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Research Article

Multicenter Real-World Experience from the Turkish Oncology Group: Sotorasib in KRAS G12C-Mutated NSCLC

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Abstract

Objectives: Non-small cell lung cancer (NSCLC) is a common and aggressive type of lung cancer, with KRAS p.G12C mutations found in approximately 13% of cases. Sotorasib, a KRAS G12C inhibitor, has shown promise in clinical trials, but real-world data is limited. This study aims to evaluate the real-world efficacy and safety of sotorasib in Turkish patients with KRAS p.G12C-mutated NSCLC.

Methods: A multicenter retrospective cohort study was conducted across 15 centers in Turkey, including 41 patients treated with sotorasib between August 2020 and May 2023. Data were collected from electronic hospital databases and included patient demographics, treatment details, and outcomes. The primary endpoints were overall survival (OS), progression-free survival (PFS), and treatment response. Secondary endpoints included treatment-related adverse effects (TRAEs).

Results: Among the 41 patients, the median age was 64.5 years, with 78% being male and 93% having adenocarcinoma. Sotorasib was used as first-line treatment in 39% of patients. The overall response rate (ORR) was 34.2%, with a median PFS of 8.3 months and a median OS of 15.8 months. TRAEs were reported in 48.7% of patients, with grade 3-4 events in 12.2%, primarily diarrhea and liver enzyme elevations. No treatment-related deaths occurred.

Conclusion: This real-world study confirms the efficacy and safety of sotorasib in treating KRAS p.G12C-mutated NSCLC, with outcomes consistent with clinical trial data. Sotorasib provides a valuable treatment option for this patient population, although further research is needed to optimize patient selection and management strategies.

Keywords: Non-small cell lung cancer (NSCLC), KRAS p.G12C mutation ,Sotorasib, Real-world study, Treatment efficacy, Safety profile

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The most common subtype of lung cancer is adenocarcinoma, and the course of the disease varies greatly depending on the molecular subtype and available treatment options.[1, 2] In particular, targeted therapies developed in recent years have provided more effective and safer treatment alternatives to chemotherapy.[3] The Kirsten rat sarcoma viral oncogene homolog (KRAS) gene is the most common driver mutation, occurring in 25% of lung adenocarcinomas, while the KRAS p.G12C mutation is found in 13% of non-small cell lung cancers (NSCLCs).[4] Sotorasib specifically targets the KRASG12C protein and is the first of its kind to irreversibly inhibit downstream oncogenic signaling pathways.[5]

Results from the Phase I-II CodeBreak 100 study of sotorasib demonstrated efficacy with a disease control rate (DCR) of 84%, a median progression-free survival (PFS) of 6.7 months, and a favorable safety profile in patients with KRASG12C-mutated advanced NSCLC in the second or further lines of treatment.[6] Subsequently, the Phase III CodeBreak-200 randomized trial demonstrated a lower incidence of toxicity and improved quality of life in favor of sotorasib compared to docetaxel in patients with KRASG12C-mutant NSCLC who had failed prior immunotherapy and/or chemotherapy-based regimens.[7]

Despite the positive evidence from clinical studies, there is currently little real-world data to inform the clinical efficacy and tolerability of sotorasib. Our study aimed to evaluate the efficacy and toxicity of sotorasib treatment in NSCLC patients receiving sotorasib through the early access program (EAP).

Methods

Study Design

We conducted a multicenter, retrospective cohort study to evaluate the outcomes of sotorasib in KRAS p.G12C-mutated NSCLC patients treated between August 2020 and May 2023 across 15 centers in Turkey. Data were collected from electronic hospital registration databases and encrypted after de-identification in a shared database.

Study Population and Treatment

Patients aged 18 years and older with histologically or cytologically confirmed advanced NSCLC, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤2 and KRASp.G12C mutated disease were eligible.

All patients receiving sotorasib monotherapy as part of EAP, regardless of prior treatment, were included. Sotorasib treatment was initiated at 960mg/day and continued at this standard dose until adverse effects (AEs) requiring dose modification.

