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Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with *KRAS*^{G12C} mutation: a randomised, open-label, phase 3 trial

Adrianus Johannes de Langen, Melissa L Johnson, Julien Mazieres, Anne-Marie C Dingemans, Giannis Mountzios, Miklos Pless, Jürgen Wolf, Martin Schuler, Hervé Lena, Ferdinandos Skoulidis, Yasuto Yoneshima, Sang-We Kim, Helena Linardou, Silvia Novello, Anthonie J van der Wekken, Yuanbin Chen, Solange Peters, Enriqueta Felip, Benjamin J Solomon, Suresh S Ramalingam, Christophe Dooms, Colin R Lindsay, Carlos Gil Ferreira, Normand Blais, Cynthia C Obiozor, Yang Wang, Bhakti Mehta, Tracy Varrieur, Gataree Ngarmchamnanrith, Björn Stollenwerk, David Waterhouse, Luis Paz-Ares*, for the CodeBreaK 200 Investigators†*

Summary

Background Sotorasib is a specific, irreversible inhibitor of the GTPase protein, KRAS^{G12C}. We compared the efficacy and safety of sotorasib with a standard-of-care treatment in patients with non-small-cell lung cancer (NSCLC) with the *KRAS*^{G12C} mutation who had been previously treated with other anticancer drugs.

Methods We conducted a randomised, open-label phase 3 trial at 148 centres in 22 countries. We recruited patients aged at least 18 years with *KRAS*^{G12C}-mutated advanced NSCLC, who progressed after previous platinum-based chemotherapy and a PD-1 or PD-L1 inhibitor. Key exclusion criteria included new or progressing untreated brain lesions or symptomatic brain lesions, previously identified oncogenic driver mutation other than *KRAS*^{G12C} for which an approved therapy is available (eg *EGFR* or *ALK*), previous treatment with docetaxel (neoadjuvant or adjuvant docetaxel was allowed if the tumour did not progress within 6 months after the therapy was terminated), previous treatment with a direct KRAS^{G12C} inhibitor, systemic anticancer therapy within 28 days of study day 1, and therapeutic or palliative radiation therapy within 2 weeks of treatment initiation. We randomly assigned (1:1) patients to oral sotorasib (960 mg once daily) or intravenous docetaxel (75 mg/m² once every 3 weeks) in an open-label manner using interactive response technology. Randomisation was stratified by number of previous lines of therapy in advanced disease (1 *vs* 2 *vs* >2), ethnicity (Asian *vs* non-Asian), and history of CNS metastases (present or absent). Treatment continued until an independent central confirmation of disease progression, intolerance, initiation of another anticancer therapy, withdrawal of consent, or death, whichever occurred first. The primary endpoint was progression-free survival, which was assessed by a blinded, independent central review in the intention-to-treat population. Safety was assessed in all treated patients. This trial is registered at ClinicalTrials.gov, NCT04303780, and is active but no longer recruiting.

Findings Between June 4, 2020, and April 26, 2021, 345 patients were randomly assigned to receive sotorasib (n=171 [50%]) or docetaxel (n=174 [50%]). 169 (99%) patients in the sotorasib group and 151 (87%) in the docetaxel group received at least one dose. After a median follow-up of 17·7 months (IQR 16·4–20·1), the study met its primary endpoint of a statistically significant increase in the progression-free survival for sotorasib, compared with docetaxel (median progression-free survival 5·6 months [95% CI 4·3–7·8] *vs* 4·5 months [3·0–5·7]; hazard ratio 0·66 [0·51–0·86]; p=0·0017). Sotorasib was well tolerated, with fewer grade 3 or worse (n=56 [33%] *vs* n=61 [40%]) and serious treatment-related adverse events compared with docetaxel (n=18 [11%] *vs* n=34 [23%]). For sotorasib, the most common treatment-related adverse events of grade 3 or worse were diarrhoea (n= 20 [12%]), alanine aminotransferase increase (n=13 [8%]), and aspartate aminotransferase increase (n=9 [5%]). For docetaxel, the most common treatment-related adverse events of grade 3 or worse were neutropenia (n=13 [9%]), fatigue (n=9 [6%]), and febrile neutropenia (n=8 [5%]).

Interpretation Sotorasib significantly increased progression-free survival and had a more favourable safety profile, compared with docetaxel, in patients with advanced NSCLC with the *KRAS*^{G12C} mutation and who had been previously treated with other anticancer drugs.

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Introduction

Over the past decade, important advancements in the treatment of non-small-cell lung cancer (NSCLC) include the development of targeted therapies for actionable genomic alterations, anti-angiogenic therapy, and immune checkpoint inhibitors.[1–3] For patients without an actionable alteration, the standard of care in advanced disease is platinum-based chemotherapy and immunotherapy given

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for manuscripts, including randomised controlled clinical trials, published between database inception and Dec 2, 2022, without language restrictions, using the search terms "non–small-cell lung cancer", "treatment", "standard of care", and "*KRAS*^{G12C}". The *KRAS*^{G12C} mutation is a key oncogenic driver occurring in 13–16% of patients with non–squamous non-small-cell lung cancer (NSCLC). The first-line treatments for patients with advanced NSCLC without actionable mutations, which can be given concurrently or sequentially, are platinum-based therapy and immunotherapy. Following the progression of NSCLC, few treatment options exist and the prognosis is poor. The taxane docetaxel is a standard of care, but efficacy is modest with notable toxic effects and decline of health-related quality of life. Docetaxel, in combination with ramucirumab, can be used in younger patients who might tolerate greater toxicity to achieve an efficacious response. Nintedanib has also shown to be efficacious in combination with docetaxel for advanced NSCLC, but this combination is not widely adopted globally. We previously reported data from the phase 1/2 CodeBreaK 100 clinical trial indicating that sotorasib, a KRAS^{G12C} inhibitor, showed a durable overall response rate of 41%, 2-year overall survival of 33%, and a favourable safety profile in patients with advanced NSCLC with the *KRAS*^{G12C} mutation and who had been previously treated with other anticancer drugs. The KRAS^{G12C} inhibitor, adagrasib, has also been reported to be efficacious in this patient population.

Added value of this study

CodeBreaK 200 is the first global phase 3 randomised controlled trial comparing the efficacy and safety of a KRAS^{G12C} inhibitor, sotorasib, versus standard-of-care docetaxel in patients with previously treated advanced *KRAS*^{G12C}-mutant NSCLC. Sotorasib is the first KRAS^{G12C} inhibitor to show statistically significant improvement in progression-free survival compared with standard-of-care docetaxel, with a 34% decrease in the relative risk of disease progression or death with sotorasib.

Implications of all the available evidence

Our data show that oral sotorasib had improved efficacy, with a better toxicity profile and quality of life, compared with intravenous docetaxel in patients with advanced NSCLC with the *KRAS*^{G12C} mutation and who had been previously treated with other anticancer drugs. Sotorasib should be considered as a treatment option for these patients, who have a substantial unmet need.

concurrently or sequentially.[4,5] At disease progression, few clinically approved treatment options exist, with docetaxel as a recommended treatment option.[4,5] Historically, docetaxel has shown modest clinical benefit (12–14% overall response rate, median progression-free survival of 3–4 months, and median overall survival of 8–9 months) at the expense of substantial toxic effects requiring intense mitigation in both hospital and outpatient clinic.[6–10] Other treatment options for this patient population include docetaxel in combination with ramucirumab or nintedanib.[11–13] However, docetaxel in combination with ramucirumab is not widely considered for patients aged 65 years or older, who might be unable to tolerate greater toxicity to achieve an efficacy benefit, and the combination of docetaxel and nintedanib is not widely adopted globally. Safe and effective therapeutic options beyond docetaxel are urgently needed for these patients with advanced NSCLC.

