Adagrasib versus docetaxel in *KRAS*^{G12C}-mutated non-small-cell lung cancer (KRYSTAL-12): a randomised, open-label, phase 3 trial

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Summary

Background Adagrasib is a KRAS^{G12C} inhibitor that demonstrated promising activity against *KRAS*^{G12C}-mutated advanced non-small-cell lung cancer (NSCLC) in a phase 2 trial. Here we aimed to compare the efficacy and safety of adagrasib versus docetaxel in patients with *KRAS*^{G12C}-mutated advanced NSCLC previously treated with chemotherapy and immunotherapy.

Methods KRYSTAL-12 is a randomised, multicentre, open-label, phase 3 trial conducted at 230 centres in 22 countries. Patients with Kirsten rat sarcoma viral oncogene homologue (*KRAS*)^{G12C}-mutated locally advanced or metastatic NSCLC, who had previously received both platinum-based chemotherapy and anti-programmed cell death protein 1 or anti-programmed death ligand 1 therapy, were randomly allocated in a 2:1 ratio to receive 600 mg adagrasib (twice a day orally) or 75 mg/m² docetaxel (every 3 weeks intravenously) using a centralised interactive web response system. Randomisation was stratified by region (non-Asia–Pacific *vs* Asia–Pacific) and previous treatment (sequential *vs* concurrent chemotherapy or immunotherapy). Treatment continued until disease progression, unacceptable toxicity, investigator or patient decision, or death. The primary endpoint was progression-free survival assessed by blinded independent central review in all randomised patients (intention-to-treat [ITT] population). Safety was assessed in all treated patients. This trial is registered at ClinicalTrials.gov (NCT04685135), and is active but no longer recruiting.

Findings Between Feb 23, 2021, and Nov 16, 2023, 453 patients were randomly allocated to receive adagrasib (301 [66%]) or docetaxel (152 [34%]). In each group, 298 (99%) patients received adagrasib and 140 (92%) received docetaxel. In the ITT population (median follow-up 7·2 months [95% CI 5·8–8·7]), median progression-free survival was 5·5 months (95% CI 4·5–6·7) with adagrasib and 3·8 months (95% CI 2·7–4·7) with docetaxel (hazard ratio 0·58 [95% CI 0·45–0·76]; p<0·0001). Grade 3 and above treatment-related adverse events occurred in 140 (47%) of 298 patients treated with adagrasib and 64 (46%) of 140 with docetaxel. There were four (1%) treatment-related deaths in the adagrasib group and one (1%) treatment-related death in the docetaxel group.

Interpretation Adagrasib demonstrated a statistically significant improvement in progression-free survival over docetaxel in patients with previously treated *KRAS*^{G12C}-mutated NSCLC, without new safety signals.

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Introduction

Kirsten rat sarcoma viral oncogene homologue (*KRAS*) is the most prevalent oncogenic driver in human cancer,[1,2] with *KRAS*^{G12C} mutations occurring in approximately 14% of patients with lung adenocarcinoma overall,[3] but in only approximately 4% of Asian patients across all histology types of non-small-cell lung cancer (NSCLC).[4] Historically, *KRAS*^{G12C}-mutated NSCLC has been a difficult-to-treat subtype of lung cancer, with few treatment options after progression on previous chemotherapy, immunotherapy, or both. Docetaxel chemotherapy has been a standard-of-care in this setting but recent progress has led to the development of inhibitors specifically targeting KRAS^{G12C}, such as sotorasib and adagrasib.

Adagrasib is a potent, orally available, small-molecule, covalent KRAS^{G12C} inhibitor that irreversibly and selectively binds KRAS^{G12C} in its inactive, GDP-bound state.[5] Adagrasib has favourable properties, including a long half-life of 23 h, dose-dependent pharmacokinetics, and brain penetrance.[5–7] In a phase 2 cohort of the KRYSTAL-1 study (NCT03785249), adagrasib demonstrated clinical activity in patients with previously treated *KRAS*^{G12C}-mutated locally advanced or metastatic NSCLC (objective response rate 43%; median progression-free survival 6·5 months; median overall survival 12·6 months;

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See Online for appendix

Research in context

Evidence before this study

We used PubMed to search for manuscripts and major oncology congress abstracts published between database inception and Nov 26, 2024, without language restrictions, using the search terms "non-small-cell lung cancer", "previously treated", "docetaxel", and "KRAS". Kirsten rat sarcoma viral oncogene homologue (*KRAS*) mutations are common in non-small-cell lung cancer (NSCLC), with *KRAS*^{G12C} mutations occurring in approximately 14% of patients with lung adenocarcinoma, and the mutations are generally mutually exclusive from other oncogenic driver mutations. Historically there have been scant treatment options for patients with *KRAS*^{G12C}-mutated NSCLC after progression on chemotherapy, immunotherapy, or both. The most commonly used drug in this patient population was docetaxel chemotherapy, which is associated with substantial haematological toxicity. With the development of KRAS^{G12C} inhibitors, targeted therapy has become a potential treatment option for patients with *KRAS*^{G12C}-mutated NSCLC. Adagrasib and sotorasib are two small molecule covalent *KRAS*^{G12C} inhibitors that irreversibly and selectively bind *KRAS*^{G12C} in its inactive, GDP-bound state. Adagrasib has shown clinical activity and a manageable safety profile in patients with previously treated *KRAS*^{G12C}-mutated locally advanced or metastatic NSCLC in a phase 2 cohort of the KRYSTAL-1 study. Additionally, adagrasib has demonstrated promising intracranial activity in patients with *KRAS*^{G12C}-mutated NSCLC and both treated and untreated brain metastases. Sotorasib has also demonstrated clinical activity in patients with previously treated *KRAS*^{G12C}-mutated locally advanced or metastatic NSCLC in the phase 2 CodeBreaK 100 study. Based on these phase 2 data, both adagrasib and sotorasib have been granted accelerated approval in the USA, and conditional approval in the EU in this patient population. During the conduct of the phase 3 KRYSTAL-12 study presented here, results from the phase 3 CodeBreaK 200 study were published showing that sotorasib had improved efficacy compared with docetaxel in patients with *KRAS*^{G12C}-mutated NSCLC.

