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Sotorasib in KRASp.G12C mutated advanced NSCLC: Real-world data from the Italian expanded access program

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ABSTRACT

Background: Sotorasib showed a significant improvement of progression free survival (PFS), safety and quality of life over docetaxel in patients with KRASp.G12C–mutated advanced non–small-cell lung cancer (NSCLC) within the CodeBreak-200 study. Here we report real-world efficacy and tolerability data from NSCLC patients who received sotorasib within the Italian expanded access program (EAP).

Methods: Sotorasib (960 mg, orally, once daily) was available on physician request for KRASp.G12C mutant advanced NSCLC patients. Clinical-pathological and molecular data were collected from the Italian ATLAS real-world registry. Patients underwent CT-scan and responses were evaluated by RECIST criteria. Efficacy and tolerability outcomes have been assessed.

Results: A total of 196 advanced NSCLC patients were treated across 30 Italian centers. Median age was 69 years old (range 33–86). Most patients were male (61 %), former (49 %) or current smokers (43 %), with ECOG-PS 0/1 (84 %) and adenocarcinoma subtype (90 %). 45 % and 32 % of patients received sotorasib in 2nd and 3rd line, respectively. Overall, response rate was 26 % and the median duration of response was 5.7 months (95 % CI: 4.4–7.0). Median PFS and OS were 5.8 months (95 % CI: 5 – 6.5) and 8.2 months (95 % CI: 6.3 – 9.9). Grade 3–4 TRAEs occurred in 16.5 % of patients, with Grade $\geq$ 3 liver enzyme increase and TRAEs-related discontinuation reported in 12 % and 4.6 % of cases.

Conclusion: Real-world data from the Italian EAP confirm the tolerability and effectiveness of sotorasib in patients with KRASp.G12C-mutated advanced NSCLC and highlight the value of the national ATLAS network as source of real-world evidence driving the clinical management of NSCLC patients.

1. Background

Kirsten rat sarcoma (KRAS) viral oncogene mutations have been detected in about one third of non-small cell lung cancer (NSCLC) (39 % non-squamous vs 4 % squamous histology), with p.G12C being the most common pathogenic variant, reported in 12 % of overall NSCLC and 39 % of KRAS-mutant patients, respectively [1]. Differently from other oncogenic drivers (e.g EGFR, ALK, ROS1), KRASp.G12C mutations are more common in Caucasian and smoker populations [2,3], and are generally characterized by high levels of both programmed death ligand-1 (PD-L1) and tumor mutational burden (TMB) [4]. However, the composition of the tumor microenvironment (TME) is significantly modulated by co-mutation patterns, involving TP53, STK11, and/or KEAP1 genes, with relevant implication on clinical efficacy of available treatments [4–6]. The prognostic role of KRAS mutations is controversial, with historical series showing no significant survival differences between KRAS-mutant versus wild-type surgically resected patients [7]. The prognostic value of KRASp.G12C mutations has been investigated also in the metastatic setting, showing no significant differences when compared to the wild-type population, but lower overall survival when compared to patients harboring other oncogenic driver alterations [4].

After several years of research, the recent development of a new class of small molecules that are able to selectively bind the mutant cysteine residue within the P2 domain of KRAS-G12C protein [8,9], represented a major breakthrough for the treatment of lung cancer patients, introducing KRASp.G12C mutation in the arena of positive predictive biomarkers to be tested for targeted treatments selection in the advanced disease. Sotorasib represented the first in class covalent “off” inhibitor, able to irreversibly lock the KRAS-G12C protein in its inactive state, definitively blocking the downstream oncogenic signaling pathways [9]. The results of the phase I-II CodeBreak 100 trial, including 126 KRASp.G12C mutated advanced NSCLC patients who received sotorasib 960 mg/day in second/further lines of treatment showed a promising antitumor activity (objective response rate (ORR) of 40 %, disease control rate (DCR) 84 %, median progression free survival (PFS) 6.7 months, median overall survival (OS) 12.5 months), along with a good safety profile (grade 3–4 treatment related adverse events (TRAEs) 20 %) [10], leading to the Food and Drugs Administration (FDA) approval in 2021. More recently the CodeBreak-200 randomized study [11] demonstrated a significant benefit in terms of ORR (28 % vs 13 %), DCR (82.5 % vs 60.3 %), and median PFS (5.6 vs 4.5 months, p = 0.002), along with a lower incidence of toxicities and a quality of life improvement in favor of sotorasib versus docetaxel, respectively, in KRASp.G12C mutant NSCLC patients who failed prior immunotherapy and /or chemotherapy-based regimens, supporting the regulatory approval by the European Medical Agency (EMA) in 2022. Despite the positive evidence coming from clinical trials there are currently very few data reporting the clinical effectiveness and tolerability of sotorasib in the real-world setting. Here, we reported the efficacy and safety outcomes of KRASp.G12C mutated advanced NSCLC patients who received sotorasib treatment within the Italian Expanded Access/Compassionate Use Programs (EAP/CUP).

