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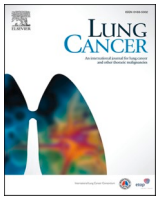

Research Paper

Patient-reported outcomes in CodeBreaK 200: Sotorasib versus docetaxel for previously treated advanced NSCLC with *KRAS* G12C mutation

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ABSTRACT

Background: In the CodeBreaK 200 phase III, open-label trial, sotorasib significantly improved efficacy versus docetaxel in previously treated *KRAS* G12C-mutated advanced non-small cell lung cancer (NSCLC). Patient-reported outcomes (PROs) for global health status, physical functioning, dyspnea, and cough favored sotorasib over docetaxel. Here, we report sotorasib's additional impact on quality of life (QOL).

Methods: In CodeBreaK 200, 345 patients who had progressed after prior therapy received sotorasib (960 mg orally daily) or docetaxel (75 mg/m^2 intravenously every 3 weeks). Validated questionnaires captured patients' perception of their QOL and symptom burden for key secondary and exploratory PRO endpoints, including

Abbreviations: BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Lung Cancer 13; EQ-5D-5L, 5-level European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire 5 dimensions; FACT-G, Functional Assessment of Cancer Therapy Tool General Form; GEE, generalized estimating equation; HR, hazard ratio; IQR, interquartile range; IV, intravenous; NSCLC, non-small cell lung cancer; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events; QOL, quality of life; TRAE, treatment-related adverse event; VAS, visual analog scale.

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the European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) and Quality-of-life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13), question GP5 from the Functional Assessment of Cancer Therapy Tool General Form (FACT-G GP5), PRO-Common Terminology Criteria for Adverse Events (PRO-CTCAE), and 5-level EuroQOL-5 dimensions (EQ-5D-5L) including visual analog scale (EQ-5D VAS). Change from baseline to week 12 was assessed with generalized estimating equations for ordinal outcomes.

Results: Patients receiving sotorasib were less bothered by treatment side effects than those receiving docetaxel (odds ratio [OR] 5.7) and experienced symptoms at lower severity (pain: OR 2.9; aching muscles: OR 4.4; aching joints: OR 4.2; mouth or throat sores: OR 4.3). Further, patients' symptoms interfered less with usual/daily activities (pain: OR 3.2; aching muscles: OR 3.9; aching joints: OR 10.7). QOL remained stable with sotorasib but worsened with docetaxel (change from baseline in EQ-5D VAS score: 1.5 vs –8.4 at cycle 1 day 5 and 2.2 vs –5.8 at week 12).

Conclusions: Patients receiving sotorasib reported less severe symptoms than those receiving docetaxel. In addition to improving clinical efficacy outcomes, sotorasib maintained QOL versus docetaxel, suggesting sotorasib may be a more tolerable treatment option for patients with pretreated, *KRAS* G12C-mutated advanced NSCLC.

1. Introduction

The development of targeted therapies has led to significant advances in the treatment of patients with non-small cell lung cancer (NSCLC) [1–3]. Activating *KRAS* mutations occur in ~ 30% of non-squamous NSCLC [4–6], with the most common (> 8%) *KRAS* point mutation occurring at codon 12 [7]. In Western countries, the *KRAS* G12C variant occurs in ~ 40% of adenocarcinomas, representing 10–13% of patients with advanced, non-squamous NSCLC [6–8]. In Asian countries, the *KRAS* G12C variant occurs at rates of 5–12% in patients with lung adenocarcinoma [9–12]. *KRAS* G12C is generally mutually exclusive with known actionable driver genomic alterations such as *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, *RET*, *NTRK*, and *HER2* [13–15].

Sotorasib, a small molecule that specifically and irreversibly inhibits the $KRAS^{G12C}$ protein, covalently binds to the cysteine residue in a P2 regulatory pocket, trapping $KRAS^{G12C}$ in the inactive GDP-bound state and preventing downstream signaling in cancer cells, resulting in decreased oncogenesis [16]. Sotorasib was the first-in-class $KRAS^{G12C}$ inhibitor to receive accelerated approval for the treatment of adults with locally advanced or metastatic NSCLC with *KRAS* G12C mutation who have progressed after ≥ 1 prior line of systemic therapy [17]. To date, sotorasib has received accelerated or full approval in over 50 countries.

The randomized CodeBreaK 200 phase III trial (NCT04303780) compared oral sotorasib 960 mg daily with intravenous (IV) docetaxel 75 mg/m^2 every 3 weeks in patients with *KRAS* G12C advanced NSCLC previously treated with platinum-based chemotherapy and a checkpoint inhibitor [18] (Supplementary Fig. 1A). Sotorasib demonstrated statistically significant superiority for the primary endpoint of progression-free survival (PFS) over docetaxel (median PFS 5.6 vs 4.5 months; hazard ratio [HR] 0.66, P=0.002), with a 12-month PFS rate of 24.8% vs 10.1% [18]. Sotorasib was also associated with improved secondary endpoints, including a higher objective response rate (ORR: 28.1%; 95% confidence interval [CI]: 21.5, 35.4 vs 13.2% [8.6, 19.2]; P<0.001), faster median time to response (1.4 vs 2.8 months), longer median duration of response (8.6 vs 6.8 months), and higher disease control rate (82.5% vs 60.3%) than docetaxel [18]. No difference in overall survival (OS) was observed between sotorasib and docetaxel [18]. PFS and ORR favored sotorasib across the patient subgroups including age categories (< 65 years vs ≥ 65 years), sex, race, region, and smoking history [18]. Sotorasib was well tolerated with a lower incidence of Grade ≥ 3 treatment-related adverse events (TRAEs; 33% vs 40%) and serious TRAEs (11% vs 23%) than docetaxel [18].

Patient-reported outcomes (PROs) in the CodeBreaK 200 trial were evaluated as prespecified key secondary and exploratory endpoints (Supplementary Fig. 1A-B). In the primary publication of CodeBreaK 200, which was the first report of PROs with a $KRAS^{G12C}$ inhibitor, the outcomes for global health status, physical functioning, dyspnea, and cough—included as key secondary PRO endpoints—favored sotorasib over docetaxel [18]. Further, the primary publication already included the time to deterioration analyses for these PROs [18]. Here, we report additional PRO outcomes with respect to the secondary and exploratory endpoints, further demonstrating the impact of sotorasib treatment on patients' quality of life (QOL).

2. Methods

2.1. Study design and procedures

As previously described [18], the CodeBreaK 200 trial was a randomized, multicenter, open-label, phase III trial that enrolled 345 patients with *KRAS* G12C-mutated advanced NSCLC (Supplementary Fig. 1). Key eligibility criteria included progression after receiving ≥ 1 treatment including platinum-based chemotherapy plus a checkpoint inhibitor and no active brain metastases (Supplementary Fig. 1A). Patients were randomized 1:1 to receive either oral sotorasib 960 mg once daily or IV docetaxel 75 mg/m^2 every 3 weeks. The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The protocol and amendments were approved by the institutional review board at each participating site and regulatory authorities of participating countries. All patients provided written informed consent. A data monitoring committee provided independent oversight of safety and efficacy throughout the trial.

2.2. Study endpoints

The primary endpoint of the CodeBreaK 200 study was PFS with sotorasib treatment vs docetaxel treatment as determined by blinded independent central review [18] (Supplementary Fig. 1A). Data for the primary endpoint and key secondary endpoints, including key secondary PRO endpoints, have been previously reported [18].