Added value of this study

In this phase 3 KRYSTAL-12 study, adagrasib demonstrated statistically significant improvements in progression-free survival and objective response rate over docetaxel in patients with *KRAS*^{G12C}-mutated locally advanced or metastatic NSCLC previously treated with chemotherapy and immunotherapy, with no new safety signals. Adagrasib also demonstrated improved intracranial activity and longer duration of symptom burden control compared with docetaxel.

Implications of all the available evidence

The current study met its primary endpoint of improved progression-free survival, with adagrasib resulting in a significant decrease in the relative risk of disease progression or death compared with docetaxel in patients with previously treated *KRAS*^{G12C}-mutated advanced NSCLC. These data confirm the initial results from KRYSTAL-1 and reinforce adagrasib as an efficacious treatment option for this patient population after disease progression on prior chemotherapy and immunotherapy.

1-year overall survival rate 51%).[8] Based on these data, adagrasib was granted accelerated approval in the USA and conditional approval in the EU and the UK for patients with previously treated *KRAS*^{G12C}-mutated locally advanced or metastatic NSCLC. In pooled phase 1/2 cohorts of the KRYSTAL-1 study with a longer follow-up of 2 years, median overall survival with adagrasib was 14·1 months (2-year overall survival rate 31%), and a manageable long-term safety profile was observed.[9] Adagrasib has also demonstrated promising intracranial activity in patients with NSCLC and stable, treated brain metastases,[8] as well as untreated brain metastases.[10] Therefore, adagrasib is a recommended option by the NCCN Clinical Practice Guidelines in Oncology as NCCN Category 2a, as well as by the European Society for Medical Oncology Clinical Practice Guidelines, for patients with previously treated advanced *KRAS*^{G12C}-mutated NSCLC,[11,12] including those with brain metastases.[13]

Here we report the primary analysis results of the confirmatory, randomised, open-label phase 3 KRYSTAL-12 trial (NCT04685135), evaluating adagrasib versus docetaxel in patients with *KRAS*^{G12C}-mutated advanced NSCLC previously treated with chemotherapy and immunotherapy.

Methods

Study design and participants

KRYSTAL-12 is a randomised, multicentre, open-label, phase 3 trial comparing adagrasib with docetaxel in adults with locally advanced or metastatic NSCLC with a *KRAS*^{G12C} mutation (detected in tumour tissue) conducted at 230 centres in 22 countries (appendix p 44). Patients must have received previous treatment with a platinum-based chemotherapy regimen, concurrently or sequentially with an anti-programmed death (ligand) 1 (PD-[L]1) therapy, with no washout period required after previous immunotherapy. Eligible patients had evaluable or measurable tumour lesions according to RECIST v1.1 and an ECOG performance status of 0 or 1. The key exclusion criterion was active brain metastases (treated, neurologically stable brain metastases for ≥2 weeks before randomisation were allowed). The study protocol and full eligibility criteria can be found in the appendix (pp 30, 49). The trial was conducted according to the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. Independent ethics committees or institutional review boards at each participating centre approved the protocol (appendix pp 4–29). All patients provided written

informed consent. An independent data and safety monitoring committee monitored safety.

Randomisation and masking

Patients were randomly allocated in a 2:1 ratio to receive either adagrasib or docetaxel using a centralised interactive web response system. Randomisation was stratified by region (non-Asia–Pacific *vs* Asia–Pacific) and previous treatment (sequential *vs* concurrent chemotherapy and anti-PD-[L]1) in a block size of six. As an open-label trial, there was no masking.

Procedures

Patients received either 600 mg adagrasib twice a day orally (tablet formulation in continuous 3-weekly cycles) or 75 mg/m² docetaxel intravenously every 3 weeks, until disease progression, unacceptable toxicity, investigator or patient decision, or death (appendix p 44). Following a protocol amendment, which occurred after 87 patients had already been enrolled in the study (in either treatment group), patients were allowed to crossover from docetaxel to adagrasib in cases of disease progression per RECIST v1.1 confirmed by blinded independent central review (BICR) and subject to specific criteria detailed in the appendix (p 31). All patients underwent baseline imaging of the brain, chest, abdomen (including pelvis), and bone (appendix p 34). Disease evaluation during the study was performed using RECIST v1.1 for all patients, every 6 weeks from randomisation until approximately 1 year, and every 12 weeks thereafter. Brain scans (for patients with no brain metastases at baseline) and bone scans were performed at 12-week intervals. Data for patient-reported outcomes were collected on days 1 and 15 of the first four treatment cycles, then on day 1 of every cycle until the end of treatment visit (28–35 days after the last dose of study treatment).

Outcomes

The primary endpoint was progression-free survival assessed by BICR per RECIST v1.1. Secondary endpoints included objective response rate by BICR per RECIST v1.1, duration of response, overall survival, 1-year overall survival rate, patient-reported outcomes, safety, and pharmacokinetics of adagrasib. Exploratory endpoints included intracranial activity (intracranial objective response rate, duration of response, progression-free survival, and time to progression), assessed using CNS-adapted RECIST v1.1, in patients with brain metastases at baseline according to an independent CNS imaging charter and neuroradiologist review. Patient-reported outcomes were assessed using the Lung Cancer Symptom Scale (LCSS)[14] and the 5-level version of the EQ-5D (EQ-5D-5L).[15] Further details on endpoint definitions are given in the appendix (pp 31–33). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0, and reported using the Medical Dictionary for Regulatory Activities, version 26.0. Patients were followed for adverse events for at least 28 days after the last study dose.