Activating mutations in *KRAS* are present in 25–39% of non-squamous NSCLCs, with the *KRAS*^{G12C} mutation occurring in 13–16% of lung adenocarcinomas.[14–17] The *KRAS*^{G12C} mutation is nearly mutually exclusive with known actionable driver genomic alterations (eg, *EGFR, ALK, ROS1, BRAF, MET, RET, NTRK,* and *HER2*).[18–20] For over 40 years, *KRAS* was considered undruggable, underscoring the unmet need for a targeted therapy versus chemotherapy for these patients. In 2013, a targetable regulatory pocket on the KRAS^{G12C} protein was discovered.[21] Sotorasib, a small molecule that specifically and irreversibly inhibits the KRAS^{G12C} protein, covalently binds the cysteine residue in this P2 regulatory pocket, trapping KRAS^{G12C} in the inactive GDP-bound state and preventing downstream signalling in cancer cells, thereby producing a decrease in oncogenesis (appendix p 4).[22]

We previously reported the phase 2 CodeBreaK 100 data,[23] showing that sotorasib has clinical efficacy when used as monotherapy in patients with advanced NSCLC with the *KRAS*^{G12C} mutation and who had been previously treated with other anticancer drugs, with an overall response rate of 37·1%, median progression-free survival of 6·8 months, and a median overall survival of 12·5 months.[23] Treatment-related adverse events were generally mild and manageable, and patient-reported outcomes improved or remained stable.[23,24] Here, we report results from the phase 3, randomised, controlled CodeBreaK 200 trial, comparing the efficacy, safety, and patient-reported outcomes of sotorasib with those of docetaxel in patients with *KRAS*^{G12C}-mutated advanced NSCLC who had disease progression on previous platinum-based chemotherapy and a checkpoint inhibitor.

Methods

Study design and participants

In this randomised, multicentre, open-label, phase 3 trial, we enrolled patients with *KRAS*^{G12C}-mutated advanced NSCLC, who had disease progression after previous platinum-based chemotherapy and a PD-1 or PD-L1 inhibitor, at 148 academic and community centres in 22 countries (appendix p 5).

Initially, the study was planned to enrol 650 patients and powered for progression-free survival and overall survival. Following the observed clinical benefits of sotorasib in the CodeBreaK 100 phase 2 trial[23] and per regulatory feedback, the protocol was amended in February, 2021, to decrease the sample size to approximately 330 patients, which was only powered for progression-free survival, to limit the overall number of patients treated with docetaxel. Additionally, crossover from docetaxel to sotorasib upon centrally confirmed radiological progression was allowed.

Eligible patients were aged at least 18 years, with histologically or cytologically documented, locally advanced and unresectable or metastatic NSCLC, with the *KRAS*^{G12C} mutation confirmed via central laboratory testing using the therascreen *KRAS* RGQ PCR Kit (Qiagen, Germantown, MD, USA). Brain MRI with contrast or brain contrast-enhanced CT was obtained at screening. Eligible patients should have had tumour progression after receiving at least one previous systemic therapy for advanced disease, including platinum-based combination chemotherapy and a checkpoint inhibitor (as one line or individual lines, unless contraindicated), have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1). Patients with treated, stable brain metastases were eligible.

Key exclusion criteria included new or progressing untreated brain lesions or symptomatic brain lesions, previously identified oncogenic driver mutation other than *KRAS*^{G12C} for which an approved therapy is available (eg, *EGFR* or *ALK*), previous treatment with docetaxel (neoadjuvant or adjuvant docetaxel was allowed if the tumour did not progress within 6 months after the therapy was terminated), previous treatment with a direct KRAS^{G12C} inhibitor, systemic anticancer therapy within 28 days of study day 1, and therapeutic or palliative radiation therapy within 2 weeks of treatment initiation. Complete eligibility criteria are provided in the appendix (p 55). 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.

Randomisation and masking

Patients were randomly assigned (1:1) to either sotorasib or docetaxel in an open-label manner using interactive response technology. The randomisation number was provided to the study centre by the interactive response technology system. Randomisation was stratified by the number of previous lines of therapy in advanced disease (1 *vs* 2 *vs* >2), ethnicity (Asian *vs* non-Asian), and history of CNS metastases (present or absent).

Procedures

Patients received either sotorasib 960 mg orally once daily or docetaxel 75 mg/m² intravenously every 3 weeks. Treatment continued until an independent central confirmation of disease progression, intolerance, initiation of another anticancer therapy, withdrawal of consent, or death, whichever occurred first. Patients were allowed to continue with either drug after independent central confirmation of radiographic progression if there appeared to be clinical benefit; treatment was discontinued if continued growth of tumour was detected on a subsequent scan.

Tumour assessment was done by contrast-enhanced MRI or CT scan of brain, chest, abdomen, and pelvis at screening, every 5–7 weeks from the first day of treatment (defined as cycle 1 day 1, with each cycle being 21 days) until week 49, then every 8–10 weeks thereafter until independent central confirmation of progression, start of another anticancer therapy, withdrawal of consent, loss to follow-up, or death, whichever occurred first.

Outcomes

The primary endpoint was progression-free survival by blinded independent central review (BICR) per RECIST (version 1.1). Key secondary endpoints included overall survival, overall response rate, and patient-reported outcomes (change from baseline to week 12 for dyspnoea, cough, chest pain, global health status, and physical functioning). Other secondary endpoints were duration of response, disease control rate, time to response, safety, patient-reported outcomes (time to deterioration), and pharmacokinetics of sotorasib and its major metabolites. Progression-free survival 2 was an exploratory endpoint.

Progression-free survival was defined as the time from randomisation until disease progression or death from any cause, whichever occurred first (appendix p 9). Overall survival was defined as the time from randomisation to death from any cause. Overall response rate was defined as the sum of the confirmed complete response rate and confirmed partial response rate by BICR. Duration of response was measured from the first complete or partial response until progressive disease or death, whichever occurred first. Progression-free survival 2 was defined as the time from randomisation to disease progression on subsequent treatment, as assessed by an investigator, or death from any cause, whichever occurred first. Patient-reported outcomes were assessed using European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) and Quality-of-life Questionnaire Core 13 (EORTC QLQ-LC13). We recorded adverse events from the first study dose through up to 30 days after the end of treatment and graded them according to the National

Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

Statistical analysis

Approximately 330 patients were planned for enrolment. At least 230 progression-free survival events would be required to have 90% power to show a statistically significant difference in progression-free survival between treatment groups at a one-sided α level of 2·5% assuming a hazard ratio (HR) of 0·65 for the sotorasib versus docetaxel group. Efficacy was assessed in the intention-to-treat population, according to the treatment to which they were randomly assigned. Patients who were randomly assigned but withdrew before receiving the treatment were censored at the date of randomisation. Safety was assessed in patients who received at least one dose of the trial drug. We planned one interim analysis for progression-free survival at approximately 70% information fraction followed by the progression-free survival primary analysis using the Lan-DeMets O'Brien-Fleming spending function to minimise the overall type I error. Overall survival and overall response rate were tested after statistical significance was found in the primary endpoint of progression-free survival with the use of Maurer-Bretz multiple testing procedure.

As per the protocol amendment that decreased the sample size by half, the study was powered to test the superiority of sotorasib over docetaxel for progression-free survival but not overall survival. We estimated the distribution of progression-free survival and overall survival using the Kaplan-Meier method. The HRs (95% CI) were estimated using a Cox proportional hazards model stratified by the randomisation stratification factors. We made an inferential comparison using a stratified log rank test. We calculated the percentage of patients with an objective response or disease control, along with its associated 95% CI, using the Clopper-Pearson method. We made the inferential comparison for overall response rate using the Cochran-Mantel-Haenszel χ^2 test, which controlled for the randomisation stratification factors.