Among the PRO endpoints included in the trial (Supplementary Fig. 1B), key secondary PRO endpoints were based on the instruments European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) [19–21] and Quality-of-life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13) [22]. The specific endpoints were the change from baseline to week 12 for the outcomes of the global health status (QOL), physical functioning, chest pain, cough, and dyspnea. Secondary PRO endpoints included further subscales of the EORTC QLQ-C30 and EORTC QLQ-LC13 instruments, as well as time to deterioration analyses. Additional secondary PRO endpoints included the change from baseline of the visual analog scale (VAS) scores as measured by the 5-level European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire 5 dimensions (EQ-5D-5L) [23,24]. Exploratory PRO endpoints included the comparison of sotorasib vs docetaxel on the "GP5" item of the Functional Assessment of Cancer Therapy Tool General Form (FACT-G GP5)

[25], named "I am bothered by side effects of treatment". Further exploratory measures were selected items of the Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) instrument [26]. In addition, and to provide additional context, the Brief Pain Inventory-Short Form (BPI-SF) [27], the Patient Global Impression of Change (PGIC) [28], and the Patient Global Impression of Severity (PGIS) [28] were included. Details of the PRO questionnaire are provided in Supplementary Methods.

2.3. Statistical analysis

Data reported previously for the primary and key secondary endpoints [18] and PRO data reported here are from the cutoff date of August 2, 2022. Completion rate (defined as the percentage of patients who completed ≥ 1 item in the subscale of the questionnaire at each visit over the number of all randomized patients) was determined by PRO instrument. Additionally, compliance rate (defined as the percentage of the number of patients who completed ≥ 1 item in the subscale of the questionnaire at each visit over the number of eligible patients who were expected to complete the PRO assessment per protocol at each visit [i.e., still on study and still alive, excluding the patients who were missing by design, such as death, disease progression, study discontinuation, etc.]) was also determined.

The PRO instrument-specific analysis sets included all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements. The continuous PRO scores (i.e., PRO outcomes excluding single-item categorical outcomes) were summarized descriptively by visit and by treatment group using the number of patients with non-missing data (n), mean, standard deviation, median, and minimum and maximum. The change from baseline of these scores was also reported descriptively. The ordinal (i.e., categorical) PRO items were summarized descriptively by visit and by treatment group using the number and percentage of patients with non-missing data (n) within each ordinal level. In addition, percentages of combined ordinal levels were reported.

The inferential comparison for the categorical endpoints of change from baseline over time to week 12 were made through the generalized estimating equation (GEE) method for cumulative logits model [29] and expressed as odds ratios (ORs) and 95% CIs. The model included intercept, time, baseline score, treatment, treatment by time interaction, and randomization stratification factors.

3. Results

3.1. Patients and baseline characteristics

Between June 4, 2020 and April 26, 2021, 345 patients with *KRAS* G12C advanced NSCLC who had disease progression after receiving ≥ 1 prior therapy were enrolled and randomized to receive sotorasib (n = 171) or docetaxel (n = 174). Baseline patient characteristics, as previously reported [18] and also shown in Supplementary Table 1, were generally well balanced. Baseline PRO scores were generally similar between the treatment groups. These included treatment side effects such as symptom bother (FACT-G GP5); severity, frequency, and interference of treatment-related symptoms (PRO-CTCAE); functional domains and symptom subscales (EORTC QLQ-C30 and EORTC QLQ-LC13); quality of life (EQ-5D-5L including VAS); pain (BPI-SF); and lung cancer symptoms of cough, chest pain, and dyspnea (PGIS). The median study follow-up at the primary data cutoff date of August 2, 2022 was 17.7 months (interquartile range [IQR] 16.4–20.1). The median duration of treatment exposure was 19.9 weeks (range 0.4–101.3) for patients receiving sotorasib and 12 weeks (at cycle 5 day 1) (range 3.0–101.0) for patients receiving docetaxel [18].

3.2. Completion and compliance rates

As PRO data were collected while patients were on treatment only, PRO data availability rates (completion rates) showed a natural drop of responses over time (Supplementary Fig. 2A-C). However, despite this natural drop, compliance rates for both sotorasib and docetaxel remained at a relatively high level, meaning that most patients who were supposed to answer the questionnaires in general did answer them (Supplementary Fig. 2A-C). The reported number of patients at baseline for each PRO outcome, compared with the number of patients in the randomized population, were lower across the PROs (provided in results table or figure for each PRO outcome). This is due to two reasons: 1) patients were included in the PRO analysis set if, in addition to the baseline assessment, they had at least another PRO assessment and 2) some patients were never treated and therefore did not report PRO outcomes.

3.3. Level of bother by treatment side effects (FACT-G GP5)

Patients treated with sotorasib compared with those treated with docetaxel were less bothered by the side effects of treatment. The FACT-G GP5 score suggested that sotorasib was better tolerated compared with docetaxel, with the OR at week 12 (cycle 5 day 1) of selecting a superior category while being treated with sotorasib at 5.7 (95% CI: 3.0, 10.9; $P<0.001$) (Supplementary Table 2). The OR corresponds to the likelihood of patients selecting a more favorable response category. Similar results were observed at other cycles and overall (Supplementary Table 2).

Regarding the descriptive responses from baseline up to cycle 15 in the sotorasib group (Fig. 1 and Supplementary Table 3), the proportion of patients who were bothered by the side effects of treatment was low. Between both treatment arms, there were no substantial differences at baseline. In the sotorasib arm, over the course of time, the distribution of responses remained stable: the distribution of the proportion of patients who were "somewhat", "quite a bit", or "very much" bothered by the side effects ranged between 2.0% (cycle 15) and 20.5% (cycle 6). In contrast, in the docetaxel group, the proportion of patients who were "somewhat", "quite a bit", or "very much" bothered by the side effects increased substantially from baseline (6.3%). In all but one of the cycles of follow-up (20.0% [cycle 10]), the proportion of these patients was substantially above 25%, ranging from 30.0% (cycle 15) to 47.9% (cycle 3; Supplementary Table 3).

3.4. Impact of treatment on symptoms by PRO-CTCAE

Overall, PRO-CTCAE scores suggested that sotorasib was better tolerated compared with docetaxel (Fig. 2, Supplementary Figs. 3–5, Supplementary Tables 4–12) as detailed in the subsections below. In particular, for docetaxel, the symptoms showed a higher severity and stronger interference with daily/usual activities. However, in terms of frequency, both trial groups were similar.

3.4.1. Severity of symptoms

The impact of treatment on severity of symptoms suggested better outcomes with sotorasib compared with docetaxel (Fig. 2, Supplementary Table 4). At week 12 (cycle 5 day 1), compared with docetaxel, sotorasib improved the severity of pain (OR 2.9, 95% CI: 1.2, 7.0; $P=0.014$), aching muscles (OR 4.4, 95% CI: 1.6, 12.4; $P=0.005$), aching joints (OR 4.2, 95% CI: 1.4, 12.2; $P=0.009$), mouth or throat sores (OR 4.3, 95% CI: 1.6, 11.5; $P=0.004$), numbness (OR 2.1, 95% CI: 1.0, 4.3; $P=0.050$), and mouth cracking (OR 6.7, 95% CI: 0.0, 97873.0; $P=0.700$). In addition, based on PRO-CTCAE, sotorasib patients were less likely to lose fingernails (OR 0.13, 95% CI: 0.07, 0.25), have bumps on the nails (OR 0.16, 95% CI: 0.08, 0.30), or have a change in nail color (OR 0.06, 95% CI: 0.03, 0.12) (Supplementary Fig. 3). The severity of itchy skin was similar between sotorasib and docetaxel treatment groups