Statistical analysis

Approximately 450 patients were planned to undergo 2:1 random allocation to receive adagrasib or docetaxel. For the primary endpoint of progression-free survival by BICR, the study had 90% power to detect a hazard ratio (HR) of 0·645 (under the assumption of median progression-free survival of approximately 4 months for the docetaxel group compared with 6·2 months for the adagrasib group) at a two-sided level of significance of 0·05 based on 246 events. Efficacy was assessed in the intention-to-treat population; safety was evaluated in all patients who received a treatment dose. The study had one planned analysis for progression-free survival and objective

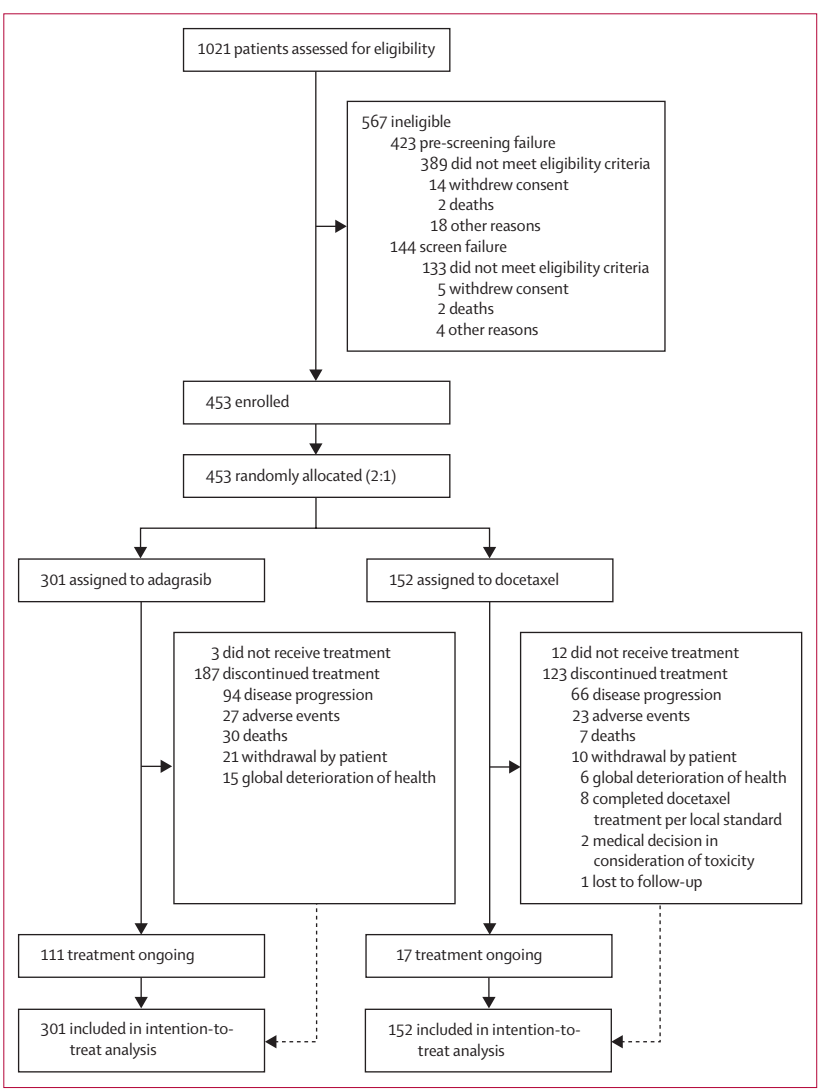

Figure 1: **Trial profile**
One patient with screen failure was not counted due to an Interactive Response Technology integration issue.

	Adagrasib (n=301)	Docetaxel (n=152)
Age, years		
Median (IQR)	64·0 (59·0–69·0)	65·0 (59·0–69·5)
<65 yr	160 (53%)	74 (49%)
≥65 yr	141 (47%)	78 (51%)
Sex		
Male	193 (64%)	110 (72%)
Female	108 (36%)	42 (28%)
Race		
White	135 (45%)	81 (53%)
Asian	72 (24%)	37 (24%)
Other	2 (1%)	1 (1%)
Not reported*	81 (27%)	30 (20%)
Missing†	11 (4%)	3 (2%)
Geographic region		
Non-Asia–Pacific	223 (74%)	112 (74%)
Asia–Pacific	78 (26%)	40 (26%)
ECOG performance status score‡		
0	96 (32%)	47 (31%)
1	205 (68%)	104 (68%)
Disease stage		
Locally advanced	18 (6%)	8 (5%)
Metastatic	283 (94%)	144 (95%)
Histological type of tumour		
Adenocarcinoma	283 (94%)	147 (97%)
Squamous	6 (2%)	0
Other§	12 (4%)	5 (3%)
Smoking status‡		
Never smoked	17 (6%)	9 (6%)
Current or former smoker	284 (94%)	142 (93%)
Metastases at baseline		
Brain¶	78 (26%)	36 (24%)
Liver‖	46 (15%)	18 (12%)
Bone‖	68 (23%)	39 (26%)
PD-L1 expression level**		
<1%	61 (20%)	34 (22%)
1–49%	126 (42%)	69 (45%)
≥50%	71 (24%)	29 (19%)
Not available	43 (14%)	20 (13%)
Previous chemotherapy and immunotherapy		
Sequential	80 (27%)	41 (27%)
Concurrent	221 (73%)	111 (73%)
Previous lines of therapy in advanced or metastatic setting		
1	205 (68%)	110 (72%)
2	74 (25%)	35 (23%)
>2	20 (7%)	7 (5%)
Time since previous immunotherapy		
<30 days	22 (7%)	8 (5%)
≥30 days	276 (92%)	132 (87%)

Data are n (%) unless otherwise stated. Percentages might not add up to 100 due to rounding. PD-L1=programmed death ligand 1. RECIST v1.1=Response Evaluation Criteria In Solid Tumors version 1.1. *Not reported due to country-specific restrictions or patient discretion not to report race. †Missing after removal due to local regulations. ‡Data missing for one patient in docetaxel group. §Other histologies for adagrasib and docetaxel groups, respectively, were large-cell carcinoma (n=4 and n=1), unclassified or undifferentiated (n=6 and n=1), and other (n=2 and n=3). ¶In accordance with CNS-adapted RECIST v1.1 per separate CNS imaging charter and neuroradiologist review. ‖In accordance with RECIST v1.1 per blinded independent central review. **PD-L1 expression data are based on previous testing performed.

Table 1: **Baseline characteristics**

response rate by BICR (presented here), and an interim and final analysis for overall survival (the final overall survival analysis will only be conducted if the interim overall survival analysis is not statistically significant).

A hierarchical testing procedure was used to control the familywise error rate for the primary and secondary efficacy endpoints, with an overall type I error rate (two-sided) of 0·05: objective response rate was to be tested if progression-free survival was statistically significant; overall survival was to be tested if objective response rate was statistically significant. The overall survival hypothesis was to be tested with the O'Brien–Fleming boundary as implemented by the Lan–DeMets alpha spending method at interim analysis. The sample size and power calculation were performed using the software East version 6.5.

