Poster #989P

Sotorasib in Advanced *KRAS* p.G12C–Mutated Non-Small Cell Lung Cancer: Safety and Efficacy Data From the Global Expanded Access Program

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BACKGROUND

- Sotorasib is a first-in-class $KRAS^{G12C}$ inhibitor that is approved in over 40 countries for the treatment of patients with pretreated advanced NSCLC harboring the *KRAS* p.G12C variant.[1-3]
- In the CodeBreaK 100 trial, sotorasib demonstrated an ORR of 41%, a median PFS of 6.3 months, and a median OS of 12.5 months.[4] In a post hoc analysis, treatment with sotorasib resulted in intracranial disease control in the majority (88%) of patients with evaluable brain metastases.[5]
- We present the safety and efficacy data from two protocols of the global Expanded Access Program (EAP), evaluating sotorasib in *KRAS* p.G12C–mutated advanced NSCLC beyond the registrational clinical trial setting.
  - Includes previously treated patients with ECOG PS 2 and stable untreated brain metastases.

METHODS

Study Design for Two Global EAP Protocols

Key Eligibility Criteria

- Adults (≥ 18 years old) with locally advanced and unresectable or metastatic NSCLC
- Exhausted other standard-of-care treatment options
- *KRAS* p.G12C mutation per local testing guidelines
- ECOG PS ≤ 2
- Patients with treated or stable untreated brain metastases

Study-436 (Brazil, Israel, Taiwan, and USA)

Screening (28 days)/ Enrollment → Sotorasib (oral daily) at 960 mg → Safety follow-up 30 (± 7) days after the last dose → Long-term follow-up (2 years)

Study-442 (Italy and Spain)

Screening (28 days)/ Enrollment → Sotorasib (oral daily) at 960 mg → Safety follow-up 30 (± 7) days after the last dose

Primary endpoints: Safety (TEAEs, AEs of interest, TRAEs, SAEs, TEAEs leading to sotorasib discontinuation)

Key secondary endpoints: OS (Study-436), *KRAS* p.G12C testing modalities, and treatment duration

Ad hoc endpoint: rwPFS (estimated for Study-436 [allowed for long-term follow-up] based on the time from the start of treatment to the end of protocol sotorasib due to disease progression or death, any death before new anticancer therapy, or end of commercial sotorasib, whichever occurred earlier)

First patient enrolled: January 29, 2021, for Study-436; July 8, 2021, for Study-442

Data cut-off: June 24, 2022

RESULTS

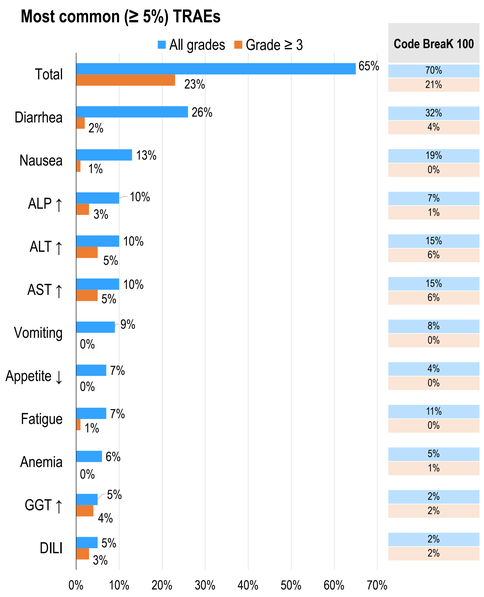
At Baseline, Patients Were Heavily Pretreated, 21% had ECOG PS 2, and 35% had Brain Metastases