2. Methods

2.1. 2.1 Study design and treatment

This is a multicenter, retrospective, observational study conducted on KRASp.G12c mutant, advanced NSCLC patients receiving sotorasib treatment within the EAP/CUP activated in Italy.

Patients were eligible if they aged $\geq$18 years; had histologically or cytologically confirmed diagnosis of NSCLC; stage IIIB-C/IV (according to the 8th version of the American Joint Committee on Cancer (AJCC) /International Association for the Study of Lung Cancer (IASLC) TNM Staging System); ECOG Performance Status (PS) <3; KRASp.G12C mutated disease; disease progression or recurrence after receiving at least one prior systemic therapy for advanced/metastatic disease, or clinically unfit for first-line standard regimes; received sotorasib 960 mg orally once daily within the Italian EAP/CUP from November 2020 to December 2022; participated to the ATLAS real-word registry; signed and dated the ATLAS Informed Consent & privacy Form (ICF) indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study and allowing data collection and source data verification in accordance with Italian requirements, if applicable. Clinical, pathological, and molecular data as well as treatment efficacy/tolerability outcomes were retrospectively collected from patients’ medical charts and/or electronic healthcare records across 30 Italian centeres participating to the ATLAS real-world registry and were subsequently archived by using a specific electronic case report form (eCRF) available at the investigators’ sites. Patients who received sotorasib treatment within the Italian EAP/CUP were ineligible only in case of impossibility to collect the required clinical information. The study was conducted in accordance with the International Conference on Harmonization Guidelines on Good Clinical Practice and the Declaration of Helsinki. The ATLAS protocol was previously approved by the Independent Ethic Committee of the coordinating center at University of Turin (ethics approval number: 0006981) and then at the local Ethic Committees of all the participating centers and all the patients provided a written informed consent before enrollment.

2.2. Objectives and outcomes

The primary objective of this study is to assess the safety profile of sotorasib in KRASp.G12C mutant, advanced NSCLC patients, included within the Italian EAP/CUP, in order to provide a reliable picture of treatment-tolerability in the real-world clinical setting.

The primary outcome of the study includes the incidence of TRAEs under sotorasib therapy, according to the Common Terminology Criteria (CTCAE version 5.0).

The secondary objectives of this study are: to assess the effectiveness profile of sotorasib in KRASp.G12C mutated, advanced NSCLC patients, included within the Italian EAP/CUP, in order to provide a reliable picture of patients' efficacy outcomes in the real-world clinical setting; to assess the potential correlation between clinical, pathological, and molecular characteristics and the efficacy of sotorasib in KRASp.G12C mutated, advanced NSCLC patients.

The secondary outcomes of the study include: ORR, DCR, PFS, and OS under sotorasib therapy; any differences of sotorasib efficacy and/or safety outcomes in specific patients' subgroups selected according to the following characteristics: smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, age, tumor type, tumor stage, metastatic site, treatment line, previous anti-PD1/PD-L1 therapies, PD-L1 tumor proportion score, best response to sotorasib therapy.