Progression-free survival, overall survival, and time to deterioration of LCSS were estimated using the Kaplan–Meier method, and a stratified log-rank test was used to compare between treatment groups. The HR was obtained using a stratified Cox proportional hazard model. Time to deterioration of LCSS was defined as definitive deterioration per Walding and colleagues (appendix p 33).[16] Descriptive statistics for objective response rate and intracranial objective response rate were calculated, and the Cochran–Mantel–Haenszel test was used to compare systemic objective response rate between treatment groups. Duration of response was summarised descriptively using the Kaplan–Meier estimate. This study is registered at ClinicalTrials.gov (NCT04685135) and is active but no longer recruiting.

Role of the funding source

The sponsor Mirati Therapeutics, a Bristol Myers Squibb company, was involved in the design and conduct of the study, the analysis and interpretation of the data, and the decision to submit this manuscript. The sponsor also provided medical writing support.

Results

Between Feb 23, 2021, and Nov 16, 2023, a total of 1021 patients were screened; 567 (56%) were ineligible and 453 (44%) patients underwent random allocation in a 2:1 ratio to adagrasib (301 [66%]) or docetaxel (152 [34%]). Overall, 298 (99%) patients received adagrasib

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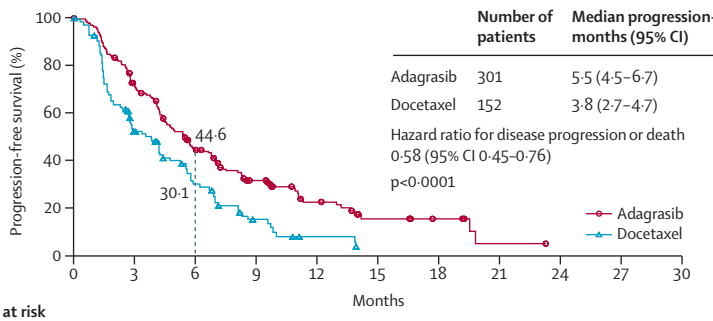


	Number of patients	Median progression-free survival, months (95% CI)
Adagrasib	301	5·5 (4·5–6·7)
Docetaxel	152	3·8 (2·7–4·7)

Hazard ratio for disease progression or death 0·58 (95% CI 0·45–0·76)
p<0·0001

Number at risk (censored)											
Adagrasib	301 (0)	160 (68)	77 (96)	41 (112)	19 (125)	8 (131)	5 (134)	1 (136)	0 (137)	0 (137)	0 (137)
Docetaxel	152 (0)	51 (43)	24 (51)	9 (55)	2 (58)	0 (59)	0 (59)	0 (59)	0 (59)	0 (59)	0 (59)

B

	Number of patients	Median progression-free survival, months (95% CI)		Unstratified hazard ratio for disease progression or death (95% CI)
		Adagrasib (n=301)	Docetaxel (n=152)	
Overall	453	5·5 (4·5–6·7)	3·8 (2·7–4·7)	0·58 (0·45–0·75)
Age				
<65 years	234	5·4 (4·2–6·0)	2·9 (1·8–5·6)	0·56 (0·40–0·79)
≥65 years	219	5·9 (4·5–7·4)	4·2 (2·7–6·2)	0·60 (0·40–0·89)
Sex				
Male	303	5·4 (4·4–6·7)	2·9 (2·3–4·2)	0·55 (0·41–0·75)
Female	150	5·6 (4·3–7·4)	5·6 (3·4–5·9)	0·64 (0·39–1·06)
Geographic region				
Non-Asia–Pacific	335	5·7 (4·6–7·0)	3·4 (2·0–4·7)	0·55 (0·40–0·74)
Asia–Pacific	118	5·4 (4·1–6·9)	3·9 (2·7–6·9)	0·66 (0·40–1·08)
ECOG performance status score				
0	143	11·1 (5·8–13·9)	5·8 (2·7–6·9)	0·44 (0·26–0·74)
1	309	4·6 (4·1–5·6)	2·8 (1·8–3·9)	0·61 (0·45–0·82)
Smoking status				
Current or former smoker	426	5·5 (4·5–6·8)	3·6 (2·7–4·4)	0·56 (0·43–0·74)
Never smoked	26	5·5 (1·7–10·9)	6·2 (0·9–NE)	0·70 (0·26–1·88)
Brain metastases				
Yes	114	4·4 (3·1–5·8)	2·9 (2·0–6·2)	0·70 (0·43–1·15)
No	339	5·9 (4·8–7·2)	3·9 (2·4–5·6)	0·54 (0·40–0·73)
Liver metastases				
Yes	64	4·5 (2·8–7·0)	1·4 (0·5–3·9)	0·43 (0·22–0·83)
No	389	5·6 (4·6–6·9)	4·2 (2·8–5·6)	0·59 (0·45–0·78)
Bone metastases				
Yes	107	4·4 (2·8–7·0)	2·8 (1·4–5·8)	0·56 (0·34–0·93)
No	346	5·8 (4·8–6·9)	4·2 (2·7–5·6)	0·58 (0·43–0·78)
Tumour PD-L1 expression				
<1%	95	5·8 (3·3–11·2)	2·8 (1·6–6·2)	0·44 (0·25–0·80)
1–49%	195	5·9 (4·5–7·2)	3·6 (1·8–5·3)	0·56 (0·38–0·82)
≥50%	100	5·0 (4·1–7·1)	3·9 (2·3–7·0)	0·62 (0·35–1·12)
Previous chemotherapy and immunotherapy				
Sequential	121	5·8 (4·5–7·2)	2·9 (1·6–6·9)	0·53 (0·31–0·90)
Concurrent	332	5·4 (4·3–6·7)	3·9 (2·7–5·6)	0·60 (0·45–0·81)

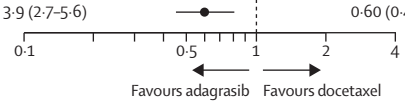


Figure 2: **Progression-free survival according to masked independent central review**
(A) Progression-free survival in the intention-to-treat population was assessed by masked independent central review according to RECIST v1.1. Median follow-up for progression-free survival was 7·2 months (95% CI 5·8–8·7). (B) Progression-free survival in patient subgroups. Brain metastases at baseline were assessed using CNS-adapted RECIST v1.1 per separate CNS imaging charter and neuroradiologist review. Liver and bone metastases at baseline were assessed using RECIST v1.1 per masked independent central review. PD-L1=programmed death ligand 1. RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1.