Multicenter study approval was obtained from Gazi University Ethics Committee (No:321955) and permission was obtained from Turkish Pharmaceuticals and Medical Devices Agency (No: E-24931227-514.07-1050493) for our study evaluating early access data from Turkey. The study was conducted in accordance with the Declaration of Helsinki.

Efficacy and Safety Assessments

Primary endpoint of this study was overall survival (OS), progression-free survival (PFS) and response to sotorasib (complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD and objective response rate (ORR)). Progression-free survival (PFS) is the duration between the commencement of sotorasib treatment and the occurrence of disease progression or the final follow-up. Overall survival is assessed from the initiation of sotorasib treatment to the date of death or the last follow-up. Treatment responses were evaluated according to RECIST version 1.1 in radiological imaging.[8]

The secondary outcome of the study was treatment related adverse effects (TRAEs) with sotorasib treatment according to the Common Terminology Criteria (CTCAE version 5.0).

Computed tomography (CT) scans of the thorax and abdomen were performed every 6-12 weeks at each institution to assess tumour response and progression.

Treatment efficacy under sotorasib treatment; any differences in sotorasib efficacy and/or safety outcomes in specific subgroups of patients selected according to the following characteristics: ECOG PS, age, tumor type, treatment line, prior immunotherapies Programmed death-ligand 1 (PD-L1) tumor ratio score, best response to sotorasib treatment.

Statistical Analysis

Categorical variables, including clinical and demographic characteristics of the patients, were summarized using frequencies and percentages. Continuous variables were described using either the mean±standard deviation (SD) or the median and interquartile range, as appropriate. The chi-square test, or Fisher's exact test for smaller sample sizes, was used to compare categorical variables. For continuous variables, comparisons were made using either the Student's t-test or the Wilcoxon rank-sum test, depending on the data distribution.

The Log-rank test was utilized for comparing survival curves across different patient subgroups. Multivariate analysis included variables that reached a significance level of P<.10 in the univariate analysis. The significance threshold for all tests was set at a p-value of less than 0.05. The Cox proportional hazards model was utilized to evalu-

ate the association between groups with results reported as hazard ratios (HR) and 95% confidence intervals (CI). All statistical analyses were performed using SPSS version 27, and graphical representations were created using the MedCalc software.

Results

Patient Characteristics

This study included 41 patients in total from 15 qualifying centres. The median age was 64.5 years (43-83). Seventy-eight percent of the patients were male, and 93% had the adenocarcinoma subtype.

While 39% of the patients received sotorasib as first-line treatment, 36% had previously received one-line of treatment, and the remaining 25% had received at least two lines of treatment. 49% of the patients had brain metastases, 10% were treated with surgery, and 90% were treated with radiotherapy. Twenty percent of the patients had received immunotherapy in previous lines. The Serine Threonine Kinase 11 (STK11) mutation was not evaluated in the majority of patients (63%) but was detected in 2 of the evaluated patients (5%). Clinical characteristics of the patients are summarized in Table 1.

Table 1. Baseline Patients' Characteristics

Characteristic	Total (n=41)
Sex — no. (%)	
Male	32 (78)
Female	9 (22)
Age — median year (range)	64.5 (43-83)
Histological Subtypes— no. (%)	
Adenocarcinoma	38 (93)
Squamous Cell Carcinoma	1 (2)
NOS	2 (5)
ECOG PS — no. (%)	
0	22 (54)
1	11 (27)
2	8 (19)
PD-L1 expression levels — no. (%)	
>50 %	2 (5)
1–49 %	9 (22)
<1 %	27 (66)
Not available	3 (7)
Previous Treatment lines for metastatic disease— no. (%)	
0	19 (39)
1	15 (36)
2	8 (20)
3	2 (5)
Previous Immunotherapy for metastatic disease— no. (%)	
Yes	8 (20)
No	33 (80)
M stage at initial diagnosis — no. (%)	
De novo metastatic	32 (78)
Recurrent metastatic	9 (22)
Metastatic disease at start of sotorasib— no. (%)	
Brain	20 (49)
Liver	7 (17)
Bone	19 (46)
Adrenal glands	10 (24)
STK11 mutations, — no. (%))	
Yes	2 (5)
No	13 (32)
Unknown	26 (63)

NOS (not otherwise specified); Eastern Cooperative Oncology Group Performance Status (ECOG PS); Programmed death-ligand 1 (PD-L1); Metastases stage (M stage).

