Supplementary Material

Title

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

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Supplementary Methods

Details of PRO questionnaires

FACT-G GP5

FACT-G GP5 is the single item, GP5, “I am bothered by side effects of treatment” that is rated on a 5-point Likert scale ranging from “not at all”, “a little bit”, “somewhat”, “quite a bit” to “very much” included in the FACT-G of the PRO instrument [25]. FACT-G GP5 has been evaluated and validated as a useful summary index of side effect impact or burden to the individual patient [25]. Patients completed the FACT-G GP5 at clinic visits on day 1 of each cycle (administered by tablet in the clinic) and at the safety follow-up (SFU).

PRO-CTCAE

PRO-CTCAE is a validated PRO instrument that was developed to evaluate symptomatic toxicity in patients in response to cancer treatments [26]. The PRO-CTCAE item library (version 1.0) consists of 124 individual questions developed to cover 78 symptoms, including pain, aching muscles, aching joints, mouth or throat sores, mouth cracking, numbness, and itchy skin. Depending on the symptom, the following attributes were assessed: severity (“none”, “mild”, “moderate”, “severe”, “very severe”); interference with usual or daily activities (“not at all”, “a little bit”, “somewhat”, “quite a bit”, “very much”); and frequency (“never”, “rarely”, “occasionally”, “frequently”, “almost constantly”). The specific questions asked in this study were composed of the general pain, muscle and joint aches, mouth or throat sores, numbness, and itchy skin items from the library. Patients completed the PRO-CTCAE questionnaire at clinic visits on day 1 of each cycle and at the SFU.

EORTC QLQ-C30 and EORTC QLQ-LC13

The EORTC QLQ-C30 is a validated self-reporting 30-item generic instrument that assesses 5 functional domains (physical, role, emotional, cognitive, and social), 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and

financial difficulties), and a global health status/QOL scale [19-21], with a recall period of the past week. The EORTC QLQ-LC13, used in conjunction with the QLQ-C30, incorporates one multi-item scale to assess dyspnea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis [22]. Patients completed the EORTC QLQ-C30 and EORTC QLQ-LC13 at clinic visits only.

EQ-5D-5L and EQ-5D VAS

The EQ-5D-5L is a validated PRO instrument for describing and valuing health [23, 24]. This includes the EQ-5D-5L instrument comprised of a short descriptive system questionnaire as well as the VAS (EQ-5D VAS). The EQ-5D-5L has five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels of responses: “no problems”, “slight problems”, “moderate problems”, “severe problems”, and “extreme problems” [23, 24]. The EQ-5D VAS asks respondents to rate their present health status on a vertical scale from 0 to 100, with 0 labeled as “the worst health you can imagine” and 100 labeled as “the best health you can imagine.” The EQ-5D-5L questionnaire was completed in the clinic on clinic visit days, including screening and SFU, and at home (data collected by phone) for the scheduled non-clinic assessment days (day 5 of cycles 1, 2, and 3), and during long-term follow up (LTFU).