(four patients initially received the capsule formulation; all others received the tablet formulation) and 140 (92%) received docetaxel (figure 1). Three (1%) patients did not receive adagrasib due to death, global deterioration of health, and disease progression (one patient each); 12 (8%) patients did not receive docetaxel, one due to global deterioration of health and 11 due to patient withdrawal. At the data cutoff on Dec 31, 2023, 111 (37%) patients were still receiving adagrasib and 17 (11%) were still receiving docetaxel, while 187 (62%) and 123 (81%) had discontinued adagrasib or docetaxel, respectively (figure 1). The median duration of treatment was 3·9 months (IQR 1·8–7·6) with adagrasib and 2·7 months (1·4–4·2) with docetaxel (median number of cycles 4·0 [IQR 2·0–6·0]). Overall, 74 (25%) patients in the adagrasib group and 69 (45%) in the docetaxel group received any subsequent anti-cancer therapy; 44 (29%) patients crossed over from the docetaxel group to the adagrasib group following confirmation of disease progression by BICR (appendix p 35).

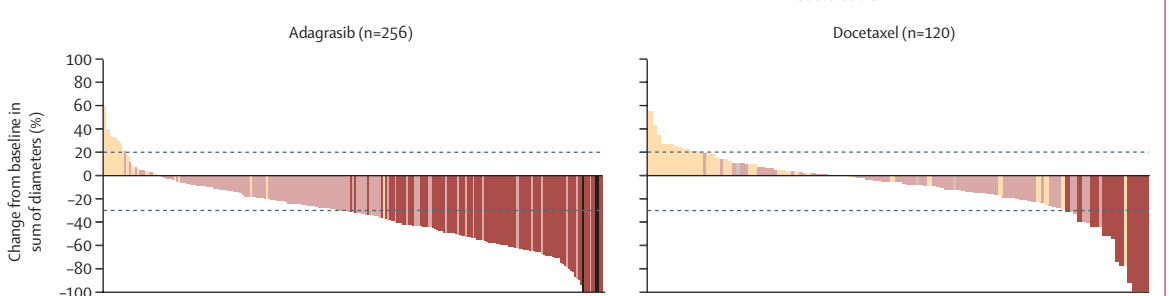
Patient baseline characteristics are shown in table 1. Although race was not reported for approximately one-quarter of patients due to country-specific restrictions or patient discretion, the patients included were broadly representative of the overall population with *KRAS*^{G12C}-mutated NSCLC (appendix p 36).

With a median follow-up for progression-free survival of 7·2 months (95% CI 5·8–8·7), median progression-free survival by BICR with adagrasib was 5·5 months (95% CI 4·5–6·7) versus 3·8 months (2·7–4·7) with docetaxel (HR 0·58 [95% CI 0·45–0·76]; p<0·0001; figure 2A). Similar results were observed for progression-free survival per investigator assessment (median progression-free survival 5·4 months [95% CI 4·6–6·9] *vs* 2·9 months [2·5–4·2] with adagrasib *vs* docetaxel, respectively; HR 0·57 [95% CI 0·45–0·74]; appendix p 45). Improvement in progression-free survival with adagrasib over docetaxel was consistent across all patient subgroups, including patients with brain metastases at baseline (figure 2B). Objective response rate by BICR was significantly higher with adagrasib compared with docetaxel (32% [95% CI 26·7–37·5] *vs* 9% [5·1–15·0], respectively; odds ratio 4·68 [95% CI 2·56–8·56]; p<0·0001), with three (1%) complete responses and 93 (31%) partial responses observed with adagrasib, and 14 partial responses (9%) with docetaxel (figure 3; appendix p 37). The disease control rate was 78% versus 59% for adagrasib versus docetaxel, respectively (figure 3A; appendix p 37). Median duration of response was longer with adagrasib than with docetaxel (8·3 months [95% CI 6·1–10·4] *vs* 5·4 months [2·9–8·5], respectively; figure 3A). Overall, reduction in tumour size was observed in 227 (75%) and 72 (47%) patients in the adagrasib and docetaxel groups, respectively (figure 3A). Improvement in objective response rate with adagrasib over docetaxel was consistent across all patient subgroups, including patients with brain metastases at baseline (figure 3B).

78 (26%) patients with measurable or non-measurable baseline brain metastases in the adagrasib group and 36 (24%) patients in the docetaxel group (identified by an independent CNS imaging charter and neuroradiologist review) were assessed for intracranial response in accordance with CNS-adapted RECIST v1.1. The

A

Tumour response	Adagrasib (n=301)	Docetaxel (n=152)
Objective response	96 (32%)	14 (9%)
Complete response	3 (1%)	0
Partial response	93 (31%)	14 (9%)
Disease control rate	236 (78%)	89 (59%)
Median duration of response, months (95% CI)	8·3 (6·1–10·4)	5·5 (2·9–8·5)
Patients with a response who had ongoing responses at 6 months, % (95% CI)	64% (50·9–74·0)	39% (12·6–65·3)



(Figure 3 continues on next page)