We used mixed models for repeated measurement (MMRM)[25] to assess the change from the baseline to week 12 in global health status, physical functioning and dyspnoea (four-item composite). For cough and chest pain, which were scored in a single item with ordinal response outcomes (low scores represent lower symptom burden), we used the generalised estimating equations (GEE) method[26] to model cumulative log odds of low scores compared with high scores. In these MMRM and GEE regression models, all data from baseline to week 12 were considered. For patients without data at week 12, the trend from baseline to week 12 affected the outcome of the key secondary endpoint. In terms of the outcomes of the primary analysis, this regression model, which also considers a patient-level random effect, is robust with respect to missing data. The level of missing data was low. As a sensitivity analysis to the primary analysis, we conducted a multiple imputation and showed the robustness of the analyses. We performed hypothesis tests in these patient-reported outcomes using Holm's procedure and after progression-free survival, overall response rate, and overall survival endpoints reached statistical significance.

We performed time-to-deterioration analyses for patient-reported outcome endpoints using Cox proportional hazards regression. We adjusted all MMRMs, GEEs, and time-to-deterioration analyses for randomisation stratification factors. MMRMs and GEEs included time, treatment, and the interaction of time and treatment as covariates. The MMRM used the change from baseline as the response variable (ie, the patient-reported outcome score at each visit minus the baseline patient-reported outcome score). We assessed the thresholds used to identify clinically meaningful deterioration or clinically meaningful change in the specified patient-reported outcome endpoints on the basis of a pooled analysis on a subgroup of patients enrolled in CodeBreaK 200 before the study unblinding (appendix pp 6, 10). We constructed the thresholds as minimally important change within-individual and within-group change, as well as minimally important difference between treatment groups (appendix p 6). The analysis to identify minimally important change and minimally important difference was done by an independent external analytic group. This study is registered at ClinicalTrials.gov, NCT04303780.

Role of the funding source

The sponsor Amgen was involved in the design and conduct of the study, the analysis and interpretation of the data, and the decision to submit this manuscript. Amgen managed patient data collected at the study sites and provided medical writing support.

Results

From June 4, 2020, to April 26, 2021, we screened 616 patients. After excluding 271 (44%) patients, we enrolled 345 (56%) patients with advanced NSCLC with the *KRAS*^{G12C} mutation who had been previously treated with other anticancer drugs (figure 1). Patients were randomly assigned to sotorasib (n=171 [50%]) or docetaxel (n=174 [50%]). 169 (99%) patients in the sotorasib group and 151 (87%) in the docetaxel group received at least one dose (figure 1). Of the 23 (13%) patients randomly assigned to the docetaxel group who withdrew before receiving treatment (20 consent withdrawal, one death, one investigator decision, one lost to follow-up), 21 (91%) withdrew within the first 2 weeks following randomisation (figure 1). Subsequent off-protocol therapies were not known for 20 (87%) patients because they withdrew consent and of the other three (13%) patients, one (4%) did receive subsequent

anticancer therapy (non-platinum chemotherapy). The 23 patients who withdrew before receiving docetaxel, in comparison with the 151 patients treated with docetaxel, were more likely to have a history of CNS involvement (10 [44%] *vs* 50 [33%]), to be refractory to previous therapy (10 [44%] *vs* 47 [31%]), have an ECOG performance status of 1 (17 [74%] *vs* 98 [65%]), and liver metastases (seven [30%] *vs* 28 [19%]) at baseline. Two (1%) patients withdrew before receiving sotorasib.

Baseline characteristics were generally well balanced between the treatment groups (table 1; appendix p 11). 126 (74%) patients in the sotorasib group and 126 (72%) in the docetaxel group were enrolled from Europe, and 58 (34%) patients in the sotorasib group and 60 (34%) in the docetaxel group had a history of CNS involvement (table 1). 167 (98%) patients in the sotorasib group and 170 (98%) in the docetaxel group received both platinum-based chemotherapy and immunotherapy (contraindication for four (2%) patients in each group). 88 (51%) patients in the sotorasib group and 86 (49%) in the docetaxel group received previous platinum-based chemotherapy and immunotherapy sequentially, most often chemotherapy followed by immunotherapy (appendix p 12).

At the data cutoff of Aug 2, 2022, the median study follow-up time was 17·7 months (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 12·0 weeks (range 3·0–101·0) for patients receiving docetaxel. The number of patients who were continuing to receive the assigned trial treatment at the time of the data cutoff was 22 (13%) in the sotorasib group and seven (4%) in the docetaxel group. Crossover from docetaxel to sotorasib per protocol occurred in 46 (26%) patients (figure 1).

The study met its primary endpoint of a statistically significant improvement in progression-free survival with sotorasib compared with docetaxel (HR 0·66 [95% CI 0·51–0·86]; p=0·0017; figure 2A; appendix p 13). The median progression-free survival was 5·6 months (95% CI 4·3–7·8) for sotorasib versus 4·5 months (3·0–5·7) for docetaxel. Kaplan-Meier event curves showed early and sustained separation between the two treatment groups (figure 2A). At 12 months, the progression-free survival rate was 24·8% for sotorasib versus 10·1% for docetaxel (figure 2A). Results for progression-free survival as assessed by investigator were consistent with those per central review (appendix p 14). We found a consistent progression-free survival benefit of sotorasib over docetaxel across all prespecified subgroups regardless of demographics, ECOG performance status, previous lines of therapy, PD-L1 expression levels, and history of CNS involvement (figure 2B). The median progression-free survival 2 was 9·6 months (95% CI 8·1–11·1) for sotorasib, compared with 7·6 months (6·5–9·9) for docetaxel.

The overall response rate, which was assessed by BICR, was significantly increased with sotorasib, compared with