BPI-SF

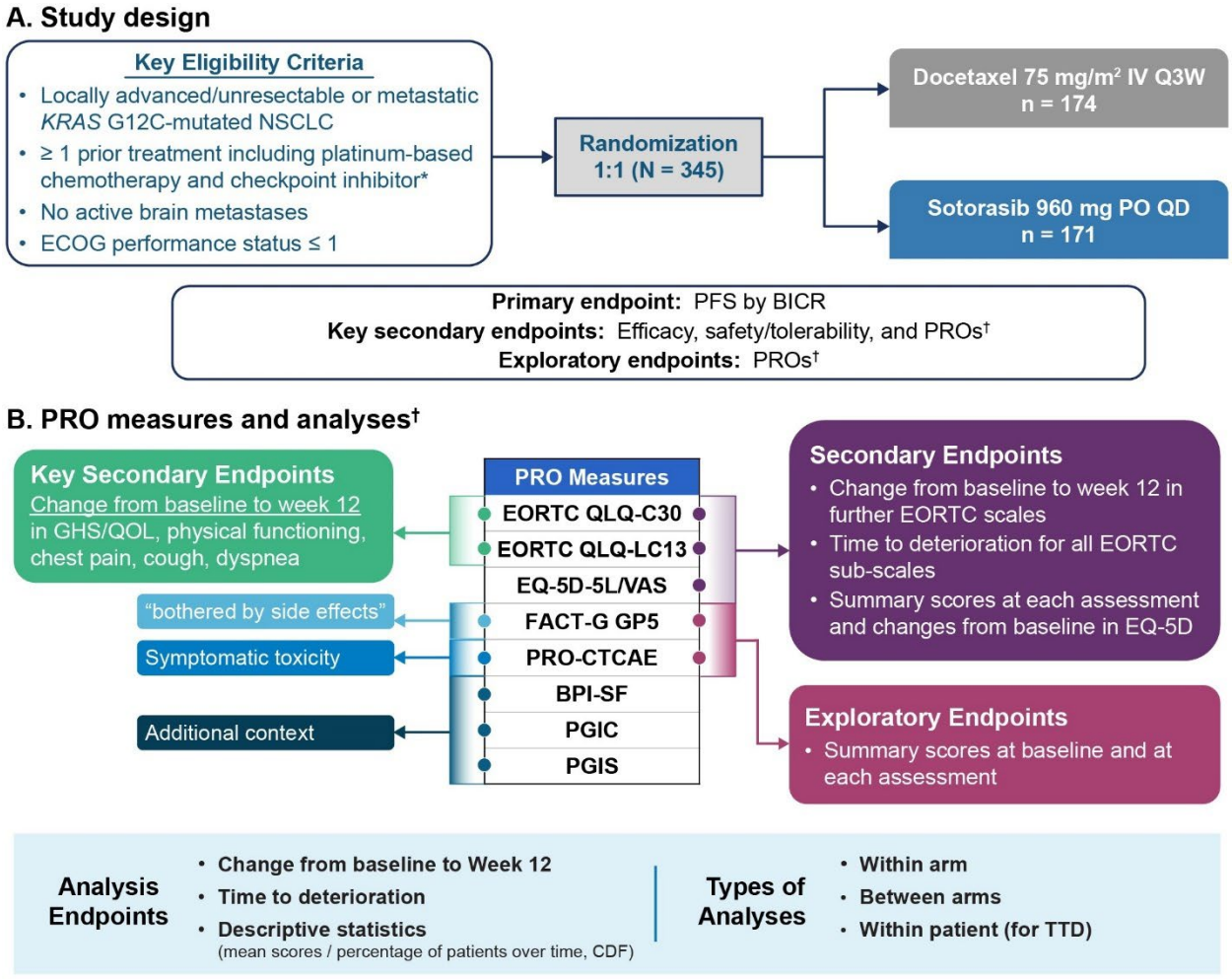
The BPI-SF is a 9-item self-administered questionnaire used to evaluate the severity of a patient’s pain and the impact of this pain on the patient’s daily functioning [27]. The patient was asked to rate their worst, least, average, and current pain intensity, list current treatments and their perceived effectiveness, and rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on an 11-point scale (0-10, where higher scores indicate worse pain). The BPI-SF was administered in the clinic at screening, at clinic visits on day 1 of each cycle, and at SFU.

PGIC and PGIS

The PGIC is a single, self-administered question asking patients to rate how their condition has changed since a certain point in time [28]. In contrast, the PGIS is a single-item, 6-point, self-administered tool that asks patients to rate their symptom or disease severity at a given time, and it is administered at multiple time points, including the start and the end of the test-retest period [28]. PGIC was collected in the clinic on day 1 of cycles 3 and cycle 5, with no collection needed at screening or cycle 1. PGIS was collected in the clinic at screening and day 1 of cycles 1, 3, and 5.