Efficacy Outcomes

Among the 41 patients included in the study, 1 (2.4%) had CR, 13 (31.8%) had PR, 17 (41.4%) had SD and 10 (24.4%) had PD as the best response to sotorasib.

In the study, disease progression occurred in 28 patients and 21 patients died away within the median follow-up duration of 17.2 months. Median progression-free survival (mPFS) was 8.3 months (95% CI 3.4-13.1) (Fig. 1). In the analysis of 16 patients who received sotorasib as first-line treatment, the mPFS was 4.3 months (95% CI 1.3-12.4), the mPFS was 11.6 months (95% CI 8.1-15.2) in patients who received sotorasib as second-line treatment, and the mPFS was 4.9 months (95% CI 0.7-9.2) in patients who received sotorasib after 2 or more lines of treatment (Fig. 2). After the progression of the disease with sotorasib, 37% of patients were administered chemotherapy, 7% chemoimmunotherapy, 10% immunotherapy, and 22% best supportive care as the subsequent treatment.

When the effect of cranial metastasis status on treatment response was evaluated, there was no difference in mPFS between 20 previously treated patients with cranial metastasis and 21 patients without a history of cranial metastasis. (p=0.404) The mPFS was 8.9 months (95% CI 0.9-16.9) in the group with cranial metastasis and 7.2 months (95% CI 1.0-13.4) in the group without cranial metastasis.

There was no statistically significant difference in mPFS between patients who received immunotherapy in previous treatment lines and those who did not (p=0.390). In eight patients who received sotorasib after immunotherapy, mPFS was 3.8 months (95% confidence interval [CI] 0.2-12.2), while in 33 patients who did not, it was 8.3 months (95% CI, 2.6-14).

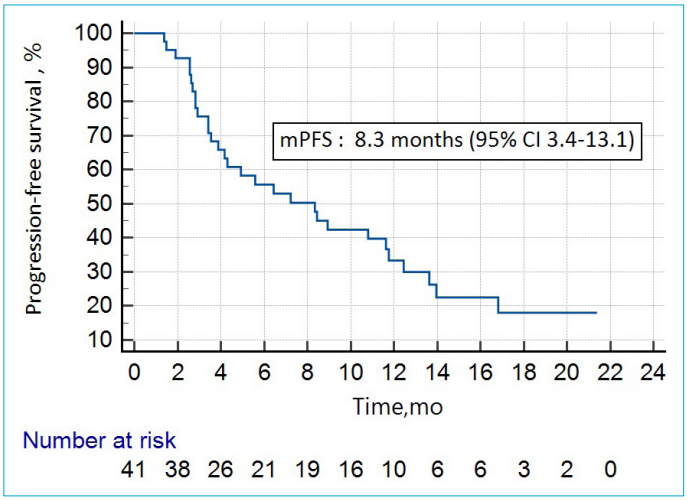

Figure 1. Kaplan Meier curves for Progression-free survival.