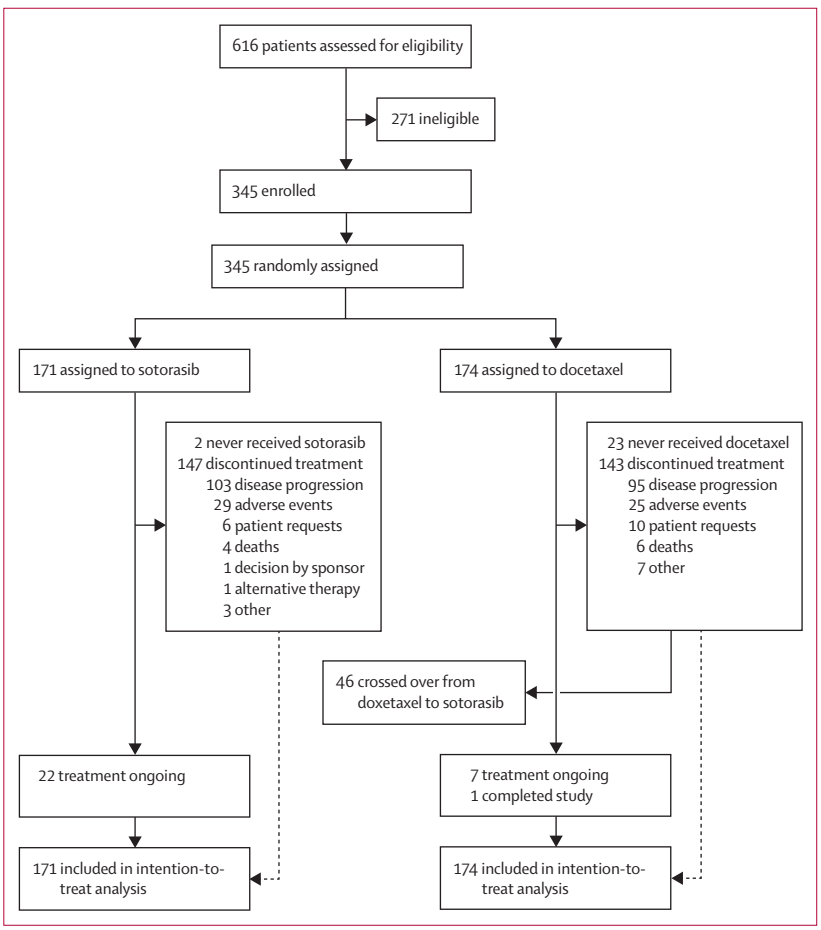


Figure 1: **Trial profile**

docetaxel (28·1% [95% CI 21·5–35·4] *vs* 13·2% [8·6–19·2]; p<0·001; difference of proportions of objective response 14·8 [6·4–23·1]; figure 3A). The disease-control rate was 82·5% (75·9–87·8) in the sotorasib group, compared with 60·3% (52·7–67·7) in the docetaxel group (figure 3A). Among patients who had a response, sotorasib was associated with a faster time to response (median 1·4 months *vs* 2·8 months) and a longer duration of response (median 8·6 [7·1–18·0] months *vs* 6·8 [4·3–8·3] months), compared with docetaxel (figure 3A; appendix p 7). The median best percentage decrease from baseline in tumour burden (defined as the sum of the longest diameters of all target lesions) among responders was 58·8% in the sotorasib group, compared with 48·7% in the docetaxel group. Sotorasib showed a consistent benefit in the overall response rate, compared with docetaxel, in all prespecified subgroups across demographics, ECOG performance status, previous lines of therapy, PD-L1 expression levels, and history of CNS involvement (appendix p 8).

Overall survival was not different between the treatment groups (HR 1·01 [95% CI 0·77–1·33]; figure 3B). Median overall survival was 10·6 months

	Sotorasib (n=171)	Docetaxel (n=174)
Age, years	64·0 (32–88)	64·0 (35–87)
Sex		
Male	109 (63·7%)	95 (54·6%)
Female	62 (36·3%)	79 (45·4%)
Ethnicity		
Hispanic or Latino	5 (2·9%)	9 (5·2%)
Not Hispanic or Latino	165 (96·5%)	163 (93·7%)
Unknown	1 (0·6%)	2 (1·1%)
Race*		
Asian	21 (12·3%)	22 (12·6%)
Black or African American	2 (1·2%)	0
White	142 (83·0%)	144 (82·8%)
Multiple	1 (0·6%)	0
Other	4 (2·3%)	7 (4·0%)
Unknown	1 (0·6%)	1 (0·6%)
Region		
North America	20 (11·7%)	22 (12·6%)
Europe	126 (73·7%)	126 (72·4%)
Rest of world	25 (14·6%)	26 (14·9%)
Smoking history		
Never	5 (2·9%)	8 (4·6%)
Current	32 (18·7%)	35 (20·1%)
Former	134 (78·4%)	131 (75·3%)
ECOG performance status (at screening)		
0	59 (34·5%)	59 (33·9%)
1	112 (65·5%)	115 (66·1%)
History of CNS involvement		
Yes	58 (33.9%)	60 (34.5%)
No	113 (66.1%)	114 (65.5%)
Liver metastasis		
Yes	30 (17·5%)	35 (20·1%)
No	141 (82·5%)	139 (79·9%)
Histology		
Squamous	1 (0·6%)	7 (4·0%)
Non-squamous	169 (98·8%)	165 (94·8%)
Other	1 (0·6%)	2 (1·1%)
Disease stage		
Locally advanced and unresectable	9 (5·3%)	8 (4·6%)
Metastatic	162 (94·7%)	166 (95·4%)
Previous lines of therapy†		
1	77 (45·0%)	78 (44·8%)
2	65 (38·0%)	69 (39·7%)
>2	29 (17·0%)	27 (15·5%)
PD-L1 protein expression‡		
<1%	57 (33·3%)	55 (31·6%)
≥1% to <50%	46 (26·9%)	70 (40·2%)
≥50%	60 (35·1%)	40 (23·0%)
Unknown	8 (4·7%)	9 (5·2%)

Data are n (%) or median (range). The patient with Multiple race listed White as primary race in clinical report form; thus, is considered under White in the subgroup analysis by race. ECOG=Eastern Cooperative Oncology Group. *No patients of race American Indian or Alaska Native or Native Hawaiian or Other Pacific Islander were enrolled. †Previous lines of therapy for advanced disease. ‡PD-L1 protein expression per local testing was collected, but not mandated.

Table 1: **Baseline patient demographic and clinical characteristics**

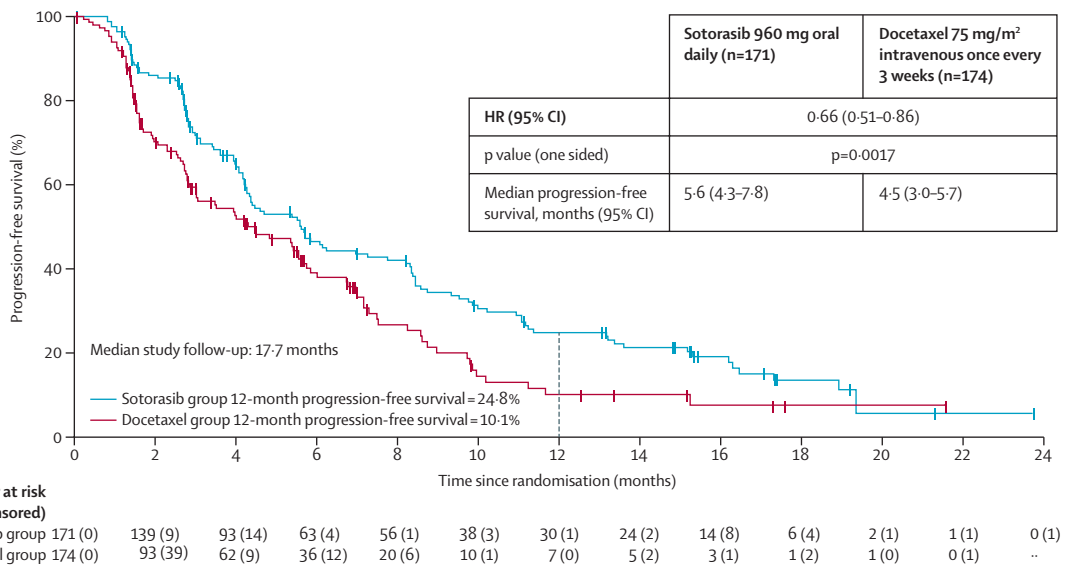
(95% CI 8·9–14·0) in the sotorasib group and 11·3 months (95% CI 9·0–14·9) in the docetaxel group (figure 3B). As per the statistical analysis plan, we did no further statistical testing on patient-reported outcomes.

Among randomly assigned patients, 62 (36%) received subsequent therapy after treatment with sotorasib, compared with 73 (42%) with docetaxel (appendix p 15). For the docetaxel group, 59 (34%) patients were known to have subsequently received a $KRAS^{G12C}$ inhibitor, including 46 (26%) who crossed over to sotorasib as per the study protocol and 13 (7%) who received a $KRAS^{G12C}$ inhibitor as a subsequent therapy following discontinuation from study treatment (figure 1; appendix p 15). For the sotorasib group, 36 (21%) patients were known to have received subsequent chemotherapy (appendix p 15).

In a pre-planned exploratory analysis of patients with previous CNS disease, the median time to recurrence of CNS disease, as per investigator assessment, was delayed with sotorasib compared with docetaxel (15·8 months [95% CI 9·7–not estimable] *vs* 10·5 months [5·8–not estimable]; HR 0·52 [95% CI 0·26–1·0]; appendix p 16).