Supplementary Figures

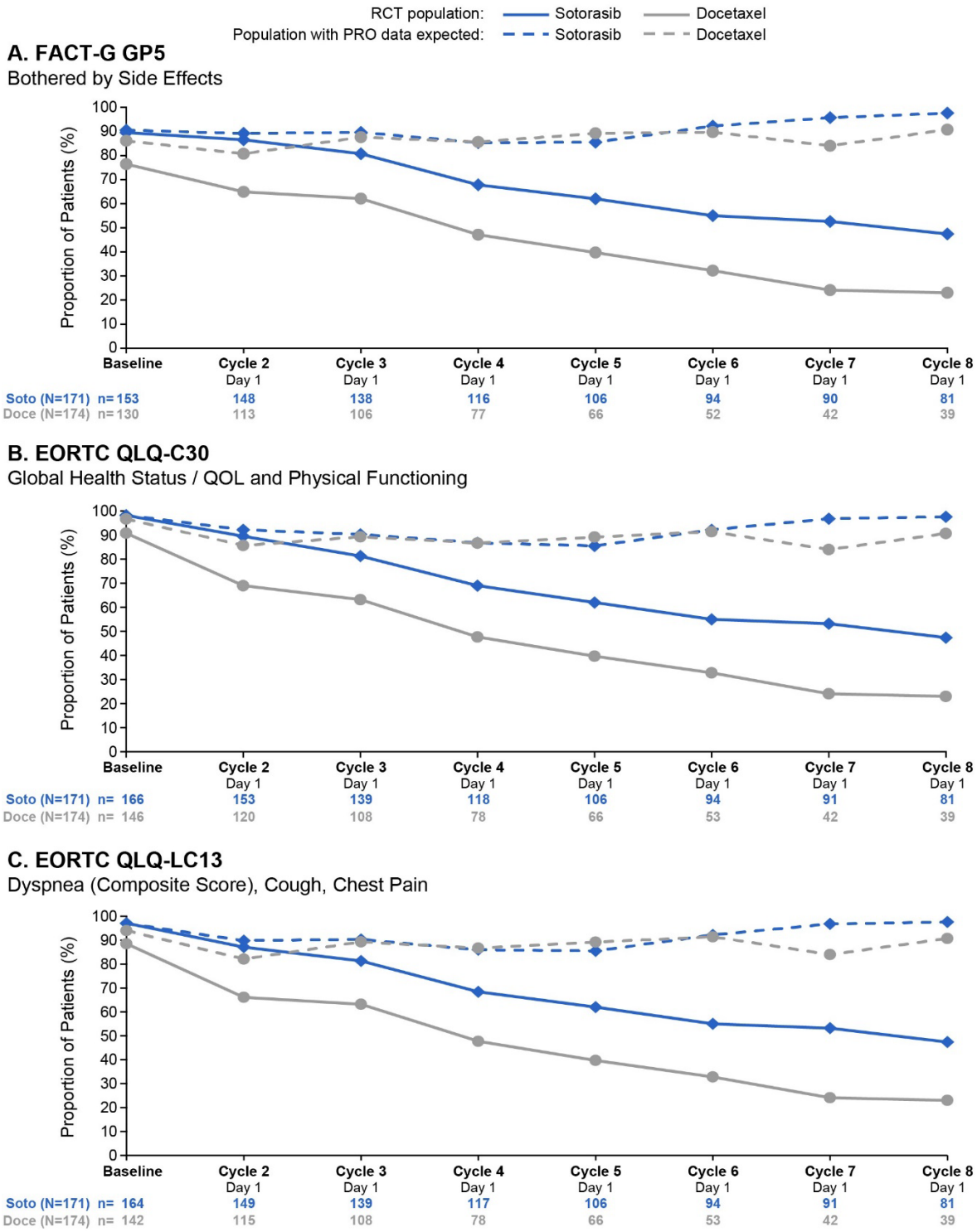
Supplementary Fig. 1. CodeBreak 200 phase III study design and endpoints



Enrollment period: June 4, 2020 to April 26, 2021; protocol amendment: February 15, 2021;‡ data cutoff date: August 2, 2022. NCT04303780; EudraCT: 2019-003582-18. Stratification factors: prior lines of therapy (1 vs 2 vs > 2), race (Asian vs non-Asian), and history of CNS involvement (yes vs no). *Treatment with chemotherapy and checkpoint inhibitor could be concurrent or sequential; patients with medical contraindication to these therapies could be included with approval. †Classified as key secondary, secondary, or exploratory PRO endpoints. ‡Per regulatory guidance, the protocol was amended to reduce the planned enrollment from 650 to ~330 patients, and crossover from docetaxel to sotorasib was permitted. BICR, blinded independent central review; BPI-SF, Brief Pain Inventory-Short Form; CDF, cumulative distribution function; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 13; EQ-5D, European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire 5 dimensions; EQ-5D-5L, 5-level European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire 5 dimensions; FACT-G GP5, Functional Assessment of Cancer Therapy Tool General Form, single item "I am bothered by side effects of treatment", rated on a 5-point Likert scale; GHS, global health status, IV, intravenously; NSCLC, non-small cell lung cancer; PFS, progression free survival; PO, orally; PRO, patient-reported outcome; PRO-CTCAE, Patient-