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	Number of patients	Objective response rate, % (95% CI)		Unweighted difference in objective response rate, % (95% CI)
		Adagrasib (n=301)	Docetaxel (n=152)	
Overall	453	32% (26·7–37·5)	9% (5·1–15·0)	22·7% (15·1–29·3)
Age				
<65 years	234	33% (25·9–41·0)	11% (4·8–20·2)	22·3% (10·9–31·6)
≥65 years	219	30% (23·0–38·8)	8% (2·9–16·0)	22·8% (12·1–31·8)
Sex				
Male	303	30% (23·2–36·5)	9% (4·4–16·1)	20·4% (11·4–28·4)
Female	150	36% (27·1–45·9)	10% (2·7–22·6)	26·6% (11·5–37·6)
Geographic region				
Non-Asia–Pacific	335	33% (26·6–39·3)	10% (5·0–16·9)	22·9% (13·9–30·6)
Asia–Pacific	118	29% (19·7–40·9)	8% (1·6–20·4)	22·0% (6·7–33·9)
ECOG performance status score				
0	143	35% (25·9–45·8)	17% (7·6–30·8)	18·4% (2·6–31·3)
1	309	30% (24·0–37·0)	6% (2·1–12·1)	24·5% (15·9–31·8)
Smoking status				
Current or former smoker	426	31% (26·0–37·1)	9% (5·0–15·1)	22·2% (14·4–28·9)
Never smoked	26	41% (18·4–67·1)	11% (0·3–48·2)	30·1% (-7·8–54·6)
Brain metastases				
Yes	114	27% (17·5–38·2)	3% (0·1–14·5)	24·1% (9·9–35·1)
No	339	34% (27·5–40·2)	11% (6·1–18·4)	22·4% (13·3–30·3)
Liver metastases				
Yes	64	28% (16·0–43·5)	6% (0·1–27·3)	22·7% (-0·3–37·7)
No	389	33% (26·8–38·7)	10% (5·3–16·0)	22·8% (14·6–30·0)
Bone metastases				
Yes	107	34% (22·8–46·3)	8% (1·6–20·9)	26·1% (10·0–39·0)
No	346	31% (25·4–37·7)	10% (5·0–16·8)	21·6% (12·7–29·1)
Tumour PD-L1 expression				
<1%	95	36% (24·2–49·4)	9% (1·9–23·7)	27·2% (9·4–41·1)
1–49%	195	33% (24·5–41·5)	12% (5·1–21·6)	20·9% (8·7–31·2)
≥50%	100	25% (15·8–37·1)	7% (0·8–22·8)	18·5% (1·1–30·7)
Previous chemotherapy and immunotherapy				
Sequential	121	38% (26·9–49·0)	10% (2·7–23·1)	27·7% (11·6–40·2)
Concurrent	332	30% (23·9–36·4)	9% (4·4–15·9)	20·9% (12·0–28·4)

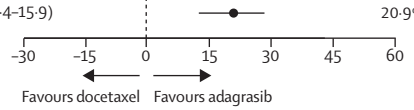

Figure 3: **Tumour response according to blinded independent central review**

(A) Objective response rate, disease control rate, and duration of response among all patients, and maximum tumour change from baseline among patients who had at least one target lesion at baseline and at least one post-baseline tumour assessment. Tumour response was assessed by blinded independent central review according to RECIST v1.1. Duration of response was only calculated for patients with confirmed complete or partial response. (B) Objective response rates in patient subgroups. Brain metastases at baseline were assessed using CNS-adapted RECIST v1.1 per separate CNS imaging charter and neuroradiologist review. Liver and bone metastases at baseline were assessed using RECIST v1.1 per blinded independent central review. PD-L1=programmed death ligand 1. RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1.

intracranial objective response rate was 24% (95% CI 15·3–35·4) with adagrasib and 11% (3·1–26·1) with docetaxel, with complete intracranial responses observed in 11 (14%) and three (8%) patients, respectively (figure 4). Intracranial disease control was reached in 82% of patients in the adagrasib group and 56% in the docetaxel group. In a subgroup of patients with baseline brain metastases who had at least one measurable CNS target lesion at baseline and at least one post-baseline CNS tumour assessment, the intracranial objective response rate was 40% (ten of 25) with adagrasib and 11% (one of nine) with docetaxel (figure 4). Median intracranial time to progression with adagrasib was 18·6 months (95% CI 9·6–not evaluable [NE]) versus NE (95% CI 4·2–NE) with docetaxel (HR 0·60 [95% CI 0·26–1·40]; appendix p 46). The HR for intracranial progression-free survival was 0·93 (95% CI 0·50–1·73).

Symptom burden and quality of life were assessed using the LCSS and the EQ-5D-5L (not reported here). In the patient-reported outcome analysis population (patients with data at baseline and ≥1 post-baseline visit), over 80% of patients in both treatment groups completed

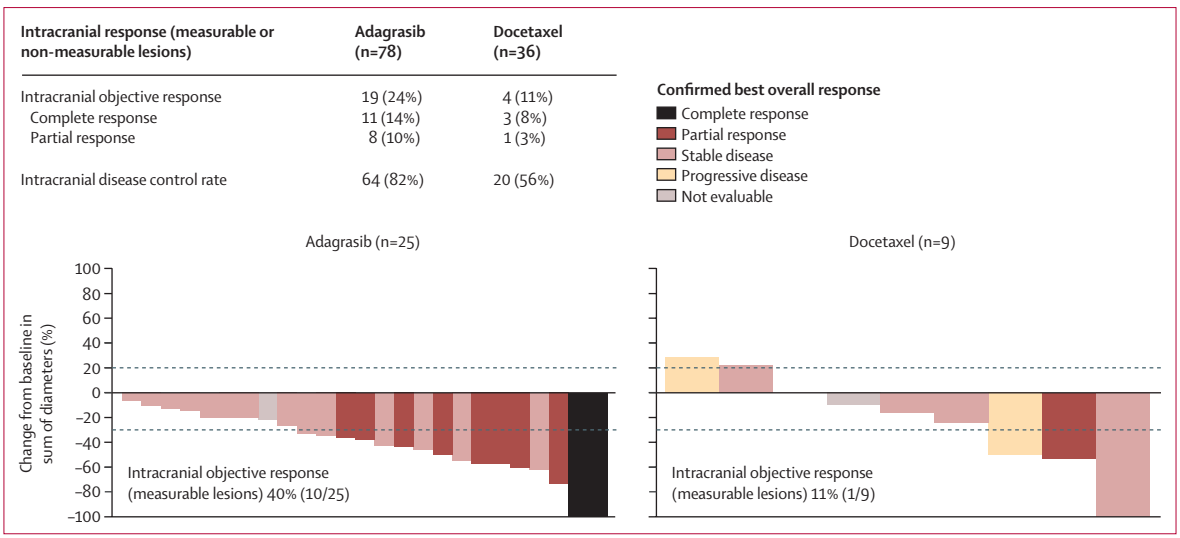

Figure 4: **Intracranial tumour response**
Intracranial objective response rates and intracranial disease control rates among all patients with measurable or non-measurable baseline brain metastases assessed by blinded independent central review according to CNS-adapted Response Evaluation Criteria in Solid Tumors version 1.1. CNS data (including identification of patients with baseline brain metastases) were based on a separate CNS imaging charter and neuroradiologist review. Waterfall plots show the maximum intracranial tumour change from baseline among patients who had at least one measurable CNS target lesion at baseline and at least one post-baseline CNS tumour assessment. For lesions to be considered target lesions, they must have been measurable and either not previously treated with CNS-directed therapy or must have progressed after prior CNS-directed therapy.