Treatment-emergent adverse events of any grade, regardless of the cause, were reported in 166 (98%) patients in the sotorasib group and 148 (98%) patients in the docetaxel group (appendix pp 17–28). Treatment-related adverse events of grade 3 or worse were reported in 56 (33%) patients in the sotorasib group and in 61 (40%) patients in the docetaxel group (tables 2, 3). In the sotorasib group, the most common treatment-related adverse events of grade 3 or worse were diarrhoea (n=20 [12%]), alanine aminotransferase (ALT) increase (n=13 [8%]), and aspartate aminotransferase (AST) increase (n=9 [5%]; table 3). In the docetaxel group, the most common treatment-related adverse events of grade 3 or worse were neutropenia (n=18 [12%]), fatigue (n=9 [6%]), and febrile neutropenia (n=8 [5%]; table 3). In the sotorasib group, all treatment-related adverse events of grade 3 or worse of diarrhoea and increased ALT or AST resolved after dose interruption, reduction, or both (appendix p 34). The full list of treatment-related adverse events of any grade is given in the appendix (pp 29–33). Fatal treatment-related adverse events were reported in one patient (<1%) in the sotorasib group (interstitial lung disease) and two patients (1%) in the docetaxel group (ileus and multiorgan failure; table 2). In the sotorasib group, 60 (36%) dose interruptions, 26 (15%) dose

A



Number at risk (number censored)

Sotorasib group	171 (0)	139 (9)	93 (14)	63 (4)	56 (1)	38 (3)	30 (1)	24 (2)	14 (8)	6 (4)	2 (1)	1 (1)	0 (1)
Docetaxel group	174 (0)	93 (39)	62 (9)	36 (12)	20 (6)	10 (1)	7 (0)	5 (2)	3 (1)	1 (2)	1 (0)	0 (1)	..

B

	Patients (n)		Median PFS, months (95% CI)		Hazard ratio (95% CI)
	Sotorasib	Docetaxel	Sotorasib	Docetaxel	
All randomly assigned patients	**171**	**174**	**5·6 (4·3–7·8)**	**4·5 (3·0–5·7)**	**0·66 (0·51–0·86)**
Age at baseline (years)					
<65	91	95	4·4 (3·6–8·3)	3·1 (2·7–5·4)	0·68 (0·48–0·96)
≥65	80	79	5·9 (4·4–8·6)	5·6 (3·5–7·0)	0·64 (0·41–0·99)
Sex					
Male	109	95	5·7 (4·3–8·4)	4·5 (3·0–5·9)	0·56 (0·39–0·80)
Female	62	79	4·6 (4·0–8·3)	4·2 (2·3–7·0)	0·69 (0·45–1·08)
Region					
North America	20	22	5·9 (2·8–13·2)	6·8 (2·6–9·7)	0·49 (0·21–1·13)
Europe	126	126	5·6 (4·3–7·8)	4·0 (2·8–5·7)	0·68 (0·50–0·92)
Other	25	26	5·7 (2·8–11·1)	5·6 (1·5–7·2)	0·47 (0·20–1·09)
Smoking history (tobacco)					
Never	5	8	NE (NE–NE)	NE (NE–NE)	NE (NE–NE)
Current	32	35	5·7 (2·9–8·4)	2·8 (1·6–7·0)	0·69 (0·36–1·32)
Former	134	131	5·6 (4·3–8·3)	5·4 (3·0–6·0)	0·68 (0·50–0·92)
Race					
Asian	21	22	8·3 (2·8–11·1)	5·6 (1·5–7·2)	0·33 (0·14–0·80)
Non-Asian	149	151	5·6 (4·2–7·8)	4·2 (3·0–5·8)	0·71 (0·54–0·95)
ECOG performance status					
0	59	59	8·4 (5·7–11·2)	6·7 (4·5–7·5)	0·63 (0·38–1·05)
1	112	115	4·4 (3·9–5·7)	2·8 (1·9–5·4)	0·61 (0·44–0·84)
Number of previous lines in advanced disease					
1	77	78	4·2 (3·1–8·4)	4·2 (2·7–5·6)	0·70 (0·47–1·04)
2	65	69	5·7 (4·5–9·5)	4·8 (2·8–7·0)	0·61 (0·40–0·92)
>2	29	27	4·7 (4·1–8·6)	4·0 (1·5–9·0)	0·74 (0·37–1·46)
History of CNS involvement					
Yes	58	60	4·4 (3·9–8·4)	2·9 (1·6–4·5)	0·53 (0·34–0·82)
No	113	114	5·7 (4·3–8·3)	5·7 (3·9–7·2)	0·74 (0·53–1·03)
Liver metastasis					
Yes	30	35	4·2 (2·7–6·2)	1·9 (1·5–3·0)	0·47 (0·26–0·85)
No	141	139	5·9 (4·4–8·4)	5·6 (4·0–7·0)	0·67 (0·49–0·90)
Bone metastasis at baseline					
Yes	81	69	4·2 (3·0–5·4)	3·0 (2·1–4·5)	0·64 (0·44–0·93)
No	90	105	8·3 (5·6–9·8)	5·6 (4·0–7·0)	0·59 (0·40–0·87)
PD-L1 protein expression					
<1%	57	55	8·3 (4·1–8·6)	5·9 (3·5–7·2)	0·66 (0·41–1·06)
≥1% to <50%	46	70	4·6 (3·4–7·8)	3·0 (2·1–4·5)	0·61 (0·39–0·96)
≥50%	60	40	5·7 (4·0–10·0)	5·4 (2·0–10·2)	0·74 (0·44–1·23)
Best response on previous therapy					
Progressive disease	67	57	4·3 (3·0–5·7)	2·8 (1·6–5·7)	0·64 (0·40–1·04)
Objective response (with subsequent growth)	35	47	10·2 (4·0–13·4)	6·0 (3·9–9·8)	0·71 (0·39–1·28)
Stable disease	50	53	8·3 (4·4–9·5)	4·2 (2·8–6·8)	0·52 (0·31–0·87)

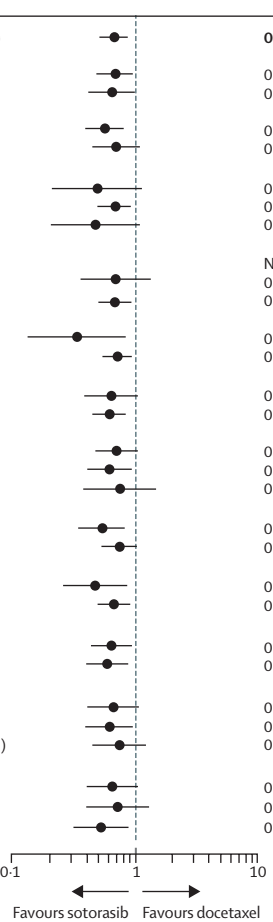


Figure 2: **Progression-free survival of sotorasib versus docetaxel**

(A) The Kaplan-Meier curve of progression-free survival among patients in the sotorasib group and patients in the docetaxel group who could be assessed for a response according to blinded independent central review. Vertical lines indicate censored data. (B) Subgroup analyses for progression-free survival per blinded independent central review, done using a stratified Cox proportional hazards model to estimate the hazard ratios (95% CIs). Race was self-reported. A hazard ratio of less than 1 implies a lower risk of disease recurrence or death with sotorasib than with docetaxel. ECOG=Eastern Cooperative Oncology Group. PFS=progression-free survival. NE=not estimable.