Reported Outcome version of the Common Terminology Criteria for Adverse Events; PGIS, Patient Global Impression of Severity; PGIC, Patient Global Impression of Change; Q3W, every 3 weeks; QD, daily; QOL, quality of life; TTD, time to treatment discontinuation; VAS, visual analog scale.

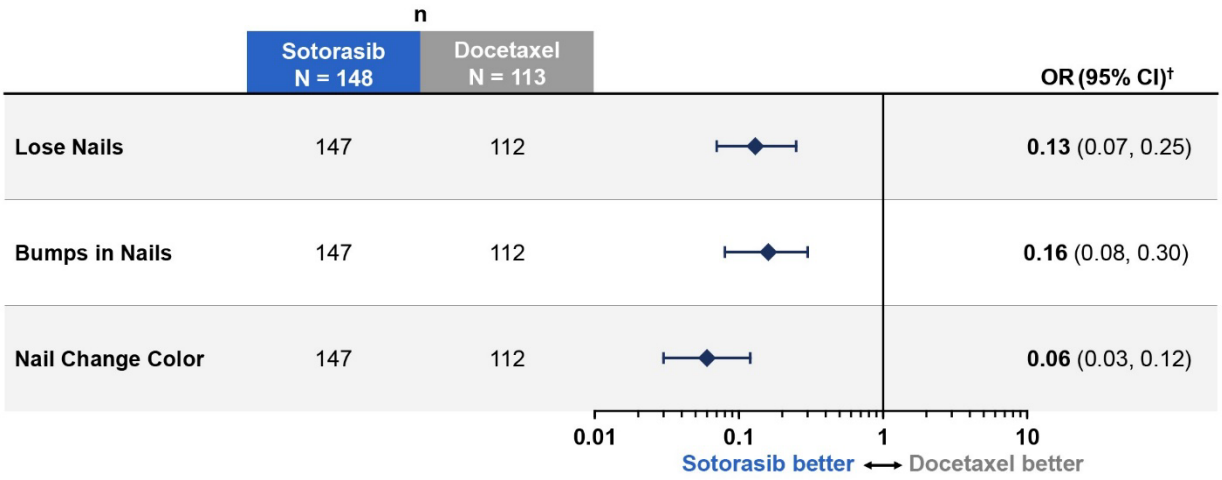
Supplementary Fig. 2. PRO data availability rates for FACT-G GP5, EORTC QLQ-C30, and EORTC QLQ-LC13



Data cutoff date: August 2, 2022. Doce, docetaxel; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30; EORTC QLQ-LC13, European