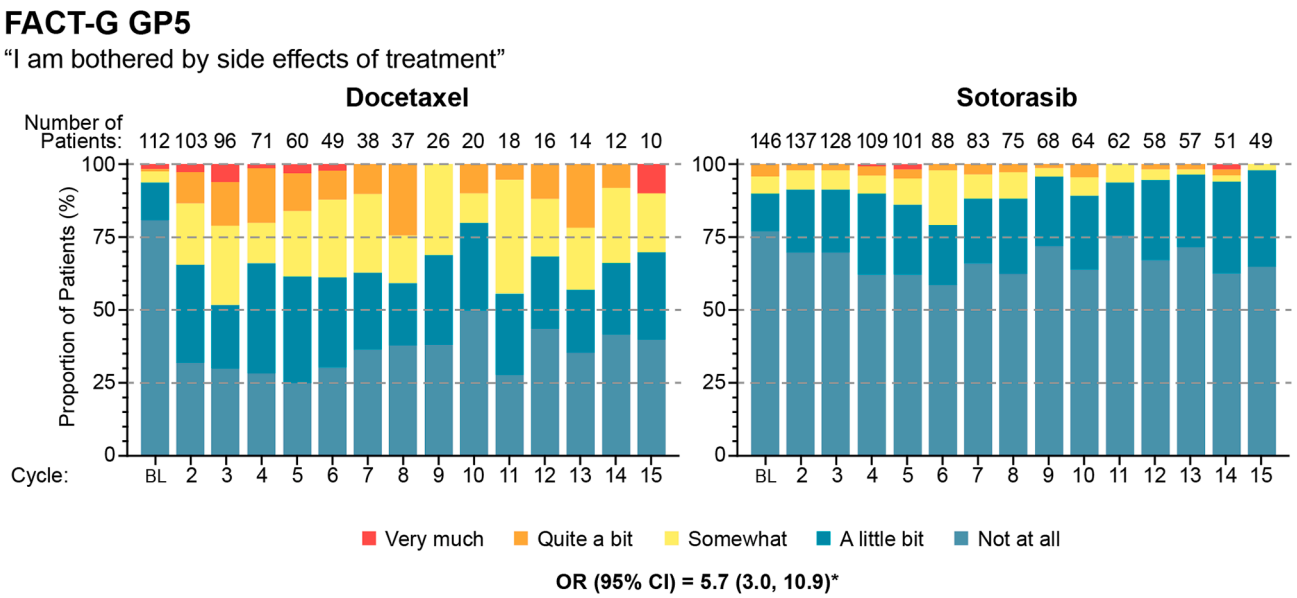

Fig. 1. Treatment side effects over time by FACT-G GP5. Data cutoff date: August 2, 2022. Patients completed the FACT-G GP5 on day 1 (administered by tablet in the clinic) of each cycle and at the safety follow-up. *OR of change from baseline to week 12, based on GEE model. BL, baseline; CI, confidence interval; FACT-G GP5, Functional Assessment of Cancer Therapy Tool General Form, single item "I am bothered by side effects of treatment", rated on a 5-point Likert scale; GEE, generalized estimating equation; OR, odds ratio.

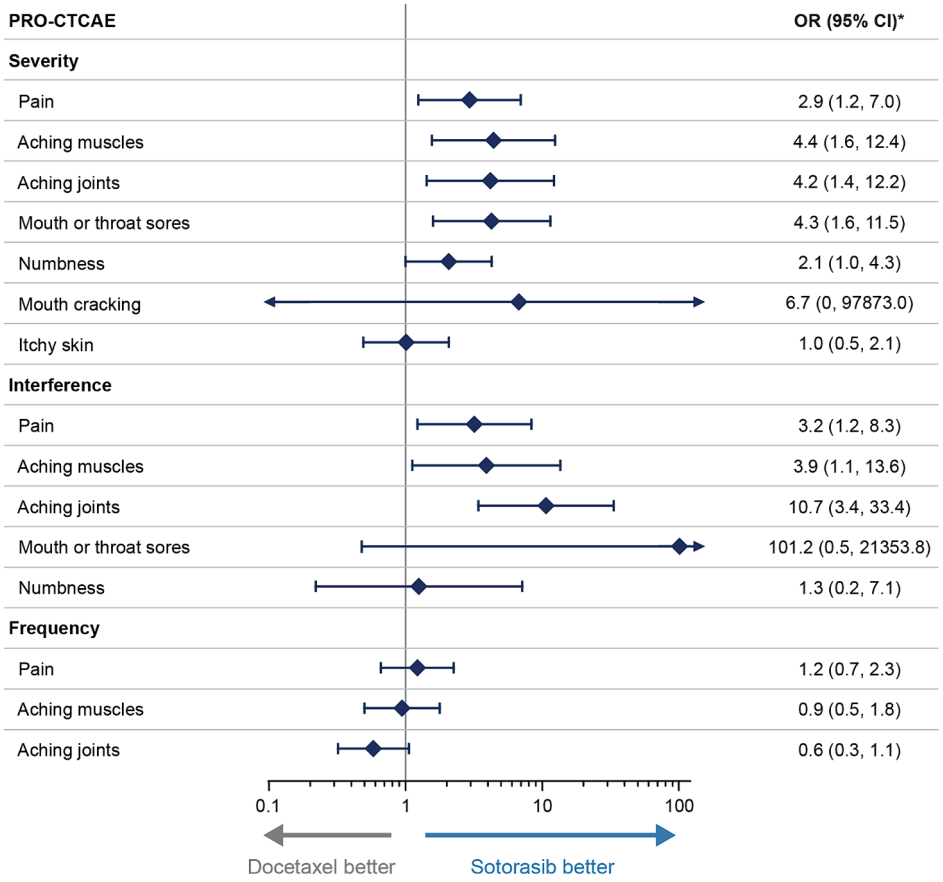

Fig. 2. Impact of treatment on symptoms by PRO-CTCAE (including severity, interference, and frequency) after 12 weeks of treatment. Data cutoff date: August 2, 2022. The analysis set included all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements (sotorasib, n = 148; docetaxel, n = 113). The displayed PRO-CTCAE list is comprehensive: there were no further assessments on severity, interference, or frequency of symptoms beyond the list presented here. *OR and 95% CIs were estimated using a generalized estimating equations model. Arrows indicate continuation of 95% CI past the OR graph range. An OR > 1.0 indicates higher improvement in symptom scale for sotorasib relative to docetaxel. CI, confidence interval; OR, odds ratio; PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events.

(OR 1.0, 95% CI: 0.5, 2.1; P=0.990) at week 12, with similar results observed at other cycles and overall (Fig. 2, Supplementary Table 4).

Consistent with the GEE analyses, the distribution of the severity responses from baseline up to cycle 15 suggested generally better outcomes with sotorasib over docetaxel (Fig. 3, Supplementary Table 5). The category "very severe" was more frequent in the docetaxel group compared with the sotorasib group post-baseline, with ranges for "severity of pain", "severity of aching muscles", and "severity of aching joints" up to 20.0% (cycle 15), 33.3% (cycle 10), and 20.0% (cycle 14), respectively, in the docetaxel group and much lower in the sotorasib group at up to 9.0% (cycle 4), 5.6% (cycle 2), and 3.2% (cycles 3 and 4), respectively. Post-baseline responses for the symptom severity categories "mild" and "none" combined were more frequent in the sotorasib group, with ranges of 45.2% (cycle 6) to 72.9% (cycle 8) for sotorasib vs 9.1% (cycle 10) to 57.1% (cycle 14) for docetaxel for pain, 56.3% (cycles 15) to 78.4% (cycle 7) for sotorasib vs 33.3% (cycle 12) to 75.0% (cycle 15) for docetaxel for aching muscles, and 50.0% (cycle 15) to 76.3% (cycle 7) for sotorasib vs 29.4% (cycle 7) to 72.2% (cycle 8) for docetaxel for aching joints. The distribution of the severity responses for mouth or throat sores, numbness, mouth cracking, and itchy skin is shown in Supplementary Table 5. Severity by worst response at baseline or all scheduled on-treatment visits, excluding follow-up visits, is shown in Supplementary Table 6.