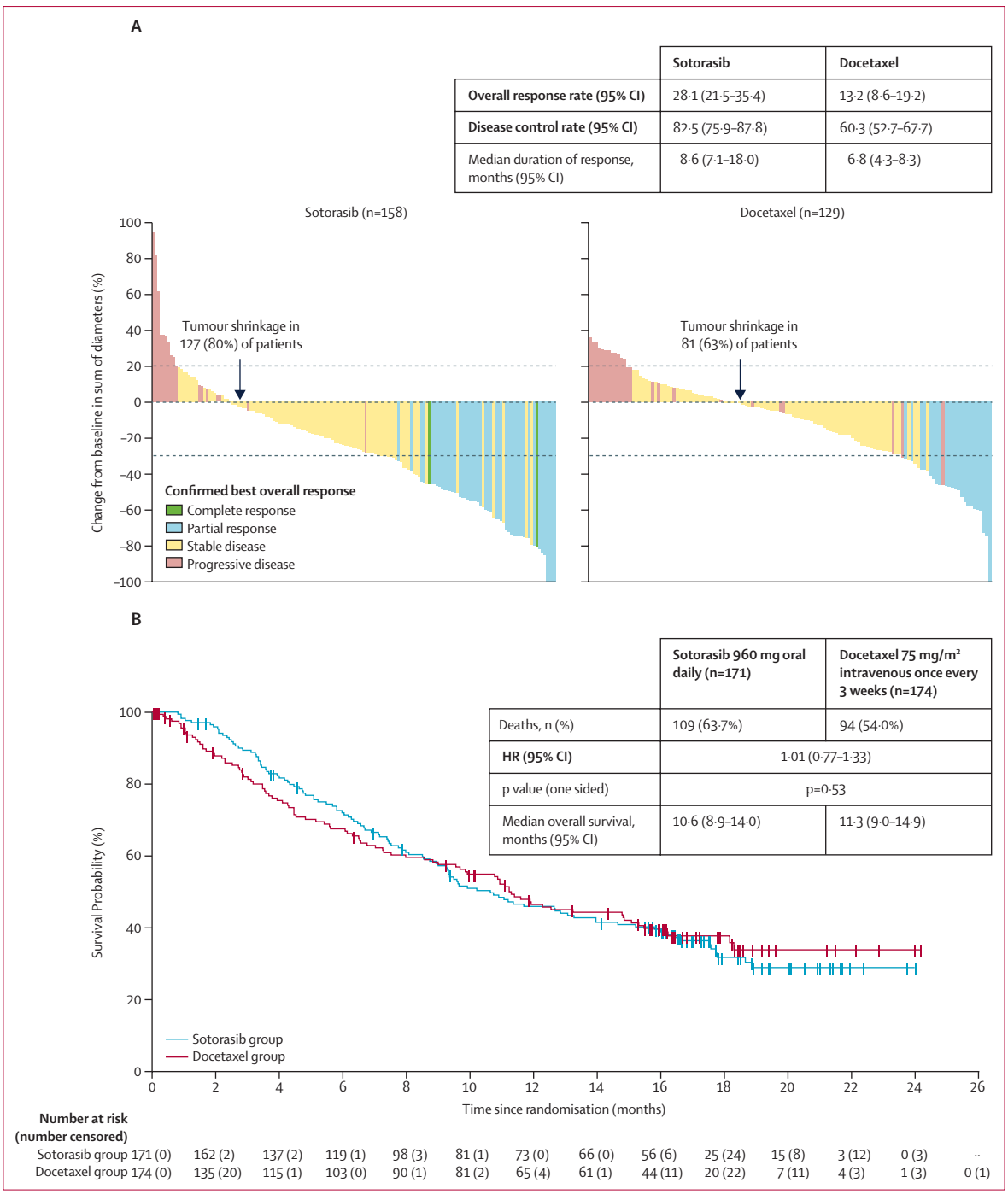


Figure 3: **Overall response and overall survival**

(A) Best percentage decrease from baseline in the tumour burden (defined as the sum of the longest diameters of all target lesions) in 158 (92%) of 171 patients in the sotorasib group and 129 (74%) of 174 patients in the docetaxel group. Patients without baseline target lesions or post-baseline percentage changes, or with best overall response of not evaluable, are not shown. (B) Kaplan-Meier curve of overall survival among all 171 patients in the sotorasib group and all 174 patients in the docetaxel group. Vertical lines indicate censored data.

reductions, and 16 (10%) discontinuations of trial regimen because of treatment-related adverse events occurred; in the docetaxel group, 23 (15%) dose interruptions, 40 (27%) dose reductions, and 17 (11%) discontinuations of trial regimen because of treatment-related adverse events occurred (appendix pp 35–40).

In a post hoc analysis, exposure-adjusted event rates were favourable for sotorasib, except for treatment-emergent

	Sotorasib (n=169)						Docetaxel (n=151)					
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Fatal	Any zzrade	Grade 1	Grade 2	Grade 3	Grade 4	Fatal
Treatment-emergent adverse events	166 (98%)	14 (8%)	31 (18%)	73 (43%)	11 (7%)	37 (22%)	148 (98%)	12 (8%)	45 (30%)	56 (37%)	17 (11%)	18 (12%)
Treatment-related adverse events	119 (70%)	30 (18%)	33 (20%)	46 (27%)	9 (5%)	1 (1%)	130 (86%)	16 (11%)	53 (35%)	42 (28%)	17 (11%)	2 (1%)
Serious treatment-related adverse events	18 (11%)	..	..	..	..	..	34 (23%)	..	..	..	..	..
Treatment-related adverse events leading to dose interruption	60 (36%)	..	..	..	..	..	23 (15%)	..	..	..	..	..
Treatment-related adverse events leading to dose reduction	26 (15%)	..	..	..	..	..	40 (27%)	..	..	..	..	..
Treatment-related adverse events leading to discontinuation	16 (10%)	..	..	..	..	..	17 (11%)	..	..	..	..	..

Data are n (%). Adverse events were graded with the use of the Common Terminology Criteria for Adverse Events (version 5.0), which incorporates certain elements of *Medical Dictionary for Regulatory Activities* terminology.

Table 2: **Adverse events**

adverse events and treatment-related adverse events that caused dose interruption (appendix p 41). The exposure-adjusted event rate of fatal treatment-emergent adverse events per 100 patient-years was similar in both groups (sotorasib 35·4; docetaxel 36·0; appendix p 41]). In a post hoc analysis, we found a higher incidence of treatment-related adverse events of grade 3 or worse and hepatotoxicity events in patients treated with immunotherapy 2·6 months or less before initiation of sotorasib, compared with those treated more than 2·6 months before treatment with sotorasib (appendix p 42). Overall, the greater the time between previous immunotherapy and sotorasib, the lower the incidence of treatment-related adverse events of grade 3 or worse and hepatotoxicity events (appendix p 42).

We compared the effect of sotorasib with that of docetaxel treatment on symptom burden and quality of life on the basis of patient-reported outcomes as assessed by EORTC QLQ C30 and EORTC QLQ-LC13. The compliance rate was at least 95% at baseline and up to cycle 30 day 1 (appendix pp 43–52). Sotorasib showed clinically meaningful differences, compared with docetaxel, in delaying the time to deterioration in global health status (HR 0·69 [95% CI 0·53–0·91]), physical functioning (0·69 [0·52–0·92]), and the cancer-related symptoms dyspnoea (0·63 [95% CI 0·48–0·83]) and cough (0·55 [0·38–0·80]; figure 4A).

For our key secondary outcomes, changes from baseline for global health status (least squares means of change differences 6·93), physical functioning (8·78), and dyspnoea (–10·09) consistently favoured sotorasib over docetaxel until week 12 (descriptive p<0·0001 [descriptive due to the hierarchy of testing]; figure 4B; appendix p 53). From baseline to week 12, patients in the sotorasib group reported an improvement in symptoms for cough, compared with patients in the docetaxel group (odds ratio 3·21 [95% CI 1·55–6·65]; descriptive p=0·0016 [descriptive due to the hierarchy of testing]; appendix p 54); however, we found no differences in chest pain between the treatment groups (appendix p 54).