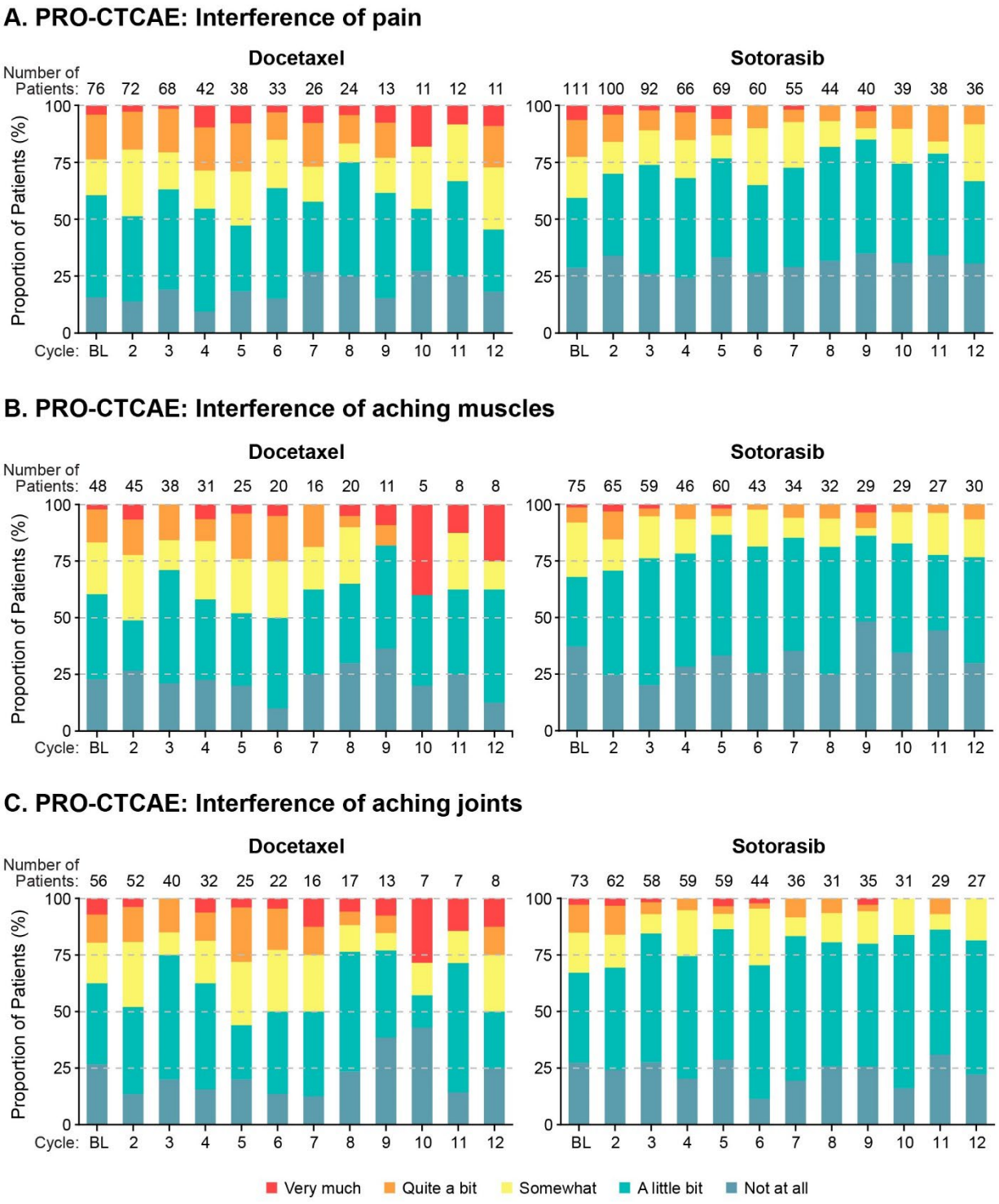
Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 13; FACT-G GP5, Functional Assessment of Cancer Therapy Tool General Form, single item “I am bothered by side effects of treatment”, rated on a 5-point Likert scale; PRO, patient-reported outcome; QOL, quality of life; RCT, randomized controlled trial; Soto, sotorasib.

Supplementary Fig. 3. Estimates of PRO-CTCAE Severity Ordinal Scales: GEE – endpoints of lose nails, bumps in nails, and nail change color (overall*)



Data cutoff date: August 2, 2022. N = number of all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements. Randomization stratification factors: number of prior lines of therapy in advanced disease (1 vs 2 vs > 2), race (Asian vs non-Asian), and history of CNS involvement (yes vs no). Due to convergence issue, we used actual assessment time as continuous variable in the model. *Overall represents all post-baseline visits, including visits beyond cycle 5 day 1, excluding follow-up visits. †OR, 95% CI, and *P*-value are estimated using a GEE model based on PRO-CTCAE results as the dependent variable, and intercept, time, baseline score, treatment, treatment-by-time interaction, and randomization stratification factors as fixed effects. All post-baseline visits are considered excluding follow-up visits. An OR > 1.0 indicates higher improvement in symptom scale for sotorasib relative to docetaxel. CI, confidence interval; CNS, central nervous system; GEE, generalized estimating equation; OR, odds ratio; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events.

