L and 4.46 in 2L+ would be required to move the observed association to the null.

Table 10-5. Quantitative Bias Analysis (G-values)

Assumed confounder prevalence in the sotorasib cohort	2L G-value (input HR=0.62)	2L+ G-value (input HR=0.64)
15%	6.45	6.05
20%	5.38	5.07
25%	4.72	4.46
30%	4.28	4.05
35%	3.96	3.75

G-value = minimum association strength with both treatment and mortality required to move the HR to 1.00. The supplement used HR 0.62 for 2L and HR 0.64 for 2L+.

10.6 Adverse Events/Adverse Reactions

Safety data were not collected or analyzed in this study.

11. DISCUSSION

11.1 Key Results

Study 20230266 directly compared sotorasib monotherapy with docetaxel monotherapy or combination therapy among patients with previously treated KRAS G12C-mutated advanced NSCLC in US routine clinical practice. After overlap weighting, measured baseline characteristics included in the propensity score models were well balanced. Sotorasib initiation was associated with longer median OS and a lower estimated hazard of all-cause mortality in both the 2L and 2L+ analyses.

All reported subgroup estimates favored sotorasib, with mortality HRs of 0.61 to 0.65 in 2L and 0.61 to 0.66 in 2L+; all subgroup 95% CIs excluded 1.00. Sensitivity analyses that added census region and prior anti-PD-(L)1 treatment or censored at treatment switching yielded HRs of 0.56 to 0.62 in 2L and 0.60 to 0.65 in 2L+. The sensitivity analysis that censored only at clinical study drug initiation or study-period end was attenuated to 0.80 in both settings, with 95% CIs including 1.00.

The magnitude and direction of the association were stable across the primary, secondary, subgroup, censoring sensitivity, model sensitivity, and quantitative bias analyses reported in the study. The findings were particularly consistent among patients with prior anti-PD-(L)1 treatment, who represent a clinically relevant contemporary population.

The use of an active comparator, the prespecified propensity score methodology, the staging and clean-room framework, and the sensitivity analyses addressing treatment switching and censoring supported the internal credibility of the analysis.

11.2 Limitations

As with all nonrandomized comparative analyses, residual confounding cannot be excluded. Information on brain and liver metastases, molecular co-alterations, baseline organ function, socioeconomic factors, and other determinants of treatment selection and prognosis was unavailable or incomplete. In the supplemental QBA, G-values ranged from 3.75 to 6.45 across assumed confounder prevalences of 15% to 35%, indicating that a substantial joint association with treatment and mortality would be required to move the observed association to the null. The QBA does not eliminate the possibility of confounding by other unmeasured factors.

The FH EDM is based on routine EHR data and may contain missing, incomplete, or misclassified information. ECOG performance status and PD-L1 expression were unavailable for some patients. Treatment and care occurring outside the FH network might not be fully observed, and treatment dose and intensity were not evaluated. Although the composite mortality endpoint improves death ascertainment, loss to follow-up and alternative censoring assumptions could affect estimates of time at risk. In the reduced-censoring sensitivity analysis, the historical docetaxel cohort had more time after last EHR activity than the sotorasib cohort, when mortality capture may have been less complete; this may have biased that sensitivity estimate toward the null.

The use of a historical docetaxel cohort introduced the potential for secular trend bias. Restricting the comparator period to the contemporary immunotherapy era and conducting a calendar-time sensitivity analysis reduced but did not fully remove this concern. The final sample sizes were modest, limiting the precision and feasibility of some subgroup analyses.

11.3 Interpretation

The weighted median OS of 10.2 months observed with sotorasib in both 2L and 2L+ was broadly consistent with survival estimates from a prior sotorasib real-world study, (Thummalapalli et al, 2023)

CodeBreaK 200 reported similar median OS for sotorasib. Differences between trial and real-world outcomes may reflect trial eligibility, performance status, treatment selection, protocol-directed monitoring, adherence, crossover, supportive care, and other differences between controlled trials and routine clinical practice. These factors support complementary interpretation of randomized and real-world evidence rather than direct substitution of one evidence source for the other.