	Sotorasib (n=169)		Docetaxel (n=151)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Diarrhoea	57 (34%)	20 (12%)	28 (19%)	3 (2%)
Fatigue	11 (7%)	1 (1%)	38 (25%)	9 (6%)
Alopecia	2 (1%)	0	31 (21%)	0
Nausea	24 (14%)	2 (1%)	30 (20%)	1 (1%)
Anaemia	5 (3%)	1 (1%)	27 (18%)	5 (3%)
Decreased appetite	18 (11%)	3 (2%)	21 (14%)	0
Stomatitis	1 (1%)	0	17 (11%)	2 (1%)
Constipation	5 (3%)	0	16 (11%)	0
Asthenia	7 (4%)	1 (1%)	16 (11%)	4 (3%)
Alanine aminotransferase increased	17 (10%)	13 (8%)	0	0
Aspartate aminotransferase increased	17 (10%)	9 (5%)	0	0
Neutropenia	2 (1%)	0	20 (13%)	18 (12%)
Neuropathy peripheral	0	0	15 (10%)	1 (1%)
Oedema peripheral	0	0	14 (9%)	1 (1%)
Dysgeusia	4 (2%)	0	13 (9%)	0
Myalgia	3 (2%)	0	13 (9%)	2 (1%)
Vomiting	8 (5%)	0	10 (7%)	0
Arthralgia	2 (1%)	0	10 (7%)	1 (1%)
Mucositis	1 (1%)	0	10 (7%)	2 (1%)
Alkaline phosphatase increased	11 (7%)	5 (3%)	1 (1%)	0
Malaise	2 (1%)	1 (1%)	9 (6%)	1 (1%)
Febrile neutropenia	0	0	8 (5%)	8 (5%)
Abdominal pain	9 (5%)	2 (1%)	6 (4%)	0
Pyrexia	1 (1%)	0	8 (5%)	0
Pneumonia	0	0	7 (5%)	5 (3%)

Data are n (%). Adverse events were graded with the use of the Common Terminology Criteria for Adverse Events (version 5.0), which incorporates certain elements of *Medical Dictionary for Regulatory Activities* terminology.

Table 3: **Treatment-related adverse events of any grade (occurring in ≥5% of patients) or of grade ≥3 (occurring in ≥3% of patients)**

Discussion

The data from the CodeBreaK 200 trial indicated that oral sotorasib has a greater efficacy, has a better toxicity profile, and is associated with better quality of life, compared with intravenous docetaxel, in patients with

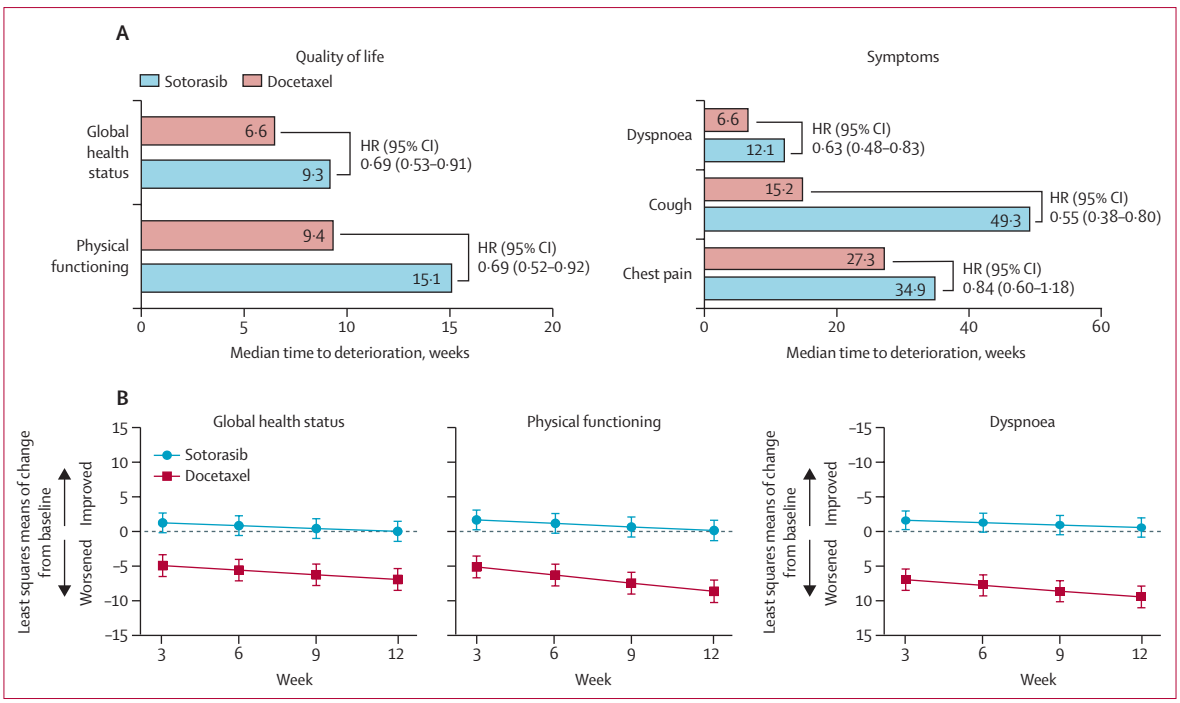


Figure 4: **Patient-reported outcomes of sotorasib versus docetaxel**

(A) Time to deterioration analysis. Cox proportional hazards regression model stratified for randomisation stratification factors, having non-missing baseline score and at least one post-baseline assessment for each subscale, and baseline threshold dyspnoea (composite score ≤92), cough (composite score ≤67), and chest pain (composite score ≤67). Randomisation stratification factors were number of previous lines of therapy in advanced disease (1 *vs* 2 *vs* >2), race (Asian *vs* non-Asian), and history of CNS involvement (yes *vs* no); within-patient clinically meaningful deterioration was prespecified as 8 for dyspnoea, 33 for cough and chest pain, –8 for global health status and –13 for physical functioning. (B) Plots of the difference of least squares means of change from baseline for global health status, physical functioning, and dyspnoea calculated using MMRM. MMRM is based on the change from baseline up to cycle 5 day 1 (week 12) as the dependent variable; intercept, time, baseline score, treatment, treatment-by-time interaction, and randomisation stratification factors as fixed effects; and patient intercept and slope of time. Global health status and physical functioning were reported on the EORTC QLQ-C30 questionnaire. Cough and chest pain were reported on the EORTC QLQ-LC13 questionnaire. Dyspnoea is a four-item composite of EORTC QLQ-C30 (one item) and EORTC QLQ-L13 (three items). Error bars represent the standard error of the mean. EORTC QLQ=European Organization for Research and Treatment of Cancer Quality-of-life questionnaire. MMRM=mixed model of repeated measures

advanced NSCLC with the *KRAS*^{G12C} mutation and who have been previously treated with other anticancer drugs. CodeBreaK 200 is the first randomised phase 3 trial for a KRAS^{G12C} inhibitor showing that sotorasib significantly increased progression-free survival, compared with docetaxel, with a 34% reduction in relative risk of having disease progression or death with sotorasib. The overall response was significantly higher with sotorasib, compared with docetaxel, with a faster time to response and longer duration of response in the sotorasib group. Progression-free survival and overall response rate favoured sotorasib across all subgroups. Sotorasib was well tolerated with fewer grade 3 or worse and serious treatment-related adverse events than with docetaxel. The most common treatment-related adverse events leading to discontinuation of sotorasib were hepatotoxicity events, which occurred with greater frequency if immunotherapy was administered less than 2·6 months before sotorasib treatment, consistent with data from the sotorasib expanded-access protocol.[27] Sotorasib also showed clinically meaningful improvement in patient-reported outcomes compared with docetaxel. Overall, these findings indicate that sotorasib represents a new treatment option in this patient population with poor prognosis and a high unmet need.

We found no differences in overall survival between the two treatment groups. Notably, 23 (13%) of 174 patients who were randomly assigned to the docetaxel group did not receive treatment and discontinued the study, in comparison with two (1%) of 171 patients for the sotorasib group. This imbalance in the drop-out rates between treatment groups is a limitation due to the open-label design of this study. In the intention-to-treat analysis for overall survival, of the patients assigned to the docetaxel group who did not receive treatment, five (22%) of these 23 patients died and 17 (74%) patients were censored at the date of consent withdrawal or the last date known to be alive, whichever was later. These 23 patients had a poorer prognosis compared with the patients treated with docetaxel (ie, higher incidence of history of CNS involvement, liver metastases, ECOG performance status of 1, and refractory to previous therapy). Additionally, 59 (34%) patients in the docetaxel group subsequently received a KRAS^{G12C} inhibitor. Given these

limitations, one cannot make a conclusion on an overall survival benefit with sotorasib.