3.4.2. *Interference of symptoms in daily/usual activities*

Patients treated with sotorasib reported less interference in daily/usual activities for pain (OR 3.2, 95% CI: 1.2, 8.3; P=0.018), aching muscles (OR 3.9, 95% CI: 1.1, 13.6; P=0.033), aching joints (OR 10.7, 95% CI: 3.4, 33.4; P<0.001), mouth or throat sores (OR 101.2, 95% CI: 0.5, 21353.8; P=0.091), and numbness (OR 1.3, 95% CI: 0.2, 7.1;

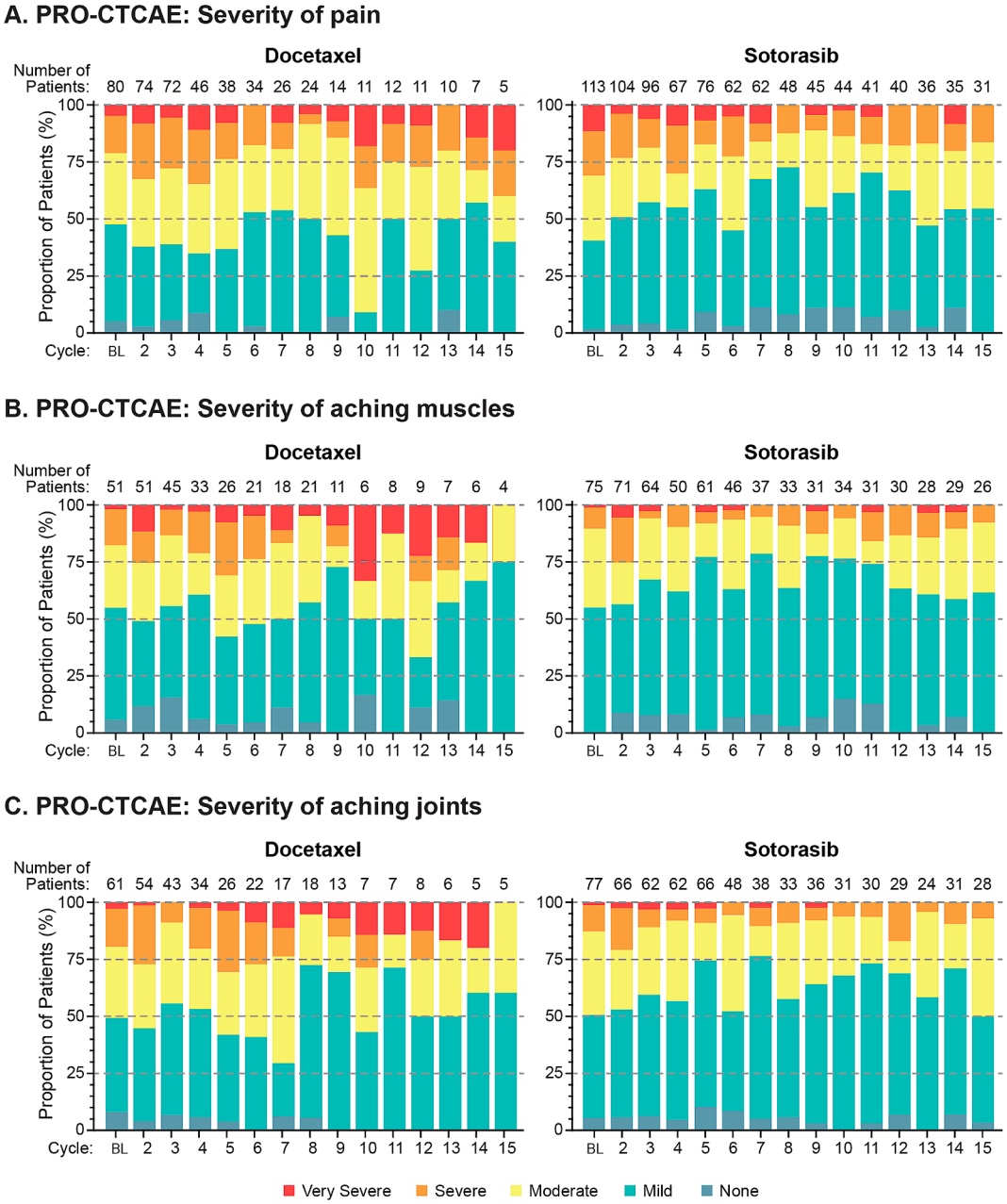

Fig. 3. Impact of side effect on QOL by PRO-CTCAE severity. Data cutoff date: August 2, 2022. Patients completed the PRO-CTCAE questionnaire at clinic visits only except for the screening visit. BL, baseline; PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events; QOL, quality of life.

P=0.80) at week 12 (Fig. 2, Supplementary Table 7). Similar results were observed at other cycles and overall (Supplementary Table 7).

Consistent with the GEE analyses, the distribution of the interference responses from baseline up to cycle 12 suggested better PROs with sotorasib compared with docetaxel (Supplementary Fig. 4; Supplementary Table 8). The category "very much" interference with daily/usual activities was more frequent in the docetaxel group compared with the sotorasib group post-baseline, with ranges for "interference of pain", "interference of aching muscles", and "interference of aching joints" up to 18.2% (cycle 10), 40.0% (cycle 10), and 28.6% (cycle 10), respectively, in the docetaxel group and much lower in the sotorasib group at up to 5.8% (cycle 5), 3.4% (cycle 9), and 3.4% (cycle 5), respectively. Post-baseline responses for the symptom interference categories of "a little bit" and "not at all" combined were more frequent in the sotorasib group, with ranges of 65.0% (cycle 6) to 85.0% (cycle 9) for sotorasib vs 44.4% (cycle 13) to 75.0% (cycle 8) for docetaxel for pain, 70.8% (cycle 2) to 86.7% (cycle 5) for sotorasib vs 48.9% (cycle 2) to 81.8% (cycle 9) for docetaxel for aching muscles, and 69.4% (cycle 2) to 86.4% (cycle 5) for sotorasib vs 44.0% (cycle 5) to 83.3% (cycle 13) for docetaxel for aching joints. The distribution of the interference responses for mouth or throat sores and numbness showed a generally similar pattern to that for pain, aching muscles, and aching joints (Supplementary Table 8). Interference by worst response at baseline or all scheduled on-treatment visits, excluding follow-up visits, is shown in Supplementary Table 9.

3.4.3. Frequency of symptoms

The frequency of pain (OR 1.2, 95% CI: 0.7, 2.3; *P*=0.520), aching muscles (OR 0.9, 95% CI: 0.5, 1.8; *P*=0.850), and aching joints (OR 0.6, 95% CI: 0.3, 1.1; *P*=0.760) were similar between treatment groups (Fig. 2, Supplementary Table 10). Generally similar results were observed in other cycles and overall (Supplementary Table 10).

Consistent with the GEE analyses, the distribution of the frequency responses from baseline up to cycle 15 are similar for sotorasib and docetaxel (Supplementary Fig. 5, Supplementary Table 11). The category "almost constantly" frequency of symptoms were similarly low for the docetaxel and sotorasib groups post-baseline, with "frequency of pain", "frequency of aching muscles", and "frequency of aching joints" ranging from 0% (cycle 15) to 16.7% (cycle 14), 0% (cycle 15) to 12.5% (cycle 12), and 0% (cycle 15) to 8.3% (cycle 14), respectively, in the docetaxel group and from 1.6% (cycle 10) to 12.3% (cycle 2), 0% (several cycles) to 2.9 (cycle 2), and 0% (several cycles) to 4.3% (cycle 2), respectively, in the sotorasib group. Results for the other categories of "frequently", "occasionally", "rarely", or "never" frequency of symptoms were in generally similar ranges between the docetaxel and sotorasib groups (Supplementary Fig. 5; Supplementary Table 11). Frequency by worst response at baseline or all scheduled on-treatment visits, excluding follow-up visits, is shown in Supplementary Table 12.

3.5. Further subscales of the EORTC QLQ-C30 and EORTC QLQ-LC13 instruments

Results for select subscales of the PRO instruments EORTC QLQ-C30 and EORTC QLQ-LC13 not previously reported in the primary article [18] are illustrated in Fig. 4A-B. Over a broad range of 38 symptoms and scales, 36 of the point estimates (change from baseline to week 12) favored sotorasib and only two-point estimates (vomiting and diarrhea) favored docetaxel. Of the 36 symptoms scales that favored sotorasib, significant differences between sotorasib and docetaxel were observed for 23 symptoms and scales (i.e., CIs did not cross 1; Fig. 4A-B). Of the two symptoms and scales that favored docetaxel (vomiting and diarrhea), a significant difference between sotorasib and docetaxel was observed for only diarrhea (Fig. 4A).