Within the limitations of the observational design, the study adds evidence that the effectiveness of sotorasib versus docetaxel in routine care which may differ from the OS comparison observed in CodeBreaK 200. All point estimates across the reported subgroup and sensitivity analyses favored sotorasib, although the reduced-censoring analysis was attenuated and imprecise. The consistency of most analyses and the QBA support the robustness of the association but do not prove a causal treatment effect.

11.4 Generalizability

The findings are most applicable to adults with previously treated KRAS G12C-mutated advanced NSCLC receiving care in US oncology practices represented in the FH network during the contemporary immunotherapy era. Because the database is weighted toward community practices, generalizability to academic referral centers may be limited. Results may also not extend to treatment settings with different access or sequencing patterns, or to patients who would not meet the study eligibility criteria.

12. OTHER INFORMATION

The primary results were published as: Johnson M, Younan D, Kent ST, Mesa-Frias M, Brookhart MA, Balasubramanian A, Spira A. Real-world comparative effectiveness of sotorasib versus docetaxel in second line and beyond among patients with advanced non-small cell lung cancer (NSCLC). Lung Cancer. 2024;197:107960. doi:10.1016/j.lungcan.2024.107960.

This work was supported by Amgen Inc. The data originated from and is the property of Flatiron Health, Inc.; the source dataset is not publicly available. Requests for data access for replication are subject to Flatiron Health restrictions and review.

The original protocol, final publication, publication supplement, final SAP, programming specifications, and analytic decision log should be maintained as separate supporting study records.

13. CONCLUSION

- In this retrospective real-world comparative effectiveness study, patients with previously treated KRAS G12C-mutated advanced NSCLC who initiated sotorasib monotherapy had longer weighted median OS than patients who initiated docetaxel monotherapy or combination therapy in both the 2L and 2L+ settings.
- After propensity score weighting, the mortality HR was 0.62 (95% CI, 0.41–0.93) in 2L and 0.65 (95% CI, 0.49–0.87) in 2L+.
- All reported subgroup HRs favored sotorasib, and most sensitivity analyses were consistent with the main analysis. The QBA G-values of 3.75 to 6.45 indicated that a substantial unmeasured confounder would be required to move the observed association to the null.
- The results should be interpreted considering the nonrandomized design, residual confounding, missing EHR information, historical comparator period, modest sample size, and limits to generalizability.