2.3. Statistical analysis

The number and percentage of participants receiving sotorasib therapy as well as their clinical, pathological, molecular characteristics, and administered therapies have been summarized either by descriptive statistics or categorical tables. Descriptive analysis has been performed, including means, standard deviations, medians, quartiles, and absolute/relative frequencies (with their respective two-sided 95 % confidence interval (CIs) limits, where relevant), according to the specific variables. The Mann Whitney test was used for intergroup comparisons of two independent samples while Fisher's test was used for categorical values. Radiological evaluation of treatment efficacy by CT-scan was performed every 12 weeks of therapy, thereafter until disease progression. ORR is defined as the proportion of participants who have a best overall response of either complete response (CR) and partial responses (PR) as assessed by investigator's review according to Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1). PFS, is defined as the time from the date of treatment starting until either disease progression, as assessed by investigator's review according to RECIST v1.1criteria, or death due to any cause, whichever occurs first. OS is defined as the time from the date of treatment starting to death due to any cause. The non-parametric Kaplan-Meier method has been used to estimate the survival curves. Medians and two-sided 95 % CIs have been calculated, and Kaplan-Meier plots for both PFS and OS have been provided as appropriate, with the use of the log-rank test for comparisons and a p-value < 0.05 set as threshold for statistical significance. In these analyses, patients have been considered as censored observations in case the event of interest (e.g. death or disease progression) did not occur as long as the patient is under observation, while patients have counted as failures in case the event of interest occurred. Univariate and multivariate analyses were performed using the Cox proportional hazards and logistic regression models. Adverse events have been reported and graded in severity according to the NCTCAE version 5.0. The number of months of treatment have been investigated by summarizing the number of months from the first dose of study drug to the last dose of study drug. The number of patients with at least one dose reduction or interruption have been summarized with frequencies and percentages reported. The statistical analysis has been performed by using SPSS Statistics software version 20 (IBM, Armonk, New York, USA).

3. Results

3.1. Patients' characteristics

From November 2020 to December 2022 a total of 196 patients harboring KRASp.G12C mutated advanced NSCLC, who received sotorasib 960 mg within the Italian EAP/CUP, were considered eligible and were included in the study. Clinical characteristics of the patients are summarized in Table 1. Median age was 69 years old (range 33–85). The majority of patients were males (61 %), current or former smokers (92 %) and exhibited an ECOG PS <2 (83.7 %). The most frequent histological subtype was adenocarcinoma (90.3 %), followed by squamous cell carcinoma and other rare histologies. Tumor PD-L1 expression was ≥50, 1–49 %, <1% in 36.2 %, 31.6 %, 25.5 % of cases, respectively. The bone was the most common metastatic site (40.8 %) followed by central nervous system (CNS) (32.7 %), and liver (15.8 %). Patients received a median of 2 (0–4) lines of systemic therapies, with 45 % of them receiving sotorasib in 2nd line. In 70 % of the patients the previous

Table 1
Baseline Patients' Characteristics.

Patients' Characteristics	Number (%)
Age in years (median, IQR, range)	69 (62–75) (33–85)
<70 years/old	104 (53.1)
≥70 years/old	92 (46.9)
Gender	
Male	119 (60.7)
Female	77 (39.3)
Smoking Status	
Current	84 (42.9)
Former	97 (49.5)
Never	6 (3.1)
Not available	9 (4.6)
ECOG-Performance Status	
0	79 (40.3)
1	85 (43.4)
2	15 (7.7)
Not available	17 (8.7)
Histological Subtypes	
Adenocarcinoma	177 (90.3)
Squamous Cell Carcinoma	6 (3.1)
Other	9 (4.6)
Not available	4 (2.0)
PD-L1 expression levels	
≥50 %	71 (36.2)
1–49 %	62 (31.6)
<1 %	50 (25.5)
Not available	13 (6.6)
Metastatic sites	
Brain	64 (32.7)
Liver	31 (15.8)
Bone	80 (40.8)
Previous Treatment lines for metastatic disease	
0	20 (10.2)
1	88 (44.9)
2	62 (31.6)
3	19 (9.7)
4	7 (3.6)
Previous Immunotherapy for metastatic disease	
Yes	137 (69.9)
No	59 (30.1)

lines of treatment before sotorasib administration included immunotherapy with anti-PD-1/PD-L1 inhibitors. Notably 20 patients (10.2 %) were considered unfit for standard first-line therapies and received sotorasib upfront. The median follow-up calculated with the reverse Kaplan-Meier method was 11.8 months (inter-quartile range: 6.5–16.3) for the overall population at the time of data analysis.