	Adagrasib (n=298)		Docetaxel (n=140)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
All	280 (94%)	140 (47%)	121 (86%)	64 (46%)
Leading to dose reduction	143 (48%)	78 (26%)	33 (24%)	20 (14%)
Leading to dose interruption	177 (59%)	115 (39%)	26 (19%)	11 (8%)
Leading to discontinuation of treatment	23 (8%)	15 (5%)	20 (14%)	11 (8%)
Serious	62 (21%)	56 (19%)	23 (16%)	21 (15%)
Treatment-related deaths†	4 (1%)	4 (1%)	1 (1%)	1 (1%)

Data are n (%). *Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0, and reported using the Medical Dictionary for Regulatory Activities, version 26.0. Patients were followed up for adverse events for at least 28 days after the last study dose. †Treatment-related deaths in the adagrasib group were due to epilepsy, hepatic failure, hepatic ischemia, and unknown cause (in one patient each). The treatment-related death in the docetaxel group were due to sepsis (one patient).

Table 2: **Summary of treatment-related adverse events***

assessments at baseline and during treatment (until cycle 20). Symptom burden and quality of life were similar between treatment groups at baseline; the mean LCSS average total score was 29·6 (SD 18·7) in the adagrasib group and 30·7 (19·3) in the docetaxel group (on a scale ranging from 0–100, with higher scores indicating a worse symptom burden). Patients in the adagrasib group had a longer time to deterioration of LCSS than those in the docetaxel group, with a median time of 3·0 months (95% CI 2·7–4·1) and 1·5 months (1·3–1·9), respectively (HR 0·57 [95% CI 0·45–0·74]; appendix p 47).

Treatment-related adverse events (TRAEs) of any severity were reported for 94% (280 of 298) and 86% (121 of 140) of patients in the adagrasib and docetaxel groups, respectively (table 2). Gastrointestinal-related adverse events were the most common any grade TRAEs in the adagrasib group, including diarrhoea (158 [53%] of 298), vomiting (103 [35%]), and nausea (101 [34%]), which were mostly grade 1 (appendix p 38). In the docetaxel group, the most frequently observed TRAEs were diarrhoea (43 [31%] of 140; mostly grade 1), anaemia (42 [30%]; mostly grade 2), and asthenia (38 [27%]; mostly grade 3; appendix p 38). TRAEs of grade 3 and above were reported for 140 (47%) patients treated with adagrasib (39% grade 3, 7% grade 4, 1% grade 5) and 64 (46%) treated with docetaxel (27% grade 3, 18% grade 4, 1% grade 5; table 2). The most common were alanine aminotransferase (ALT) increase (23 [8%]), aspartate aminotransferase (AST) increase (19 [6%]), and diarrhoea (16 [5%]) in the adagrasib group, and decreased neutrophil count (16 [11%]), neutropenia (14 [10%]), and asthenia (14 [10%]) in the docetaxel group (appendix p 38). A post-hoc analysis showed that among 22 patients who had received previous immunotherapy less than 30 days before the start of adagrasib, any grade ALT increase occurred in 18% of patients (5% grade ≥3) and AST increase in 23% (0% grade ≥3), while among 276 patients who had received immunotherapy 30 days or more before adagrasib treatment, any grade ALT increase occurred in 31% of patients (8% grade ≥3) and AST increase in 32% (7% grade ≥3). Time to onset and resolution of common TRAEs (post-hoc analysis) are presented in the appendix (pp 39–40). Overall, 153 (51%) of patients had an adagrasib dose reduction due to adverse events (appendix p 41). Dose reduction, dose interruption, and treatment discontinuation due to TRAEs occurred in 143 (48%), 177 (59%), and 23 (8%) patients in the adagrasib group, respectively, and

in 33 (24%), 26 (19%), and 20 (14%) patients in the docetaxel group, respectively (table 2; appendix pp 42–43). There were four treatment-related deaths with adagrasib due to epilepsy, hepatic failure, hepatic ischaemia, and unknown cause (one patient each; all in patients who had received previous immunotherapy ≥30 days before start of adagrasib), and one treatment-related death from sepsis with docetaxel.

Discussion

In the phase 3 KRYSTAL-12 trial, adagrasib demonstrated a statistically significant improvement in progression-free survival by BICR compared with docetaxel (HR 0·58 [95% CI 0·45–0·76]; p<0·0001). Furthermore, a significantly higher proportion of patients had objective tumour responses (by BICR) with adagrasib versus docetaxel (32% *vs* 9%, respectively; p<0·0001), and these responses appeared to be more durable. Improvements in progression-free survival and objective response rate were observed with adagrasib across all patient subgroups, including those with baseline brain metastases and regardless of whether previous chemotherapy and immunotherapy were given concurrently or sequentially. The robustness of these data is demonstrated by the high rate of patients receiving treatment after random allocation, the permitted crossover from docetaxel to adagrasib only after BICR confirmation of disease progression, and the consistency in BICR and investigator-assessed progression-free survival. Additionally, the efficacy of docetaxel in this study was consistent with that seen in previous studies in patients with advanced NSCLC previously treated with chemotherapy and immunotherapy.[17–19] However, we acknowledge that the treatment landscape for advanced NSCLC has evolved since the initiation of this study, and docetaxel may not be an appropriate comparator group for any future KRAS^{G12C} inhibitor studies in this patient population. Another limitation of this analysis was that overall survival data were immature at the current data cutoff and will be reported at a later date. Overall, the efficacy and safety results from the KRYSTAL-12 trial reinforce the findings from the phase 2 KRYSTAL-1 trial.[8]