14. REFERENCES

1. Biernacka A, Tsongalis PD, Peterson JD, et al. The potential utility of re-mining results of somatic mutation testing: KRAS status in lung adenocarcinoma. Cancer Genet. 2016;209(5):195–198.
2. Judd J, Abdel Karim N, Khan H, et al. Characterization of KRAS mutation subtypes in non-small cell lung cancer. Mol Cancer Ther. 2021;20(12):2577–2584.
3. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl 4):iv1–iv21.
4. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for lung cancers with KRAS p.G12C mutation. N Engl J Med. 2021;384:2371–2381.
5. Nakajima EC, Drezner N, Li X, et al. FDA approval summary: sotorasib for KRAS G12C-mutated metastatic NSCLC. Clin Cancer Res. 2022;28:1482–1486.
6. de Langen AJ, Johnson ML, Mazieres J, et al. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRAS G12C mutation: a randomized, open-label, phase 3 trial. Lancet. 2023;401:733–746.
7. Thummalapalli R, Bernstein E, Herzberg B, et al. Clinical and genomic features of response and toxicity to sotorasib in a real-world cohort of patients with advanced KRAS G12C-mutant non-small cell lung cancer. JCO Precis Oncol. 2023;7:e2300030.
8. Divan HA, Bittoni MA, Krishna A, Carbone DP. Real-world treatment patterns and outcomes of patients with metastatic nonsquamous non-small cell lung cancer after progression on standard-of-care therapy in the United States. Lung Cancer. 2023;179:107177.
9. Gray JE, Hsu H, Younan D, et al. Real-world outcomes in patients with KRAS G12C-mutated advanced non-small cell lung cancer treated with docetaxel in second-line or beyond. Lung Cancer. 2023;181:107260.
10. Curtis MD, Griffith SD, Tucker M, et al. Development and validation of a high-quality composite real-world mortality endpoint. Health Serv Res. 2018;53(6):4460–4476.
11. Zhang Q, Gossai A, Monroe S, et al. Validation analysis of a composite real-world mortality endpoint for patients with cancer in the United States. Health Serv Res. 2021;56:1281–1287.
12. Li F, Thomas LE, Li F. Addressing extreme propensity scores via the overlap weights. Am J Epidemiol. 2019;188:250–257.
13. Muntner P, Hernandez RK, Kent ST, et al. Staging and clean room: constructs designed to facilitate transparency and reduce bias in comparative analyses of real-world data. Pharmacoepidemiol Drug Saf. 2024;33:e5770.
14. Passiglia F, Reale ML, Lo Russo G, et al. Sotorasib in KRAS p.G12C-mutated advanced NSCLC: real-world data from the Italian expanded access program. Lung Cancer. 2024;187.
15. Stratmann JA, Althoff FC, Doebel P, et al. Sotorasib in KRAS G12C-mutated non-small cell lung cancer: a multicenter real-world experience from the compassionate use program in Germany. Eur J Cancer. 2024;201:113911.
16. Julve M, Kennedy O, Lindsay C, et al. United Kingdom real-world experience of sotorasib in KRAS G12C-mutant non-small cell lung cancer: a British Thoracic Oncology Group review. Ann Oncol. 2022;33:S1061–S1062.
17. Hochmair MJ, Vermaelen K, Mountzios G, et al. Sotorasib 960 mg versus 240 mg in pretreated KRAS G12C advanced NSCLC. Ann Oncol. 2024;35:142–144.

18. Franklin JM, Patorno E, Desai RJ, et al. Emulating randomized clinical trials with nonrandomized real-world evidence studies. Circulation. 2021;143:1002–1013.
19. Thompson D. Replication of randomized, controlled trials using real-world data: what could go wrong? Value Health. 2021;24:112–115.
20. Johnson M, Younan D, Kent ST, Mesa-Frias M, Brookhart MA, Balasubramanian A, Spira A. Real-world comparative effectiveness of sotorasib versus docetaxel in second line and beyond among patients with advanced non-small cell lung cancer. Lung Cancer. 2024;197:107960. doi:10.1016/j.lungcan.2024.107960.

15. SUMMARY TABLES, FIGURES, AND LISTINGS

The following tables and figures are included in this report:

- Table 10-1. Baseline and Disease Characteristics in the 2L Setting
- Table 10-2. Baseline and Disease Characteristics in the 2L+ Setting
- Treatment Characteristics Summary Table
- Outcome Data Summary Table
- Overall Survival Summary Table
- Table 10-3. Subgroup Analyses of Overall Survival
- Table 10-4. Sensitivity Analyses of Overall Survival
- Table 10-5. Quantitative Bias Analysis
- Figure 10-1. Patient Identification
- Figure 10-2. Overall Survival in the 2L Setting, Unweighted and Weighted Analyses
- Figure 10-3. Overall Survival in the 2L+ Setting, Unweighted and Weighted Analyses

No separate patient-level listings are included in this report. The publication supplement is maintained separately with the study records; its subgroup, sensitivity, and quantitative bias results are summarized in Tables 10-3 through 10-5.

16. ANNEXES

Annex	Document	Status in Current Draft
1	Original Study Protocol 20230266, Version 1.0, dated 26 January 2024	Provided separately; not embedded
2	Final Statistical Analysis Plan	Not provided; TBD
3	Published Results: Johnson et al., Lung Cancer 2024;197:107960	Provided separately; figures reproduced in report
4	Publication Supplement (Supplemental Tables 1 and 2)	Provided separately; detailed results incorporated in Section 10.5
5	Programming Specifications and Analytic Decision Log	Not provided; TBD