3.6. Impact of treatment on QOL over time by EQ-5D-5L and EQ-5D VAS

Patients treated with sotorasib reported significant improvements in mobility (OR 2.8, 95% CI: 1.4, 5.4; *P*=0.003), self-care (OR 2.9, 95% CI: 1.4, 6.3; *P*=0.006), and usual activities (OR 1.9, 95% CI: 1.0, 3.6; *P*=0.043) compared with baseline as reported in the EQ-5D-5L (Fig. 5A, Supplementary Table 13). Pain/discomfort demonstrated a trend towards improvement with sotorasib treatment (OR 1.6, 95% CI: 0.8, 3.1; *P*=0.150). Anxiety/depression was similar between both treatment arms (OR 1.0, 95% CI: 0.5, 1.8; *P*=0.920).

QOL worsened 5 days after initial docetaxel treatment (cycle 1 day 5) while remaining stable with sotorasib (mean change from baseline in EQ-5D VAS score: –8.4 vs 1.5) (Fig. 5B, Supplementary Table 14). After weeks of treatment (at cycle 5 day 1), mean EQ-5D VAS showed a long-term worsening of QOL with docetaxel while the EQ-5D VAS remained stable with sotorasib (–5.8 vs 2.2) (Fig. 5B, Supplementary Table 14).

3.7. Impact of treatment on severity of pain and daily functioning by BPI-SF

The differences in pain as assessed by BPI-SF are illustrated in Fig. 6A and in Supplementary Table 15 and Supplementary Table 16. Based on the change from baseline to week 12, the point estimates of 11 of 12 pain subscales favored sotorasib (Fig. 6A). However, all CIs included the OR 1, indicating no significant difference between treatment groups.

3.8. Impact of treatment on PGIC and PGIS

PGIC and PGIS consistently favored sotorasib over docetaxel. This was the case for all three symptoms of cough, chest pain, and dyspnea, as illustrated for the change from baseline to week 12 (Fig. 6B-C).

4. Discussion

The perceived burden of cancer-related symptoms has been reported to be higher among patients with advanced-stage (Stage IV) NSCLC, particularly for symptoms such as pain [30]. Patients with advanced disease have also reported a greater impact on their ability to carry out normal activities and on their QOL as a result of their cancer-related symptoms [30]. The FACT-G, PRO-CTCAE, EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-5L, BPI-SF, PGIC, and PGIS instruments/questionnaires have been validated [19–28] and are widely used to assess the impact of treatments on PROs in patients with NSCLC. These instruments were used to assess QOL in patients receiving sotorasib vs docetaxel in the CodeBreaK 200 trial, making this study the first to assess and report PRO data in patients receiving treatment with a $KRAS^{G12C}$ inhibitor in a randomized phase III trial vs docetaxel, which is a standard of care.

The change from baseline for PRO outcomes was assessed at week 12. This time point was used consistently over all PROs and it had been prespecified for key secondary PRO endpoints. Week 12 was selected, as it was sufficiently long to establish between-arm differences but short enough to allow for reasonably high completion rates. Furthermore, the timing is consistent with those of related NSCLC trials [31–33].

Collectively, the secondary and exploratory analyses of PROs from the CodeBreaK 200 trial demonstrated that treatment with sotorasib had more favorable outcomes with regards to treatment side effects and QOL, compared with treatment with docetaxel, in previously treated patients with advanced NSCLC bearing the *KRAS* G12C mutation. Over a broad range of instruments and outcomes, patients treated with sotorasib reported less severe symptoms than those treated with docetaxel; hence, they suffered less burden as a result of this difference. The only symptom that was significantly worse with sotorasib vs docetaxel was diarrhea. This finding is consistent with the adverse event profile of sotorasib [18]. In addition to improving clinical efficacy outcomes as already reported [18], sotorasib maintained QOL versus docetaxel suggesting that sotorasib may be a more tolerable treatment option for patients with pretreated, *KRAS* G12C-mutated advanced NSCLC.

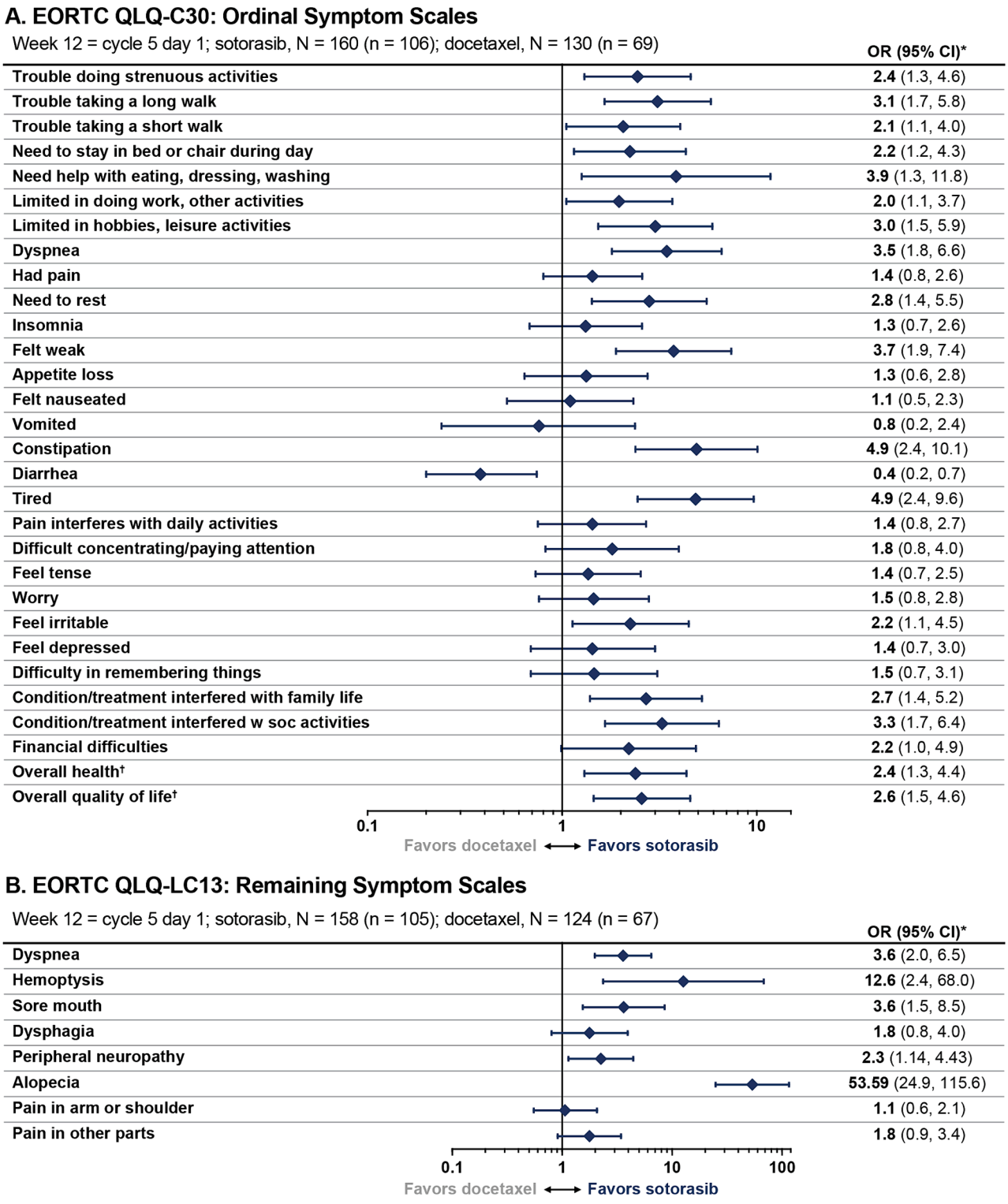

Fig. 4. Select subscales of the EORTC QLQ-C30 and EORTC QLQ-LC13 instruments: GEE model change from baseline to week 12. Data cutoff date: August 2, 2022. N=number of all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements. n = number of evaluable patients for the PRO measure. Global health status, physical functioning, cough, and chest pain were reported in the primary publication and are not reported here. *OR and 95% CIs were estimated using a GEE model. An OR > 1.0 indicates higher improvement in symptom scale for sotorasib relative to docetaxel. †Reciprocal values. CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Lung Cancer 13; GEE, generalized estimating equations; PRO, patient-related outcome; OR, odds ratio.