CNS metastases are observed in approximately 27–42% of patients with advanced *KRAS*^{G12C}-mutated NSCLC at diagnosis.[20–22] Consistent with its known brain penetrance,[8] intracranial activity was observed with adagrasib in patients with treated, neurologically stable measurable brain metastases at baseline, with an intracranial objective response rate of 40% versus 11% with docetaxel. In a retrospective, exploratory analysis of the CodeBreaK 200 study,[23] an intracranial objective response rate of 20% was seen with sotorasib in all patients with CNS lesions at baseline.[23] Of note, the intracranial efficacy data from both KRYSTAL-12 and CodeBreaK 200 are for patients with stable, treated brain metastases, and are potentially confounded by the use of prior radiotherapy or surgery. Caution should be used for cross-trial comparisons due to differences in study designs (including stratification factors), patient populations, follow-up time, and geographical footprint. Importantly, adagrasib is the only KRAS^{G12C} inhibitor that has prospectively demonstrated promising intracranial activity in patients with *KRAS*^{G12C}-mutated NSCLC and untreated brain metastases at baseline, as shown in a phase 1b cohort of the KRYSTAL-1 trial (intracranial objective response rate of 42% and intracranial duration of response of 12·7 months).[10]

In this refractory, non-curative treatment setting, patient quality of life is an important consideration; therefore, we evaluated the effect of adagrasib and docetaxel on symptom burden and health-related quality of life throughout the study. Based on LCSS assessments, patients treated with adagrasib had a decreased risk of symptom deterioration compared with patients receiving docetaxel (HR 0·57). Together with a higher disease control rate (78% *vs* 59%) and rate of reduction in tumour size (75% *vs* 47%) with adagrasib compared with docetaxel, these results suggest a longer duration of symptom burden control and overall clinical benefit with adagrasib.

In the KRYSTAL-12 study, adagrasib had a manageable safety profile, with no new safety signals, and with a longer treatment duration versus docetaxel. As previously reported,[8] the most common any grade TRAEs with adagrasib were gastrointestinal-related, including diarrhoea, vomiting, and nausea; these TRAEs, as well as other common TRAEs including decreased appetite and increased blood creatinine, were mainly grade 1 and resolved quickly. Adagrasib-related adverse events can be managed with appropriate strategies, including dose modifications, concomitant medications, lifestyle changes, and monitoring.[24] The incidence of grade 3 and higher TRAEs was similar between treatment groups, but grade 4 TRAEs were more common with docetaxel (18%) than with adagrasib (7%). The most common grade 3 or higher TRAEs with adagrasib were ALT increase (8%) and AST increase (6%). Of note, there was no increased incidence of grade 3 and higher ALT and AST elevation in patients treated with adagrasib within 30 days of previous immunotherapy, although these results should be interpreted with caution due to the small number of patients who had received immunotherapy within the 30 days before the start of adagrasib. The TRAEs of increased ALT and AST at grade 3 and above have also been reported across multiple clinical and real-world studies with sotorasib, particularly when given shortly after anti-PD-(L)1 therapy;[17,25–30] rates of 58–75% grade 3 and higher hepatotoxicity have been observed when sotorasib is administered less than 30 days after immunotherapy.[25,26] Therefore, a 28-day washout period between previous therapy and study treatment was used in the CodeBreaK 200 study, resulting in rates of 8% and 5% grade 3 and above increased ALT and AST,

respectively.[17] Overall, there was a low incidence of hepatotoxicity in KRYSTAL-12, with no mandated washout period from receiving previous systemic therapy, which better reflects clinical practice, where a prolonged treatment-free period between lines of therapy is generally not desirable for patients who experience disease progression, particularly for those with advanced disease.

In conclusion, adagrasib significantly improved progression-free survival and objective response rate compared with docetaxel, confirming the initial results from KRYSTAL-1 that supported the accelerated or conditional approval of adagrasib for patients with previously treated *KRAS*^{G12C}-mutated advanced NSCLC.[8] Additionally, adagrasib demonstrated intracranial activity in patients with baseline brain metastases, which are common in patients with advanced *KRAS*^{G12C}-mutated NSCLC. The safety profile of adagrasib was manageable and consistent with previous reports. Despite the current absence of overall survival data, these results reinforce adagrasib as an efficacious treatment option for patients with *KRAS*^{G12C}-mutated advanced NSCLC after disease progression on previous chemotherapy and immunotherapy. Adagrasib is being further evaluated as monotherapy in previously treated patients with *KRAS*^{G12C}-mutated advanced NSCLC (600 mg twice a day *vs* 400 mg twice a day; KRYSTAL-21; NCT05853575), and in the first-line setting in combination with pembrolizumab (KRYSTAL-7; NCT04613596), or with pembrolizumab and chemotherapy (KRYSTAL-4; NCT06875310).

Contributors

FB, SL, HL, MR, WYan, JNM, and TSKM contributed to study conception and design. MD, OJ-V, SL, GLR, MFM, WYan, JNM, and TSKM contributed to data analysis. FB, WYao, MD, LD, AAM, VG, OJ-V, SL, Y-CK, RJ, EF, GLR, MR, MFM, WYan, JNM, BK, and TSKM contributed to data interpretation. FB and TSKM had access to and verified the data. All authors contributed to data collection and preparation of the manuscript and approved the manuscript for submission. All authors attest that the trial was conducted in accordance with the protocol and guarantee the accuracy and completeness of the data.

Declaration of interests

FB reports personal fees from AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, F. Hoffmann-La Roche, Lilly, Novartis, Merck, MSD, Pierre Fabre, Pfizer, and Takeda. MD reports consulting fees from AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, F. Hoffmann-La Roche, Gamamabs Pharma, GSK, Guardant, MSD, Novartis, Pfizer, and Takeda; grants or contracts from Lilly; payment or honoraria from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, F. Hoffmann-La Roche, Guardant, MSD, Novartis, and Pfizer; and support for attending meetings or travel from F. Hoffmann-La Roche. LD reports payment or honoraria from Amgen; and support for attending meetings or travel from MSD. VG reports consulting fees from Bristol Myers Squibb, Pfizer, and Regeneron; payment for expert testimony from Boehringer Ingelheim, Pierre Fabre, and Regeneron; and support for travel from Genfleet and MSD. 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Data sharing

Qualified researchers can request clinical trial data from Bristol Myers Squibb. The Bristol Myers Squibb policy on data sharing can be found online.

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