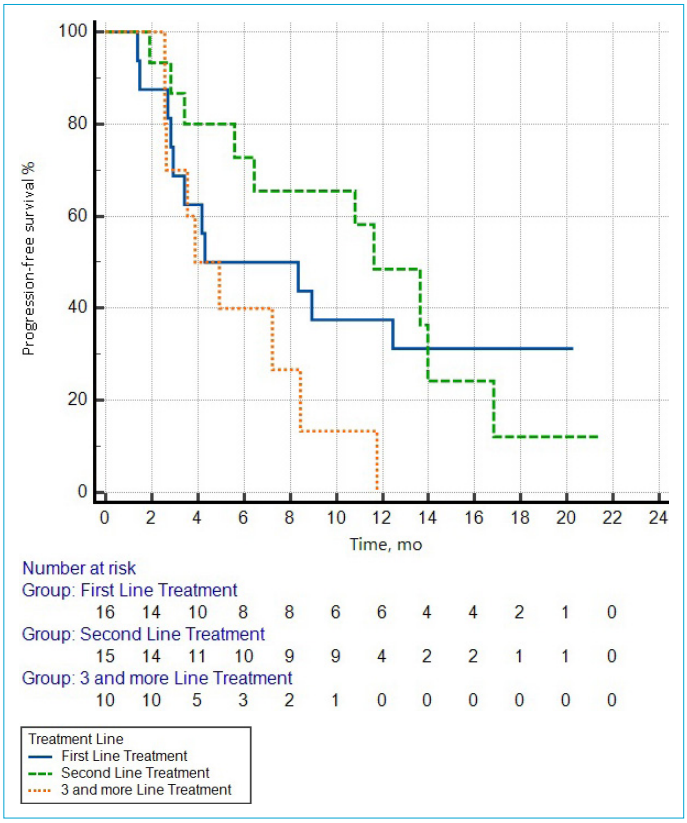

Figure 2. Kaplan Meier curves for Progression-free survival by treatment line.

Median overall survival (mOS) was 15.8 months (95% CI 14.2-17.4) in the whole population (Fig. 3). In the analysis of 16 patients who received sotorasib as first-line treatment, the mOS was 18.8 months. The mOS was 15.1 months (95% CI 11.7-18.6) in patients who received sotorasib as second-line treatment, and the mOS was 8.4 months (95% CI 1.4-15.4) in patients who received sotorasib after 2 or more lines of treatment (Fig. 4). When the effect of cranial metastasis status on

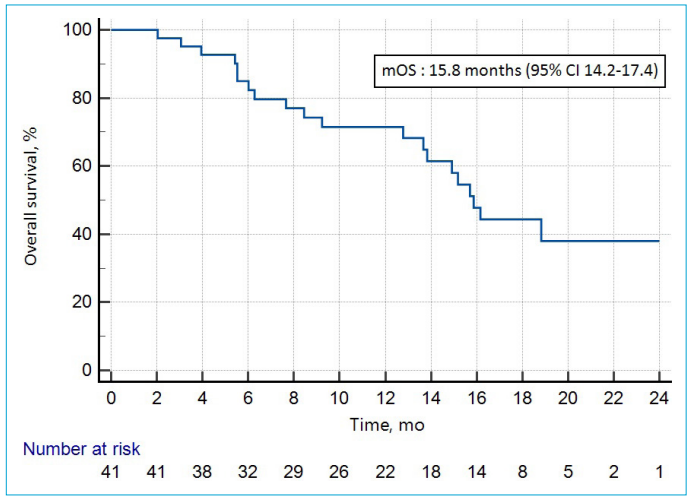

Figure 3. Kaplan Meier curves for Overall Survival.

mOS was evaluated, there was no difference in mOS between 20 previously treated patients with cranial metastasis and 21 patients without a history of cranial metastasis. (p=0.172).

As anticipated, patients with ECOG PS 2 had a significantly lower mOS compared to patients with ECOG PS 0/1. The mOS was 18.8 months (95% CI 15.6-22.0) in ECOG PS 0/1, and 5.2 months (95% CI 3.3-7.6) in ECOG PS 2 (p=0.002). (Fig. 5) Regarding survival, there was not a significant distinction between the ECOG PS 0 and ECOG PS 1 groups. (p=0.792).