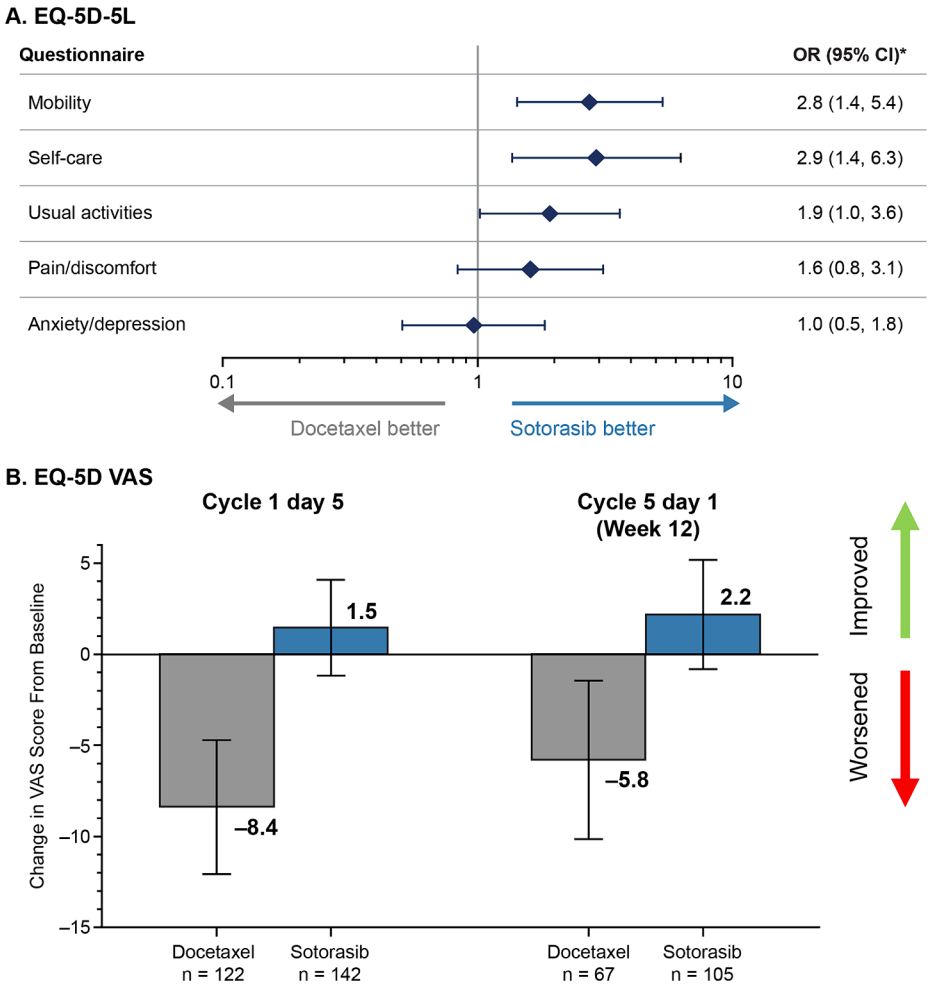

Fig. 5. Impact of treatment on health status and QOL by EQ-5D-5L and EQ-5D VAS. Data cutoff date: August 2, 2022. The analysis set included all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements (sotorasib, n = 160; docetaxel, n = 138). Randomization stratification factors were number of prior lines of therapy in advanced disease (1 vs 2 vs > 2), race (Asian vs non-Asian), and history of CNS involvement (yes vs no). *OR and 95% CIs were estimated using GEE model. An OR > 1.0 indicates higher improvement in symptom scale for sotorasib relative to docetaxel. CI, confidence interval; CNS, central nervous system; EQ-5D-5L, 5-level European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire 5 dimensions; EQ-5D, European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire 5 Dimension; GEE, generalized estimating equation; OR, odds ratio; QOL, quality of life; VAS, visual analog scale.

Previously reported findings from the CodeBreaK 200 study demonstrated that sotorasib exhibited clinically meaningful improvement in PROs compared with docetaxel [18]. The impact of sotorasib compared with docetaxel treatment on symptom burden and QOL was based on PROs as assessed by the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires [18]. Compared with docetaxel, sotorasib showed clinically meaningful differences in delaying the time to deterioration in global health status (HR, 0.69; 95% CI: 0.53, 0.91), physical functioning (HR, 0.69; 95% CI: 0.52, 0.92), and cancer-related symptoms of dyspnea (HR, 0.63; 95% CI: 0.48, 0.83), and cough (HR, 0.55; 95% CI: 0.38, 0.80) [18]. Changes from baseline for global health status, physical functioning, and dyspnea consistently favored sotorasib over docetaxel through week 12 (least square means of change differences: 6.93, 8.78, and –10.09, respectively, with descriptive *P*-values < 0.001 [descriptive due to the hierarchy of testing] [18]). From baseline to week 12, patients in the sotorasib arm reported an improvement in symptoms for cough, compared with patients in the docetaxel arm (OR 3.21, 95% CI: 1.55, 6.65; *P*=0.002); however, no differences were seen in chest pain between the treatment arms [18]. Results from the secondary and exploratory endpoints of the CodeBreaK 200 study reported here show that, overall, side effects and symptoms were generally milder for patients treated with sotorasib than for those treated with docetaxel. Frequency of side effects and symptoms appeared to be the same for the treatment groups. The data suggest that patients treated with docetaxel experienced more severe side effects and symptoms, beginning at cycle 2 of the study. These findings, along with those previously reported [18], demonstrate that sotorasib improves or maintains health-related QOL compared with docetaxel in patients with pretreated *KRAS* G12C-mutated advanced NSCLC.

Historically, treatment toxicity has been evaluated through investigators' judgements and not through the perspective of patients. Studies have demonstrated some degree of discordance between the assessment of symptom intensity from the perspective of both patients and physicians [34–36]. Those reports have demonstrated that the collection of medical records may not provide adequate documentation of symptoms and that caregivers and physicians have failed to rate patient symptoms in agreement with patients [34,35]. Patient-centered approaches, such as assessing the patient experience, are critical to understanding the impact of treatment and care.

The strength of our analysis is that it reports PROs from a randomized, multicountry, multicenter, open-label, phase III trial that were part of the secondary and exploratory endpoints and were assessed using validated instruments for measuring treatment- and disease-related symptoms and health-related QOL measures. One limitation of this