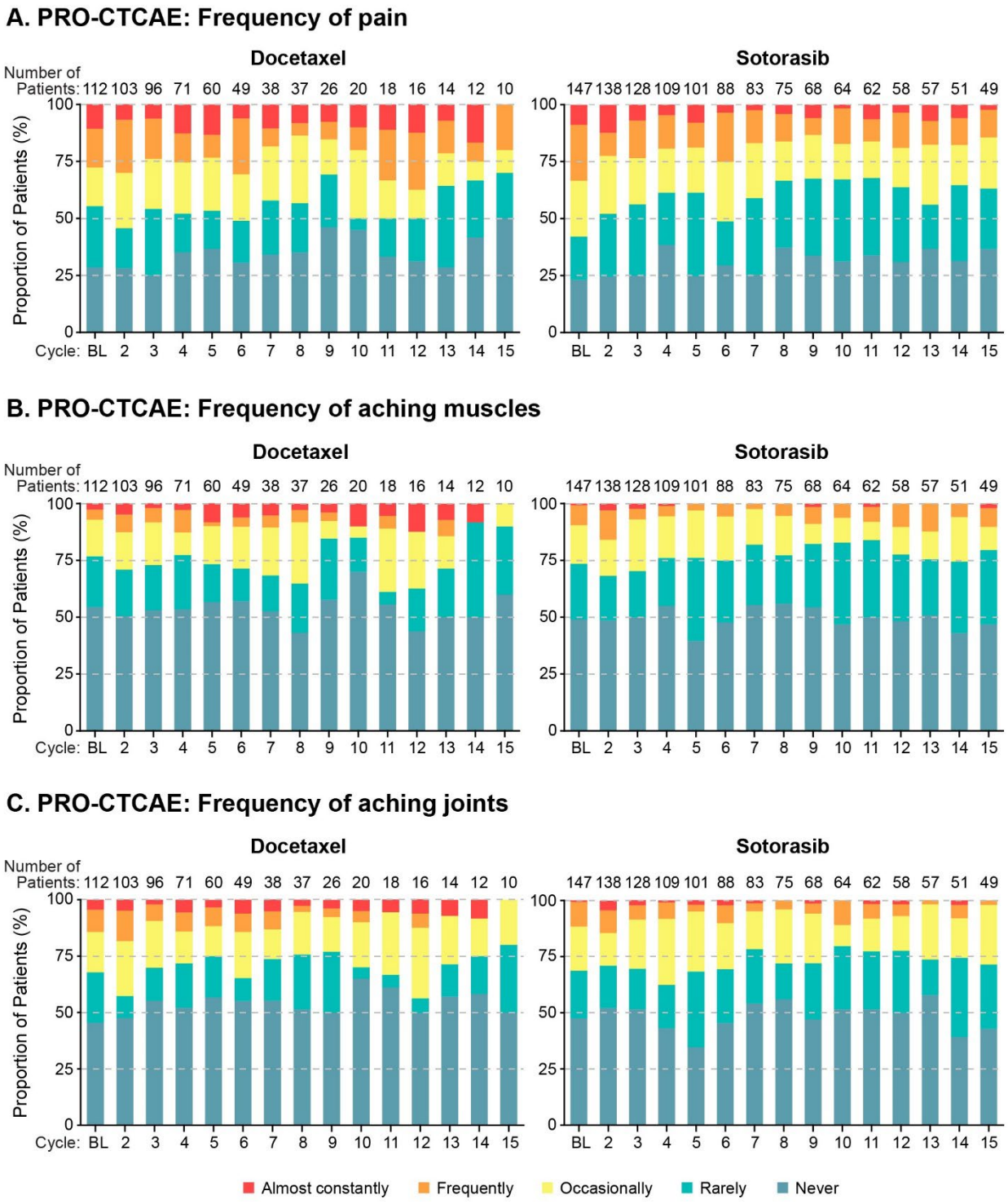
Supplementary Fig. 4. Impact of side effect on QOL by PRO-CTCAE interference



Data cutoff date: August 2, 2022.