3.2. Safety

The percentage of patients who experienced TRAEs of any grade (G) and G 3–4 was 51.5 % and 16 %, respectively, with G 3 liver enzyme increase reported in 12 % of cases. Six patients (3 %) reduced sotorasib dose from 960 mg to either 480 mg (3 cases) or 240 mg (3 cases) orally once daily because of TRAEs. Nine patients (4.6 %) definitively discontinued treatment with sotorasib because of hepatic (3.6 %) or gastrointestinal (1 %) TRAEs. No treatment-related deaths have been reported. A detailed list of TRAEs in the overall analyzed population, including both pre-treated and naïve patients is reported in Table 4. Notably, 23 out of 26 pre-treated patients (88 %) experiencing G3-G4 TRAEs received a previous anti-PD-(L)1 therapy exposure, with 19 of them (82 %) receiving immunotherapy immediately before sotorasib. In addition, 7 out of 9 patients (78 %) who discontinued sotorasib because of TRAEs have previously been treated with anti-PD(L)-1 agents in the line before sotorasib administration. No OS differences have been observed between patients experiencing or not severe TRAEs (HR: 0.83; 95 % CI 0.48 – 1.43).

3.3. Efficacy outcomes

Among the 196 patients included in the study, 51 (26 %) experienced a PR, 60 (30.6 %) a stable disease (SD) and 65 (33.2 %) a progressive disease (PD), as best response to sotorasib. The ORR was 26 % and the DCR was 56.6 % in the overall analyzed population, without significant differences between naïve and pre-treated patients (Table 2). The median duration of response was 5.7 months (95 % CI: 4.4–7.0).

The median PFS was 5.8 months (95 % CI: 5–6.5), with 3 months, 6 months, and 1-year PFS rate of 71 %, 47.5 %, 28 %, respectively. The median OS was 8.2 months (95 % CI: 6.3 – 9.9), with 3 months, 6 months, and 1-year OS rate of 83 %, 61.6 %, 42 %, respectively (Fig. 1).

The median PFS was 15.2 vs 6.4 vs 2.2 months ($p < 0.0001$) and the median OS was not reached (NR) vs 8.3 vs 3.7 months ($p < 0.0001$) in patients experiencing PR vs SD vs PD as best response to sotorasib, respectively (Fig. 2). No significant difference in terms of median PFS/OS have been reported across all other analyzed subgroups selected by clinical, pathological, and molecular characteristics (Table 3).

Notably among 20 naïve patients who received sotorasib in first-line, the median PFS was 5.4 (95 % CI: 2.2–8.6) months and the median OS was 7.0 (95 % CI: 0–16.4) months. At the time of data analysis, 19 patients (9.7 %) received sotorasib beyond progression and the baseline characteristics of this subgroup are specified in the Supplementary Table S1. Seven of them received loco-regional therapies (radiotherapy in 6 cases and surgery in one case) in combination with sotorasib. The median OS in this subgroup of patients receiving sotorasib beyond PD +/- loco-regional therapies was 14.4 (95 % Cis: 11.6–17.2) months.

Table 2
Clinical Responses to Sotorasib in the overall population.

	Overall population (N = 196)	≥2nd line (N = 176)	1st line (N = 20)
ORR	51 (26 %)	46 (26.1 %)	5 (25 %)
DCR	111 (56.6 %)	98 (55.7 %)	13 (65 %)
Best response			
CR	0 (0 %)	0 (0 %)	0 (0 %)
PR	51 (26 %)	46 (26.1 %)	5 (25 %)
SD	60 (30.6 %)	52 (29.5 %)	8 (40 %)
PD	65 (33.2 %)	59 (33.5 %)	6 (30 %)
NE	20 (10.2 %)	19 (10.8 %)	1 (5 %)

ORR, objective response rate; DCR, disease control rate; CR, complete response; PR, partial response;
SD, stable disease; PD, progression disease; NE, not evaluated.

Intracranial activity data were available for 53 out of 64 patients with brain metastases. Among them, 24 patients had received prior brain radiotherapy and 5 received local CNS treatment (4 patients radiotherapy and 1 patient surgery) concomitantly with sotorasib administration. The CNS response rate was 23 %, with 2 (3,8%) patients experiencing a complete response and 10 (18,9%) a PR as best response to sotorasib. The intracranial DCR was 48 %. The median time from sotorasib initiation to CNS response was 2.9 months (IQR: 1.8–4.5), the median duration of CNS responses was 14.2 months (95 % CI: 6.9–19), and the intracranial median PFS was 8.6 months (95 % CI: 6.0–11.2).