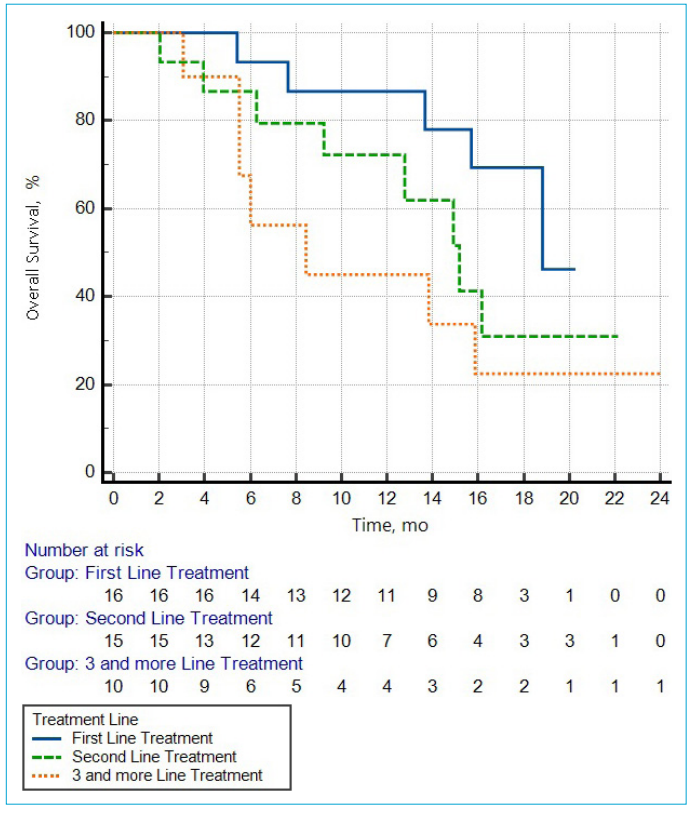

Figure 4. Kaplan Meier curves for Overall Survival by treatment line.

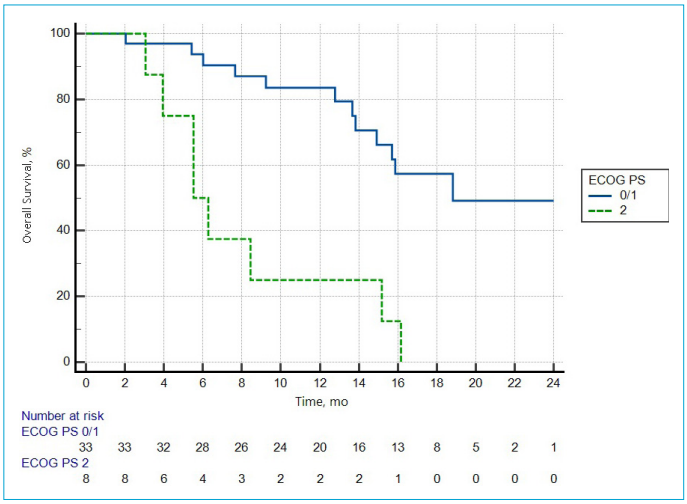

Figure 5. Kaplan Meier curves for Overall Survival by OCOG PS.

Treatment Related Adverse Events

The percentage of patients who experienced treatment-related adverse events (TRAEs) of any grade (G) and G 3-4 was 48.7% and 12.2%, respectively. Diarrhea was the most prevalent AE accounting for 29.3% of cases. Diarrhea was observed in three patients, and liver enzyme elevation was observed in two patients when we examined grade 3/4 AEs. In five patients who experienced grade 3/4 AEs,treatment was interrupted until AEs decreased to G1. The dose was reduced and the treatment continued at 480mg/day. No treatment-related deaths have been reported. The mOS was 14.9 months in patients with grade 3-4 AEs and 16.1 months in the other group (p=0.479) and the mPFS was 3.5 months in patients with grade 3-4 AEs and 8.3 months in the group with no AEs (p=0.76). In terms of survival, there was no difference between the groups when we compared patients with and without TRAEs (p=0.836).

Discussion

The findings of our study provide valuable real-world evidence on the use of sotorasib in patients with KRAS G12C-mutated NSCLC in Turkey. Our results confirm the efficacy and safety of sotorasib observed in clinical trials, and highlight some unique aspects of its application in a real-world setting.