Baseline Demographics and Clinical Characteristics	Study-436 (N = 92)	Study-442 (N = 45)	Total (N = 137)
Median age, years (range)	67.5 (46–87)	65.0 (44–85)	66.0 (44–87)
Sex, male	39 (42.4)	22 (48.9)	61 (44.5)
Race, White	87 (94.6)	45 (100.0)	132 (96.4)
Ethnicity, Hispanic or Latino	20 (21.7)	12 (26.7)	32 (23.4)
Smoking status			
Never	6 (6.5)	0	6 (4.4)
Current	11 (12.0)	10 (22.2)	21 (15.3)
Former	75 (81.5)	35 (77.8)	110 (80.3)
ECOG PS			
0	12 (13.0)	12 (26.7)	24 (17.5)
1	56 (60.9)	28 (62.2)	84 (61.3)
2	24 (26.1)	5 (11.1)	29 (21.2)
Number of prior lines of therapy, median (range)[a]	2 (0–7)	2 (0–4)	2 (0–7)
Type of prior anticancer therapy			
Platinum-based chemotherapy	88 (95.7)	38 (84.4)	126 (92.0)
Anti-PD-1 or anti-PD-L1 therapy	84 (91.3)	36 (80.0)	120 (87.6)
Anti-VEGF biological therapy	18 (19.6)	1 (2.2)	19 (13.9)
$KRAS^{G12C}$ inhibitor	4 (4.3)	0	4 (2.9)
History of brain metastases	35 (38.0)	13 (28.9)	48 (35.0)
History of liver metastases	17 (18.5)	3 (6.7)	20 (14.6)
History of bone metastases	39 (42.4)	18 (40.0)	57 (41.6)

Data presented are number (%) of patients, unless indicated otherwise.
[a]Patients could be enrolled if contraindicated to standard-of-care therapies.

OVERALL SAFETY

The Safety Profile Observed in This First Analysis of the Sotorasib EAP Was Consistent With the Profile Observed in the CodeBreaK 100 Phase 1/2 Trial[6]



- TRAEs leading to discontinuation of sotorasib were observed in 7% of the patients and those leading to dose modification (interruption and/or reduction) were observed in 26% of the patients.
- No suspected drug-induced liver injury cases by Hy's law occurred.
- One patient died due to pneumonitis, with an onset of approximately 2.5 months after the initiation of sotorasib treatment.

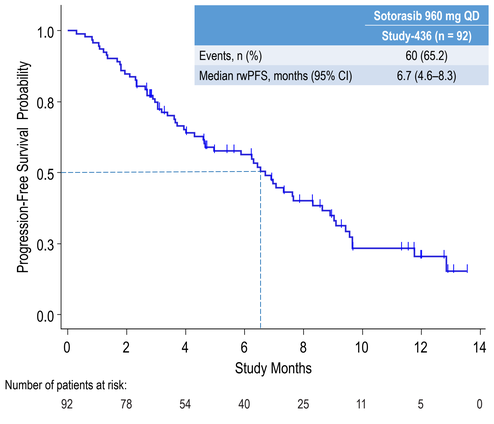
A Higher Incidence of Grade ≥ 3 TRAEs, Most Commonly Liver Enzyme Elevations, Was Observed in Patients Treated With Immunotherapy (IO) ≤ 3 Months vs > 3 Months Prior to Sotorasib Treatment

TRAEs, n (%)	Total (N = 120)	
	IO ≤ 3 months prior to sotorasib (n = 52)	IO > 3 months prior to sotorasib (n = 68)
All TRAEs	36 (69.2)	45 (66.2)
Grade ≥ 3	21 (40.4)	10 (14.7)
Most common Grade ≥ 3 TRAEs (≥ 5% incidence)		
AST increased	7 (13.5)	0
ALT increased	6 (11.5)	1 (1.5)
GGT increased	5 (9.6)	1 (1.5)
ALP increased	3 (5.8)	1 (1.5)
Serious adverse events	6 (11.5)	3 (4.4)
Leading to sotorasib discontinuation	6 (11.5)	3 (4.4)
Fatal[a]	1 (1.9)	0

Demographics and baseline characteristics were generally similar; although, it was noted that patients with IO ≤ 3 months prior to sotorasib were numerically more likely to have received chemotherapy and immunotherapy concurrently vs sequentially.
[a]Pneumonitis with an onset of approximately 2.5 months after initiating sotorasib treatment.

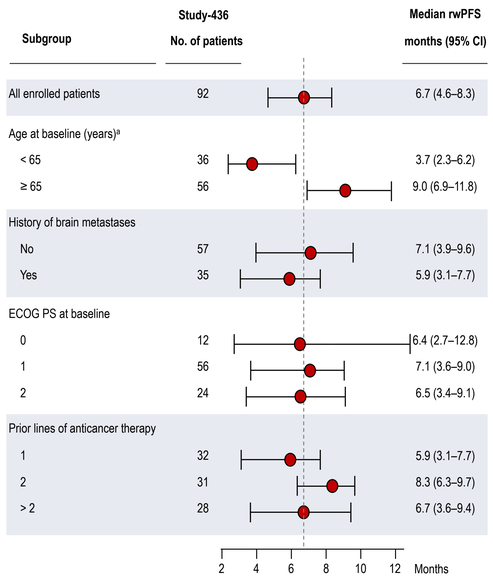
REAL-WORLD PFS

Median rwPFS for Study-436 Was Similar to That in the CodeBreaK 100 Phase 2 Trial