At the time of data analysis, 97 out of 197 patients (50 %) treated with sotorasib died and their survival outcome were compared with an historical cohort of 25 KRASp.G12C mutant advanced NSCLC patients included in the ATLAS registry who did not received sotorasib during their treatment history. The baseline characteristics of these populations are reported in the Supplementary Table S2. As shown in the Supplementary Fig. S1, the median OS in the subgroup of patients treated with sotorasib was 9.46 (95 % Cis: 7.13–30.09.2) months versus 9.95 (95 % Cis: 5.91-N.A) for patients who did not received sotorasib ($p = 0.96$).

4. Discussion

This report summarized the real-world clinical experience with sotorasib in about 200 KRASp.G12C mutated, advanced NSCLC patients treated within the Italian EAP/CUP. The characteristcs of the patients included in our real-world analysis were similar to those reported in the CodeBreack 200 randomized clinical trial [11], with near half of them receiving sotorasib in second-line and about 70 % previously treated with immunotherapy. Notably 20 patients who were not candidated to first-line chemotherapy because of their clinical status/comorbidities received sotorasib upfront, according to the EAP/CUP inclusion criteria.

The results of this real-world analysis showed that both the safety and efficacy outcomes of sotorasib in KRASp.G12C mutated NSCLC patients treated outside of a clinical trial context were similar to those reported in the CodeBreack 200 randomized study [11], confirming the optimal tolerability profile as well as the promising antitumor activity of this drug in this population. The inferior median OS observed in our analysis could be likely related to the lower percentage of patients (70 % vs 98 %) previously treated with both immunotherapy and platinum-based chemotherapy as compared to the CodeBreak 200 clinical trial [11], as well as to the high number of alive patients (60 out of 93) with a median follow-up inferior to 12 months at the data cut-off. Indeed the median OS reached 9.46 months in the subgroup of patients who died at the time of data analysis. Conversely the lack of OS difference with the KRASp.G12C mutant historical cohort who did not receive sotorasib within the ATLAS registry could be likely ascribed to the very limited number of analyzed patients.

Importantly the efficacy of sotorasib was mantained across all clinical subgroups, including patients with baseline brain metastases, with intracranial responses almost in line with that reported in the CodeBreak 200 study [12], confirming that sotorasib may have some intracranial activity but highlighting the crucial role of multidisciplinary management of brain metastasis [13]. In detail, the best radiological response to sorasib emerged as the only reliable clinical predictor of survival outcomes in our analysis, with a median PFS and OS significantly longer in those patients experiencing RECIST PR as best response as compared to SD. Conversely survival outcomes with sotorasib were similar across the different treatment lines, likely because the small treatment-naïve cohort included a frailer population with higher median age (76 years/old) as well as ECOG-PS. The evidence of a nearly doubled OS for those

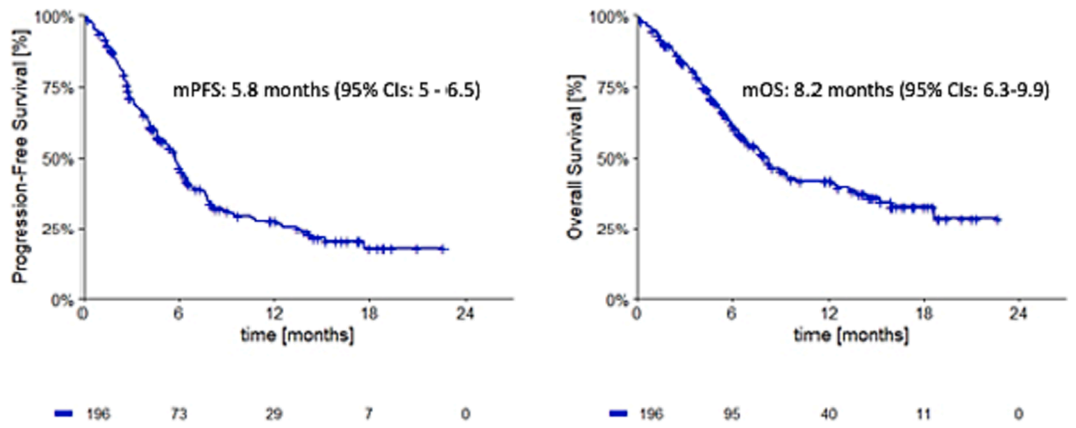

Fig. 1. Kaplan Meier curves for PFS and OS in the overall analyzed population.