Our study demonstrated a mPFS of 8.3 months and a mOS of 15.8 months among patients treated with sotorasib. These findings are consistent with the results from the CodeBreak 100 study, which reported a mPFS of 6.7 months and provide additional evidence supporting the efficacy of sotorasib in a broader patient population.[9] The real-world mPFS was notably higher in our cohort compared to clinical trial data, possibly due to patient selection criteria and the supportive care infrastructure in place at our centers. We believe that the higher mPFS and mOS were a result of the fact that over one-third of the patients received sotorasib as their first-line treatment.

The first real-world data in KrasG12c mutant NSCLC was reported in Italy with sotarasib, and the median overall survival (mOS) was 8.2 months and the median progression-free survival (mPFS) was 5.8 months.[10] Then, German early access results were added to the literature. The German real-world data study on sotorasib-treated NSCLC patients showed 4.8 months for mPFS and 9.8 months for mOS.[11] We think that the patient population is mostly responsible for the longer mPFS and mOS in our study when compared to the these data. In particular, we believe that lower survival rates are associated with receiving sotorasib later in the course of treatment. For example, if we look at the data from Germany, only 1% of patients received sotorasib in the first-line setting, while about 27% received it in the fourth-line setting and beyond.[11]

The presence of brain metastases did not significantly impact mPFS, which is an important finding given the high incidence of brain metastases in NSCLC patients. This may be due to more frequent screening for cranial metastases and earlier administration of radiotherapy. Prior administration of immunotherapy did not significantly impact the efficacy of sotorasib, highlighting its suitability as a treatment option regardless of previous therapeutic regimens.However, the ECOG PS was a significant predictor of survival, with poorer outcomes in patients with higher ECOG PS scores, underscoring the importance of patient selection and PS in treatment planning.

The safety profile of sotorasib in our study was consistent with previous reports, with diarrhea being the most common adverse event.[7, 10, 11] Grade 3 or higher adverse events were relatively infrequent, and dose reductions were effective in managing toxicity without compromising efficacy. This reinforces the manageable safety profile of sotorasib, making it a feasible option for long-term treatment.

Our study has some limitations, including its retrospective design and the inherent biases associated with such studies. The relatively small sample size and the lack of a control group also limit the generalizability of our findings. Unfortunately, information on the co-mutational patterns of STK11, KEAP1 and TP53, which are known to play a role in sotorasib treatment response[7, 10, 11], could not be obtained from the majority of our patients, as most molecular pathology laboratories do not routinely test such genes. However, the multicenter nature of the study and the inclusion of a diverse patient population enhance the robustness of our results.

Further large-scale prospective studies are warranted to validate these findings and assess the long-term outcomes of sotorasib in real-world settings. Additionally, investigating biomarkers that predict response to sotorasib could help refine patient selection and optimize treatment outcomes.

In conclusion, our multicenter real-world study provides strong evidence supporting the efficacy and safety of sotorasib in KRAS G12C-mutated NSCLC patients. The results are consistent with clinical trial data, demonstrating that sotorasib is an effective and well-tolerated treatment option in a real-world setting. These findings contribute valuable knowledge to the existing literature and have important implications for the management of NSCLC, offering hope for improved patient outcomes in this challenging disease.

Disclosures

Ethics Committee Approval: Gazi University Ethics Committee (No: 321955, Date: 25.03.2022).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – O.A., O.S., O.Y.; Design – O.A., O.S., O.Y.; Supervision – O.S., M.K.E., N.O., A.B., N.K., A.O., A.D., P.F.Y., O.Y.; Materials – O.A., O.S.; Data collection &/or processing – O.A., D.T., D.D., A.F.G., Y.K., E.A., Y.E., G.A., S.K., S.Y., O.D., K.B.Y., I.A., A.T., G.B.K., T.S., S.K.; Analysis and/or interpretation – O.A., O.S., O.Y.; Literature search – O.A., O.S., O.Y.; Writing – O.A., O.S., P.F.Y., O.Y.; Critical review – O.A., O.S., N.O., A.O., P.F.Y., O.Y.

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