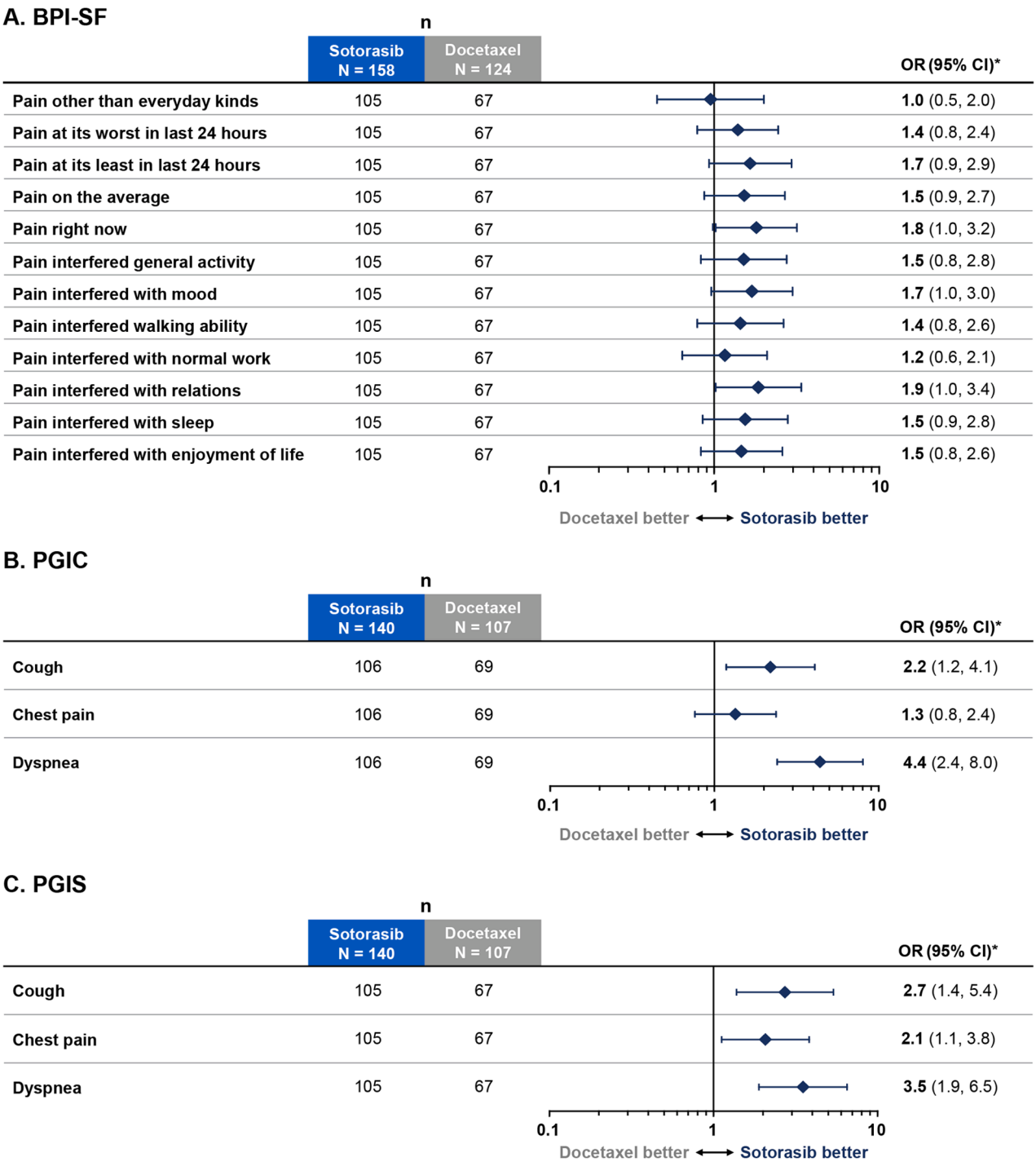

Fig. 6. Estimates of change from baseline for BPI-SF, PGIC, and PGIS. Data cutoff date: August 2, 2022. N=number of all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements. n = number of evaluable patients for the PRO measure. Randomization stratification factors: number of prior lines of therapy in advanced disease (1 vs 2 vs > 2), race (Asian vs non-Asian), and history of CNS involvement (yes vs no). *OR, 95% CI, and *P*-value are estimated using a GEE model based on PGIC results as the dependent variable, intercept, time, treatment, treatment-by-time interaction and randomization stratification factors as fixed effects. All post-baseline visits are considered excluding follow-up visits. An OR > 1.0 indicates higher improvement in symptom scale for sotorasib relative to docetaxel. BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; CNS, central nervous system; GEE, generalized estimating equation; OR, odds ratio. PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PRO, patient-reported outcome.

PRO analysis is the open-label design of the trial. However, there is a growing body of literature suggesting that open-label bias should not limit the interpretation of PRO data. In particular, if the PRO benefits are large and meaningful, as has been observed in the CodeBreaK 200 study, the conclusions from the PRO results should be considered reliable. Based on data from a study that compared blinded to unblinded PRO data in NSCLC, Lord-Bessen et al (2023) [37] concluded that open-label bias should not limit interpretation of large and meaningful treatment effects on PROs. Furthermore, Mouillet et al (2020) [38], based on an analysis of 110 prostate cancer RCTs, found no evidence of significant bias for PROs due to the absence of blinding. Finally, based on a systematic literature review of 23 immunotherapy studies of advanced/

metastatic patients, Anota et al (2022) [39] found that trial design had no impact on PRO completion rates or baseline scores.

Another potential limitation of the PRO assessment is that PROs were collected only while patients were on treatment. This trial design, however, was intentional, and this approach is aligned with PRO collection in all related key PRO studies [31,40–42]. The key rationale for this approach is the intention to quantify the PROs associated with the treatment under investigation, and not the PROs associated with subsequent treatment. A continued PRO collection after investigational product had stopped would have conflicted with this intention and would therefore have biased the results. Furthermore, a continued PRO data collection would have been associated with feasibility issues as PROs were collected on-site at clinic visits days. These on-site visits were no longer scheduled subsequently. It would have required patients to come to the site solely for the purpose of PRO data collection. Continuing PRO data collection at home via an electronic device was not feasible, as it would have required additional logistics and would have conflicted with licensing and instrument validation.

To understand the challenges associated with collecting PRO data only while patients were on the investigational product for CodeBreaK 200, it is worth looking at the patient disposition for PRO outcomes (Supplementary Fig. 6). Missing data due to death and adverse events were similar in both arms, and therefore do not seem to be a biasing factor. However, disease progression was more in the docetaxel arm. As disease progression is a negative event, the higher amount of missing data due to disease progression does not weaken but strengthen the conclusion that sotorasib is superior. In the patient disposition, the difference in treatment discontinuation for other reasons is mainly due to the 23 patients who never took docetaxel. This potential issue has been addressed via an additional sensitivity analysis, where we adjusted for clinically relevant covariates (Supplementary Table 17). This sensitivity analysis leads to the same conclusion that sotorasib is superior to docetaxel with respect to the impact of treatment on patients' QOL. All point estimates shift slightly in favor of sotorasib.

Results from our analysis show that although patients treated with sotorasib experienced cancer-related symptoms (such as pain), these symptoms were less severe and had a minimal impact on activities of daily living (such as mobility, self-care, and other activities), compared with symptoms experienced by patients treated with docetaxel. Thus, our findings demonstrate that sotorasib treatment improved the severity and interference of symptoms such as pain and positively impacted the lives of patients receiving treatment, providing further support for a clinically meaningful QOL benefit with sotorasib.

5. Role of the funding source

Representatives of the sponsor, Amgen Inc., designed the clinical study in collaboration with some of the study investigators. Amgen Inc. managed patient data collection at the study sites, maintained the study database, performed the analyses, funded medical writing support, paid publication costs, and paid the open access charge for this article.

CRediT authorship contribution statement

David M. Waterhouse: Investigation, Resources, Writing – review & editing. **Sacha Rothschild:** Investigation, Resources, Writing – review & editing. **Christophe Dooms:** Investigation, Resources, Writing – review & editing. **Bertrand Mennecier:** Investigation, Resources, Writing – review & editing. **Farastuk Bozorgmehr:** Investigation, Resources, Writing – review & editing. **Margarita Majem:** Investigation, Resources, Writing – review & editing. **Michel H. van den Heuvel:** Investigation, Resources, Writing – review & editing. **Helena Linardou:** Investigation, Resources, Writing – review & editing. **Byoung Chul Cho:** Investigation, Resources, Writing – review & editing. **Rachel Roberts-Thomson:** Investigation, Resources, Writing – review & editing. **Kentaro Tanaka:** Investigation, Resources, Writing – review & editing. **Normand Blais:** Investigation, Resources, Writing – review & editing. **Gustavo Schvartsman:** Investigation, Resources, Writing – review & editing. **Karin Holmskov Hansen:** Investigation, Resources, Writing – review & editing. **Izabela Chmielewska:** Investigation, Resources, Writing – review & editing. **Martin D. Forster:** Investigation, Resources, Writing – review & editing. **Christina Giannopoulou:** Conceptualization, Data curation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Björn Stollenwerk:** Conceptualization, Data curation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Cynthia C. Obiozor:** Conceptualization, Data curation, Methodology, Visualization, Writing – review & editing, Writing – original draft. **Yang Wang:** Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – review & editing, Writing – original draft. **Silvia Novello:** Investigation, Resources, Writing – review & editing.