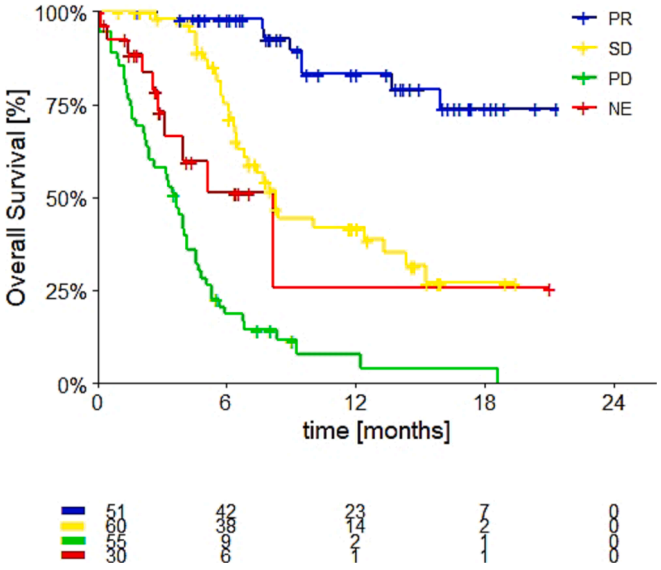

Fig. 2. Kaplan Meier curves for OS by best response to sotorasib therapy.

patients who were treated with sotorasib beyond progression +/- loco-regional therapies supports this treatment strategy in our clinical practice, in line with other oncogene-addicted diseases.

The overall incidence of either any grade or severe TRAEs as well as treatment dose reduction and discontinuation in our real-word analysis were significantly lower than those reported in the CodeBreak randomized study [11]), but similar to another study exploring sotorasib activity/toxicity in the routine practice [6], suggesting a not uniform approach for toxicity data collection between clinical trial and real-word setting.

Accordingly with recent series showing a potential correlation between a previous anti-PD-(L)1 therapy exposure and the incidence of hepatic toxicities under sotorasib therapy [6,14], our study also confirmed a significantly higher incidence of severe TRAEs as well as treatment discontinuation rate in patients who have previously received immunotherapy before sotorasib administration, suggesting as appropriate timing and sequencing of currently available therapies is crucial to optimize the tolerability profile of these drugs in clinical practice. Finally data from the randomized CodeBreak study [14] and real-word clinical series [5,6] confirmed that the efficacy of sotorasib could be influenced by KRAS co-mutational patterns, including STK11, KEAP1, CDK4, and SMARC4 co-genomic alterations, but unfortunately this information was not available from our patients since the majority of molecular pathology laboratorites do not routinary test such genes in the italian real-word clinical setting.

Although this study is limited by the lack of detailed genomic profiling and its retrospective design, it likely represents the largest real-word analysis supporting the effectiveness and tolerability of sotorasib in KRASp.G12C mutant advanced NSCLC, and highlights the relevance of tissue and/or circulating tumor DNA molecular testing [15] to identify NSCLC patients harboring this targetable driver, as well as the value of the multicenter national ATLAS registry [15] as source of real-word evidence driving the clinical management of NSCLC patients.