We found differences in efficacy outcomes between the CodeBreaK 200 phase 3 and the CodeBreaK 100 phase 2 trials.[23] The median progression-free survival (5·6 months *vs* 6·8 months), overall survival (10·6 months *vs* 12·5 months), and overall response rate (28·1% *vs* 37·1%) were slightly lower in the CodeBreaK 200 versus CodeBreaK 100 trial. Such variability is typical when a study expands in the later stage to include more global sites that are representative of different healthcare systems. Additionally, there were notable differences in the study populations. First, patients were predominantly enrolled from Europe (73%) for CodeBreaK 200 compared with North America (69%) for CodeBreaK 100.[23] Second, brain metastasis at baseline was more prevalent in CodeBreaK 200 than in CodeBreaK 100 (34% *vs* 23%). Additionally, a greater proportion of patients received both previous platinum-based chemotherapy and immunotherapy in CodeBreaK 200 than in CodeBreaK 100 (98% *vs* 83%). These differences in patient populations, together with the difference in the number of enrolment sites, probably underlie the differences in efficacy outcomes between these trials.

The CodeBreaK 200 trial provided data about the effect of sotorasib, compared with that of docetaxel, on symptom burden and quality of life. Compared with docetaxel, sotorasib showed clinically meaningful improvement in patient-reported outcomes. The events of time-to-deterioration analysis were defined on the basis of clinically meaningful within-patient change. The HRs for global health status, physical functioning, dyspnoea, cough, and chest pain favoured sotorasib, and all of the HRs except for chest pain had CIs (unadjusted for multiplicity) below 1. Regarding the change from baseline to week 12, the predefined threshold of clinical meaningfulness was exceeded for physical functioning. For global health status and dyspnoea, thresholds for clinical meaningfulness previously established for advanced NSCLC were met;[28] however, the observed differences were slightly below the predefined thresholds established for this study. These patient-reported outcome data show that sotorasib improves or maintains health-related quality of life compared with docetaxel in patients with pretreated *KRAS*^{G12C}-mutated advanced NSCLC.

CodeBreaK 200 establishes sotorasib as the first oral KRAS^{G12C}-targeted therapy in a randomised phase 3 trial to have a higher progression-free survival and overall response rate, compared with intravenous docetaxel, for treatment of patients with advanced NSCLC with the *KRAS*^{G12C} mutation who had been previously treated with other anticancer drugs. Upfront next-generation sequencing testing will allow for the identification of these patients at diagnosis but carrying through this knowledge is crucial to ensure that patients are appropriately treated in subsequent treatment lines. Combination studies are ongoing for sotorasib including in the front-line setting with chemotherapy or as a lead-in before immunotherapy, or in later lines with an SHP2 inhibitor as a mechanism to overcome resistance.[29,30] Additional analyses will further investigate the effect of sotorasib on quality of life and define biomarkers predictive of clinical response.

Contributors

All authors participated in the conception and design of the trial and the analysis and interpretation of data. Patient data were collected by AJdL, MLJ, JM, A-MCD,GM, MP, JW, MS, HL, FS, YY, S-WK, HL, SN, ADvdW, YC, SP, EF, BJS, SSR, CD, CRL, CGF, NB, DW, and LP-A, along with their CodeBreaK 200 co-investigators. LP-A, CCO, YW, BM, TV, and BS verified the data and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors had full access to the data and contributed to the preparation of the manuscript. All authors approved the manuscript for submission and verified the accuracy and completeness of the data and the fidelity of the trial to the protocol.

Declaration of interests

AJdL reports financial interests, institutional, research grant from BMS, MSD, Boehringer, AstraZeneca; non-financial interests, other from Merck Serono, Roche. MLJ reports financial interests, institutional, research grant from AbbVie, Acerta, Adaptimmune, Amgen, Apexigen, Arcus Biosciences, Array BioPharma, Artios Pharma, AstraZeneca, Atreca, BeiGene, BerGenBio, BioAtla, Boehringer Ingelheim, Calithera Biosciences, Corvus Pharmaceuticals, Curis, CytomX, Daiichi Sankyo, Dracen Pharmaceuticals, Dynavax, Lilly, EMD Serono, Erasca, Exelixis, Fate Therapeutics, Genentech/Roche, Genmab, Genocea Biosciences, GlaxoSmithKline, Gritstone Oncology, Guardant Health, Harpoon, Helsinn Healthcare, Hengrui Therapeutics, Hutchison MediPharma, IDEAYA Biosciences, IGM Biosciences, Immunocore, Incyte, Janssen, Kadmon Pharmaceuticals, Loxo Oncology, Lycera, Memorial Sloan-Kettering, Merck, Merus, NeoImmune Tech, Neovia Oncology, Novartis, Numab Therapeutics, Nuvalent, OncoMed Pharmaceuticals, Pfizer, PMV Pharmaceuticals, Regeneron Pharmaceuticals, Relay Therapeutics, Revolution Medicines, Ribon Therapeutics, Rubius Therapeutics, Sanofi, Seven and Eight Biopharmaceuticals/Birdie Biopharmaceuticals, Shattuck Labs, Silicon Therapeutics, Stem CentRx, Syndax Pharmaceuticals, Takeda Pharmaceuticals, Tarveda Therapeutics, TCR2 Therapeutics, Tempest Therapeutics, Tizona Therapeutics, Tmunity Therapeutics, Turning Point Therapeutics, University of Michigan, Vyriad, WindMIL, Y-mAbs Therapeutics, Black Diamond, Carisma Therapeutics, Elicio Therapeutics, EQRx, Immunitas Therapeutics, Kartos Therapeutics, Mirati Therapeutics, Palleon Pharmaceuticals, Rain Therapeutics; financial interests, institutional, consulting fees from AbbVie, Amgen, Astellas, AstraZeneca, Axelia Oncology, Black Diamond, Calithera Biosciences, Checkpoint Therapeutics, CytomX Therapeutics, Daiichi Sankyo, EcoR1, Editas Medicine, Eisai, Genentech/Roche, Genmab, Genocea Biosciences, GlaxoSmithKline, Gritstone Oncology, IDEAYA Biosciences, iTeos Therapeutics, Janssen, Lilly, Merck, Mirati Therapeutics, Molecular Axiom, Novartis, Oncorus, Regeneron Pharmaceuticals, Ribon Therapeutics, Sanofi-Aventis, Turning Point Therapeutics, VBL Therapeutics, Takeda Pharmaceuticals, Arrivant, Pyramid Biosciences, Revolution Medicines, Seagen. JM reports financial interests, personal fees from Amgen, AstraZeneca, Roche, Pierre Fabre, Pfizer; financial interests, institutional, research grant from AstraZeneca, Roche, Pierre Fabre; advisory board for Merck, Roche, AstraZeneca, MSD, BMS, Pfizer, Hengrui Therapeutics, Daiichi, Boehringer, Pierre Fabre, Amgen. A MCD reports other, institutional, advisory board for Amgen, Bayer, Boehringer Ingelheim, Roche, Sanofi; other, institutional, invited speaker for AstraZeneca, Janssen, Eli Lilly, Pfizer, Takeda; financial interests, institutional, research grant from Amgen; financial interests, institutional, principal investigator, local PI for Amgen, Daiichi, JNJ, Eli Lilly, Mirati Therapeutics; financial interests, institutional, principal investigator, coordinating PI for Roche; financial interests, institutional, other, steering committee member for Roche. GM reports financial interests, personal, other, consulting fees

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Data sharing

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.

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