Declaration of competing interest

David M. Waterhouse received consulting fees from Bristol Myers Squibb (BMS), Amgen, Janssen, Merck, Fresenius Kabi, and Novartis; received honoraria from BMS, AstraZeneca, Amgen, Janssen, EMD Serono, Fresenius Kabi, and Sanofi; received support to attend meetings and/or travel from BMS and Amgen; and participated on a data safety monitoring board or advisory board for BMS, AstraZeneca, AbbVie, Amgen, Janssen, Eisai, EMD Serono, Merck, Pfizer, Fresenius Kabi, Sanofi, Astellas, Gilead, Takeda, Daiichi, and Bayer. **Sacha Rothschild** received grants or research support from AstraZeneca, Merck Serono, Roche Pharma, and Amgen; received consulting fees from Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Eli Lilly, Janssen, Merck KG, MSD, Novartis, Otsuka, Pfizer, PharmaMar, Roche Pharma, Roche Diagnostics, Sanofi Aventis, and Takeda; received honoraria from Roche Pharma, BMS, AstraZeneca, Amgen, MSD Oncology, Novartis, Roche Diagnostics, and Takeda; received payment for expert testimony from Roche, AstraZeneca, and BMS; received support for attending meetings and/or travel from Roche Pharma, Eli Lilly, BMS, Amgen, AstraZeneca, and MSD; participated on a data safety monitoring board or advisory board for Roche Pharma; and is the vice president of the Swiss Group for Clinical Cancer Research (SAKK) and elected member of the Swiss Federal Drug Commission (Federal Health Office). **Christophe Dooms** has nothing to disclose. **Bertrand Mennecier** received honoraria from Amgen, Roche, AstraZeneca, Pharma Mar, Eli Lilly, BMS, MSD, Sanofi, Takeda, and Pfizer; and received support for attending meetings and/or travel from MSD, Roche, BMS, AstraZeneca, and Takeda. **Farastuk Bozorgmehr** received grant/research support from Roche and AstraZeneca; received honoraria from Novocure, Daiichi Sankyo, GSK, and AstraZeneca, received support for attending meetings and/or travel from Janssen; and participated in a data safety monitoring board or advisory board for Amgen, AstraZeneca, Daiichi Sankyo, and Janssen. **Margarita Majem** received consulting fees from AstraZeneca, Roche, MSD, Janssen, and Sanofi; received honoraria from MSD, Roche, AstraZeneca, Casen Recordati, Takeda, and Helsinn; received support for attending meetings and/or travel from MSD, Pfizer, Roche, and AstraZeneca, and is the vice president of ICAPEM and a board member of AEC Barcelona. **Michel M. van den Heuvel** participated on a data safety monitoring board or advisory board for Amgen. **Helena Linardou** received payment or honoraria for lectures and/or speakers bureaus from Roche, AstraZeneca, Pfizer, BMS, MSD, Novartis, Amgen, and GSK; received support for attending meetings and/or travel from Pfizer and Roche; participated on a data safety monitoring board or advisory board for Roche, AstraZeneca, MSD, BMS, Novartis, Pfizer, and Amgen; and held unpaid positions in non-profit organizations, including president of a scientific committee in the Hellenic Cooperative Oncology Group and board member for Hellenic Foundation of Cancer Research, FairLife Lung Cancer, and W4O-Hellas. **Byoung Chul Cho** received grant/research support from MOGAM Institute, LG Chem, Oscotec, Interpark Bio Convergence Corp, GI Innovation, GI-Cell, Abion, AbbVie,

AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, Champions Oncology, CJ Bioscience, CJ Blossom Park, Cyrus, Dizal Pharma, Genexine, Janssen, Lilly, MSD, Novartis, Nuvalent, Oncternal, Ono, Regeneron, Dong-A ST, Bridge Biotherapeutics, Yuhan, ImmuneOncia, Illumina, Kanaph Therapeutics, Therapex, J INTS BIO, Hanmi, CHA Bundang Medical Center, and Vertical Bio AG. **Rachel Roberts-Thomson** received royalties from Champions Oncology, Crown Bioscience, Imagen, and PearlRiver Bio GmbH; received consulting fees from Abion, BeiGene, Novartis, AstraZeneca, Boehringer Ingelheim, Roche, BMS, CJ, CureLogen, Cyrus Therapeutics, Ono, Onegene Biotechnology, Yuhan, Pfizer, Eli Lilly, GI-Cell, Guardant, HK Inno-N, Imnewrun Biosciences Inc., Janssen, Takeda, MSD, MedPacto, Blueprint Medicines, RaND Bio, and Hanmi; received honoraria from ASCO, AstraZeneca, Guardant, Roche, ESMO, IASLC, Korean Cancer Association, Korean Society of Medical Oncology, Korean Society of Thyroid-Head and Neck Surgery, Korean Cancer Study Group, Novartis, MSD, The Chinese Thoracic Oncology Society, and Pfizer; participated on a scientific advisory board for Kanaph Therapeutics, Bridge Biotherapeutics, Cyrus Therapeutics, Guardant Health, Oscotec Inc, J INTS Bio, Therapex Co., Ltd, Gilead, and Amgen; was a board member for J INTS BIO; owned stock in TheraCanVac Inc, Gencurix Inc, Bridge Biotherapeutics, KANAPH Therapeutic Inc, Cyrus therapeutics, Interpark Bio Convergence Corp., and J INTS BIO; was employed by Yonsei University Health System and is a founder of DAAN Biotherapeutics. **Kentaro Tanaka** received consulting fees from Pfizer and received honoraria from Chugai Pharmaceutical, AstraZeneca, Eli Lilly, Takeda Pharmaceutical, Novartis, Ono Pharmaceutical, Daiichi Sankyo, Merck, MSD, and BMS. **Normand Blais** received consulting and speakership fees from Amgen. **Gustavo Schvartsman** received consulting fees from AstraZeneca, BMS, Merck, Sharp & Dome, and Daiichi Sankyo; received honoraria from Roche, Amgen, Adiu, and Pfizer; and received support for attending meetings and/or travel from Merck, Sharp & Dome and Daiichi Sankyo. **Karin Holmskov Hansen** participated in clinical trial safety meetings for MSD and Incyte (not paid) and was head of the Danish Oncology Group until February 2023 (not paid) and a member of the Expert Committee under the Danish Medicines Council (not paid). **Izabela Chmielewska** received consulting honoraria from Amgen; and received speakership fees from Amgen, BMS, Takeda, Roche, and MSD. **Martin D. Forster** received grant/research support from Cancer Research UK Early Detection Committee Program Grant, Bristol Myers Squibb Research Grant, NIHR RfPB Grant, Cancer Research UK Science Committee Multidisciplinary Project Award, Merck Educational Grant, MSD Educational Grant, Cancer Research UK Science Committee Multidisciplinary Project Award, MRC BMC:DPFS Grant Award, and Boehringer Ingelheim Educational Grant and received consulting fees from Amgen and participated in an Advisory Board for Amgen. **Christina Giannopoulou** is an employee of Amgen Europe GmbH and holds stock in Amgen. **Björn Stollenwerk** is an employee of Amgen Europe GmbH and holds stock in Amgen. **Cynthia C. Obiozor** is an employee of and holds stock in Amgen. **Yang Wang** is an employee of and holds stock in Amgen.**Silvia Novello** received honoraria from AstraZeneca, Amgen, Thermo Fisher, MSD, Novartis, Sanofi, Roche, Pfizer, Takeda, and Janssen and participated on a data safety monitoring board or advisory board from Pfizer, AstraZeneca, Sanofi, Jannsen, and Daiichi.

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Data sharing statement

Qualified researchers can request data from Amgen clinical studies. Complete details are available at https://www.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2024.107921.

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