Conflict of interest: F.P received speakers' and consultants' fee from Astra-Zeneca, BMS, Novartis, Roche, MSD, Amgen, Janssen, Sanofi, Beigene, Thermofisher Scientific; G.L.R. received speakers' and consultants' fee from BMS, MSD, Roche, Sanofi Regeneron, Lilly, AstraZeneca, Janssen, Pfizer, Novartis, Bayern, Takeda, Amgen, Italfarmaco, GSK; G. P. has received personal fees (as consultant and/or speaker bureau) from: Amgen, AstraZeneca, BMS, Eli Lilly, MSD, Novartis, Roche, Jannsen, AstraZeneca, Roche unrelated to the current work. M.G received personal fee from advisory board Astra-Zeneca, Roche, BMS, Gilead, Novartis, Sanofi, MSD. D. G. has received personal fees (as consultant and/or speaker bureau) from Astra-Zeneca, Pfizer, Eli-Lilly, BMS, MSD, Novartis, Amgen, Roche for work performed outside of the current study. E.B has received grants or contracts from Astra-Zeneca, Roche and honoraria for lectures from Merck-Sharp & Dome, Astra-Zeneca, Pfizer, Eli-Lilly, Bristol-Myers Squibb, Novartis and Roche; E. B. has been member of Data Safety Monitoring Board or Advisory Board of Merck-Sharp & Dome, Pfizer, Novartis, Bristol-Myers Squibb, Astra-Zeneca, and Roche. S. P. reports personal fees (invited speaker, advisory board) from AstraZeneca, Eli-Lilly, Novartis, AMGEN, Takeda, Sanofi, Bristol Myers Squibb, MSD and Roche; and research grants from AstraZeneca, Bristol Myers Squibb and Roche outside the submitted work. C.G received Honoraria from AstraZeneca, BMS, Eli Lilly, Roche, Novartis, MSD, SANOFI, Takeda; personal fee from Advisory boards BMS, Roche, Sanofi. D. C. has received personal fees (as consultant and/or speaker bureau) from Advisory Amgen, AstraZeneca, BMS, MSD, Novartis, Roche, Jannsen, Sanofi Genzyme. A.D.M received advisory fee from Roche, Novartis e Sanofi. A.R received advisory board honoraria from AstraZeneca, MSD, Novartis, Pfizer, BMS, and Amgen; writing engagement honoraria from AstraZeneca, MSD, Roche, and Novartis; speaker bureau from AstraZeneca and BMS. M.T. received speakers' and consultants' fee from Astra-Zeneca, Pfizer, Eli-Lilly, BMS, Novartis, Roche, MSD, Boehringer Ingelheim, Otsuka, Takeda, Pierre Fabre, Amgen, Merck, Sanofi. M.T. received institutional research grants from Astra-Zeneca, Boehringer Ingelheim; M.B. received travel grants from Lilly and Leo Pharma; U.M declared speaker bureau/advisor's fee from Boehringer Ingelheim, Roche, Merck Sharp, and Dohme, Amgen, Thermo Fisher Scientifics, Eli Lilly, GlaxoSmithKline, Merck, AstraZeneca, Janssen, Novartis, Takeda, Bayer, Pfizer. S.N reports personal fees (as speaker bureau or advisor) from Eli Lilly, MSD, Roche, BMS, Takeda,

Table 3
Subgroup analysis for PFS and OS in the overall population.

	Median PFS (95 % CIs)	P-value	Median OS (95 % CI)	P-value
All patients	5.8 (5.0–6.5)		8.2 (6.4–10.0)	
Age				
<70 years/old	5.7 (4.7–6.7)	0.53	7.7 (6.0–9.4)	0.56
≥70 years/old	6.2 (4.7–7.7)		9.0 (3.9–14.0)	
Gender				
Male	5.8 (4.6–6.9)	0.86	7.7 (5.3–10.2)	0.97
Female	5.8 (4.7–6.9)		8.3 (6.6–9.9)	
Smoking Status				
Current	5.7 (4.5–6.9)	0.66	8.1 (5.1–11.2)	0.69
Former/never	5.8 (4.5–6.9)		7.7 (6.0–9.3)	
ECOG-PS				
0	5.6 (4.0–7.3)	0.61	7.9 (5.4–10.4)	0.41
1–2	5.8 (4.9–6.6)		7.4 (5.6–9.2)	
N of previous treatments				
0	5.4 (2.2–8.6)	0.55	7.0 (0–16.4)	0.22
1	5.1 (3.8–6.4)		6.1 (5.4–6.9)	
>=2	6.4 (5.0–7.9)		9.0 (7.7–10.2)	
PD-L1 expression				
<1%	5.8 (3.5–8.1)	0.20	9.0 (3.7–14.3)	0.35
1 %-49 %	5.6 (4.2–7.1)		6.8 (5.0–8.5)	
>50 %	5.9 (4.2–7.6)		7.9 (5.9–10.0)	
Previous immunotherapy				
Yes	5.8 (4.9–6.8)	0.96	8.3 (6.8–9.7)	0.91
No	5.5 (3.5–7.5)		7.0 (5.1–8.9)	
Brain metastasis				
Yes	5.6 (4.4–6.9)	0.77	7.7 (3.6–11.9)	0.79
No	5.9 (5.1–6.8)		8.3 (6.9–9.7)	
Liver Metastasis				
Yes	5.1 (1.2–9.1)	0.50	7.9 (2.9–13.0)	0.45
No	5.8 (5.0–6.5)		8.3 (6.3–10.3)	
Bone Metastasis				
Yes	5.7 (4.4–7.1)	0.27	7.0 (4.1–10.0)	0.23
No	5.8 (4.7–7.0)		8.3 (4.1–12.5)	
Best Response to Sotorasib				
PR	15.2 (11.4–19.1)	<0.0001	Not reached	<0.0001
SD	6.4 (5.7–7.1)		8.3 (7.2–9.4)	
PD	2.2 (1.6–2.8)		3.7 (3.0–4.3)	
NE	5.1 (2.0–8.3)		8.2 (3.6–12.7)	