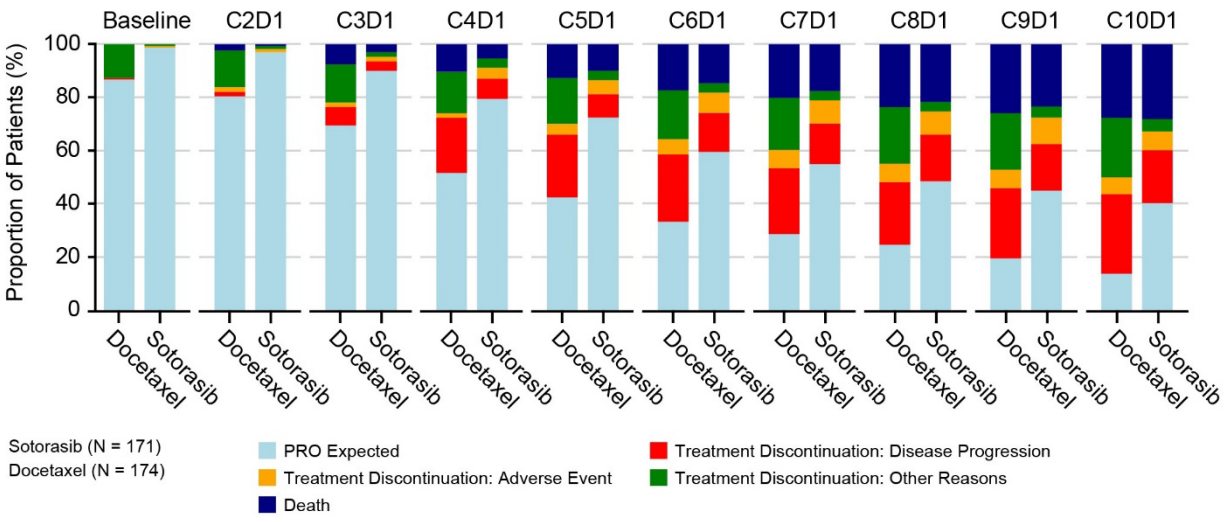
Patients completed the PRO-CTCAE questionnaire at clinic visits only except for the screening visit. BL, baseline; PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events; QOL, quality of life.

Supplementary Fig. 5. Impact of side effect on QOL by PRO-CTCAE frequency



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

Supplementary Fig. 6. Patient disposition for PRO endpoints



Data cutoff date: August 2, 2022. C, cycle; D, day; PRO, patient-reported outcome.

Supplementary Tables

Supplementary Table 1. Baseline characteristics

Characteristic	Docetaxel 75 mg/m^2 IV Q3W (N = 174)	Sotorasib 960 mg PO QD (N = 171)
Age, median (range), years	64.0 (35, 87)	64.0 (32, 88)
Female, n (%)	79 (45.4)	62 (36.3)
Race*, n (%)		
White	144 (82.8)	142 (83.0)
Asian	22 (12.6)	21(12.3)
Black or African American	0 (0)	2 (1.2)
Other	7 (4.0)	4 (2.3)
Multiple	0 (0)	1 (0.6)
Unknown	1 (0.6)	1 (0.6)
Region, n (%)		
Europe	126 (72.4)	126 (73.7)
North America	22 (12.6)	20 (11.7)
Rest of the world†	26 (14.9)	25 (14.6)
Smoking history (current or former), n (%)	166 (95.4)	166 (97.1)
ECOG performance status, n (%)		
0	59 (33.9)	59 (34.5)
1	115 (66.1)	112 (65.5)
History of CNS involvement, n (%)	60 (34.5)	58 (33.9)
Disease stage, n (%)		
Locally advanced and unresectable	8 (4.6)	9 (5.3)
Metastatic	166 (95.4)	162 (94.7)
Liver metastasis, n (%)	35 (20.1)	30 (17.5)
Previous lines of therapy,‡ n (%)		
1	78 (44.8)	77 (45.0)
2	69 (39.7)	65 (38.0)
> 2	27 (15.5)	29 (17.0)
FACT-G GP5		
Bothered by side effect (a little bit or higher), % [n1]	18.8 [112]	22.6 [146]
PRO-CTCAE		
Severity: moderate / severe / very severe, n (%) [n1]		
Pain	25 (31.3)/13 (16.3)/4 (5.0) [80]	32 (28.3)/22 (19.5)/13 (11.5) [113]
Aching joints	19 (31.1)/10 (16.4)/2 (3.3) [61]	28 (36.4)/9 (11.7)/1 (1.3) [77]
Aching muscles	14 (27.5)/8 (15.7)/1 (2.0) [51]	26 (34.7)/7 (9.3)/1 (1.3) [75]
Numbness	8 (7.1)/3 (2.7)/0 (0) [112]	11 (7.5)/ 1 (0.7)/0 (0) [147]
Itchy skin	8 (7.1)/1 (0.9)/ 0 (0) [112]	6 (4.1)/2 (1.4)/1 (0.7) [147]
Mouth of throat sores	1 (0.9)/1 (0.9)/0 (0) [112]	2 (1.4)/ 1 (0.7)/0 (0) [147]
Mouth cracking	0 (0)/0 (0)/ 1 (0.9) [112]	1 (0.7)/0 (0)/0 (0) [147]
Interference: somewhat / quite a bit / very much, n (%) [n1]		
Pain	12 (15.8)/15 (19.7)/3 (3.9) [76]	20 (18.0)/18 (16.2)/7 (6.3) [111]