- The median rwPFS reported in the CodeBreaK 100 Phase 2 trial was 6.8 (95% CI, 5.1–8.2) months with 87 (70.2%) events

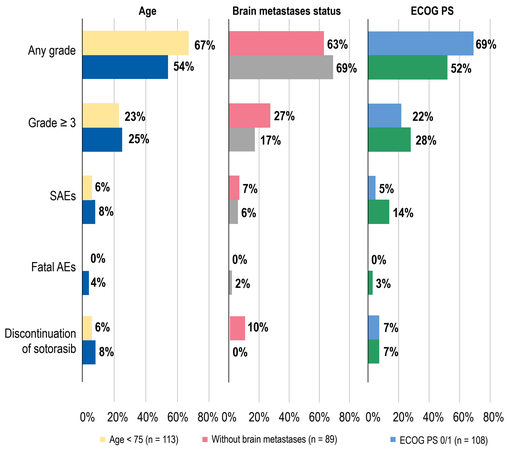
rwPFS Was Generally Consistent Across Patient Subgroups, Including the First Reported Data in Patients With ECOG PS 2



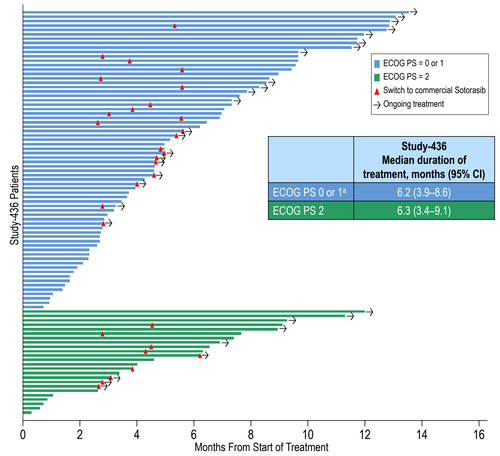
[a]Of note, a higher percentage of patients < 65 years of age (41.7%) had a best response of disease progression on last prior therapy compared to those ≥ 65 years (26.8%).

SAFETY AND EFFICACY BY SUBGROUPS

The Incidence of TRAEs, Including Grade ≥ 3, Was Generally Similar Across Key Patient Subgroups



In Study-436, the Median Duration of Sotorasib Was Consistent With the Findings From CodeBreaK 100, Even in the ECOG PS Subsets



Of the 30/92 (33%) patients who switched to commercial sotorasib, 25 initiated treatment with commercial sotorasib within 1–2 days after end of protocol sotorasib, 3 started commercial sotorasib 4, 5, and 17 days after end of protocol sotorasib, and 2 discontinued protocol sotorasib due to an AE and initiated commercial sotorasib 34 and 99 days later.

[a]The median duration of treatment was 5.8 (95% CI, 2.3–11.7) months in patients with ECOG PS 0 and 6.2 (95% CI, 3.4–9.1) months in patients with ECOG PS 1.

CONCLUSIONS

- The sotorasib EAP included patients with ECOG PS 2 and patients with a history of brain metastases.
- Overall, the safety and rwPFS findings of the sotorasib EAP were consistent with the profile observed across the CodeBreaK 100 trial.
- The safety profile of sotorasib remains consistent with the phase 2 registrational trial, even in patients with ECOG PS 2 and in patients with a history of brain metastases who have poor prognosis.
- Median rwPFS was similar across patient subgroups, including those with a history of brain metastases and those with ECOG PS 2.

LIMITATIONS

- If a patient discontinued protocol sotorasib for reasons other than disease progression or death and did not switch to commercial sotorasib, but started a new anticancer therapy, this patient was censored at date of decision to end treatment.
- Some patients were treated beyond progression.
- Scans were not collected through the EAP protocols.
- OS data are not yet mature.

ABBREVIATIONS

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DILI, drug-induced liver injury; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GGT, gamma-glutamyltransferase; IO, immuno-oncology; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; QD, once a day; rwPFS, real-world progression-free survival; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; VEGF, vascular endothelial growth factor.

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DISCLOSURES

Dr. Luca Toschi receives honoraria from Sanofi, MSD, Eli Lilly, Roche, AstraZeneca, Pfizer, and BMS.

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