N, number; PD-L1, Programmed-death ligand 1; PR, partial response; SD, stable disease; PD, progression disease; NE, not evaluated.

Table 4
Treatment-related adverse events (TRAEs) in the overall population.

Treatment-Related Adverse Events (TRAEs) in the overall population[a]	Number of patients (%)
Any grade TRAEs[a]	101 (51.5 %)
Grade 1	50 (25.8 %)
Grade 2	19 (9.7 %)
Grade 3	29 (14.8 %)
Grade 4	3 (1.5 %)
Grade 3 TRAEs[a]	
Alanine/Aspartate aminotransferase increase	21 (12.2 %)
Diarrhea	4 (2 %)
Gamma-glutamyl Transferase increase	3 (1.5 %)
Bilirubin increase	1 (0,5%)
Nausea	1 (0.5 %)
Fatigue	1 (0.5 %)
Skin Rash	1 (0.5 %)
Grade 4 TRAEs[a]	
Gamma-glutamyl Transferase increase	3 (1.5 %)
TRAEs leading to dose reduction	6 (3 %)
TRAE leading to discontinuation of therapy	9 (4.6 %)
Transaminase increase	7 (3.6 %)
Diarrhea	2 (1 %)
TRAEs in pretreated patients[a]	
Grade 3	26 (14.8 %)
Grade 4	3 (1.7 %)
TRAEs leading to dose reduction	5 (2.8 %)
TRAE leading to discontinuation of therapy	8 (4.5 %)
TRAEs in naïve patients	
Grade 3	3 (15 %)
Grade 4	0
TRAEs leading to dose reduction	1 (5 %)
TRAE leading to discontinuation of therapy	1 (5 %)

[a] Some patients reported multiple TRAEs.

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CRediT authorship contribution statement

Francesco Passiglia: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **Maria Lucia Reale:** Investigation, Validation, Visualization. **Giuseppe Lo Russo:** Investigation, Validation, Visualization. **Giulia Pasello:** Investigation, Validation, Visualization. **Gabriele Minuti:** Investigation, Validation, Visualization. **Alessandra Bulotta:** Investigation, Validation, Visualization. **Domenico Galetta:** Investigation, Validation, Visualization. **Giacomo Pelizzari:** Investigation, Validation, Visualization. **Claudio Sini:** Investigation, Validation, Visualization. **Emilio Bria:** Investigation, Validation, Visualization. **Elisa Roca:** Investigation, Validation, Visualization. **Sara Pilotto:** Investigation, Validation, Visualization. **Carlo Genova:** Investigation, Validation, Visualization. **Giulio Metro:** Investigation, Validation, Visualization. **Fabrizio Citarella:** Investigation, Validation, Visualization. **Rita Chiari:** Investigation, Validation, Visualization. **Diego Cortinovis:** Investigation, Validation, Visualization. **Angelo Delmonte:** Investigation, Validation, Visualization. **Alessandro Russo:** Investigation, Validation, Visualization. **Marcello Tiseo:** Investigation, Validation, Visualization. **Giulio Cerea:** Investigation, Validation, Visualization. **Annamaria Carta:** Investigation, Validation, Visualization. **Vieri Scotti:** Investigation, Validation, Visualization. **Tiziana Vavalà:** Investigation, Validation, Visualization. **Marta Brambilla:** Investigation, Validation, Visualization. **Lucio Buffoni:** Investigation, Validation, Visualization. **Roberta Buosi:** Investigation, Validation, Visualization. **Chiara Catania:** Investigation, Validation, Visualization. **Stefania Gori:** Investigation, Validation, Visualization. **Salvatore Grisanti:** Investigation, Validation, Visualization. **Francesco Agustoni:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **Edoardo Garbo:** . **Umberto Malapelle:** Data curation, Methodology, Validation, Visualization. **Silvia Novello:** .

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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