Characteristic	Docetaxel 75 mg/m^2 IV Q3W (N = 174)	Sotorasib 960 mg PO QD (N = 171)
Aching joints	10 (17.9)/7 (12.5)/4 (7.1) [56]	13 (17.8)/ 9 (12.3)/2 (2.7) [73]
Aching muscles	11 (22.9)/7 (14.6)/1 (2.1) [48]	18 (24.0)/ 5 (6.7)/ 1 (1.3) [75]
Numbness	2 (5.6)/2 (5.6)/0 (0) [36]	3 (5.9)/0 (0)/0 (0) [51]
Mouth of throat sores	1 (12.5)/0 (0)/ 0 (0) [8]	1 (12.5)/0(0)/0 (0) [15]
Frequency: “rarely” or higher, n (%) [n1]		
Pain	80 (71.4) [112]	113 (76.9) [147]
Aching joints	61 (54.5) [112]	77 (52.4) [147]
Aching muscles	51 (45.5) [112]	75 (51.0) [147]
EQ-5D-5L VAS, mean (SD) [n1]	68.3 (20.3) [138]	67.6 (19.9) [160]
BPI-SF, pain at its worst, mean (SD) [n1]	3.0 (2.8) [122]	3.5 (2.7) [157]
PGIS: mild/moderate/severe, n1 (%) [n1]		
Cough	48 (44.9)/16 (15.0)/8 (7.5) [107]	67 (47.9)/20 (14.3)/4 (2.9) [140]
Chest pain	28 (26.2)/12 (11.2)/0 (0) [107]	45 (32.1)/22 (15.7)/2 (1.4) [140
Dyspnea	50 (46.7)/22 (20.6)/6 (5.6) [107]	74 (52.9)/22 (15.7)/6 (4.3) [140]

Data cutoff date: August 2, 2022. N = number of patients in treatment group. n = number of patients with observed data. n1 = number of evaluable patients for the PRO measure. *No patients of race American Indian or Alaska Native or Native Hawaiian or Other Pacific Islander were enrolled. †Other includes South America, Asia, and Australia. ‡Prior lines of therapy for advanced disease. BPI-SF, Brief Pain Inventory-Short Form; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, 5-level European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire 5 dimensions; FACT-G GP5, Functional Assessment of Cancer Therapy Tool General Form, single item “I am bothered by side effects of treatment”, rated on a 5-point Likert scale; IV, intravenously; PO, orally; PRO, patient-reported outcomes; PGIS, Patient Global Impression of Severity; PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events; Q3W, every 3 weeks, QD, daily; VAS, visual analog scale.

Supplementary Table 2. GEE estimates of change from baseline for FACT-G GP5

	Docetaxel 75 mg/m^2 IV Q3W N = 113 n	**Sotorasib 960 mg PO QD N = 147 n**	**OR*,† (95% CI)**	***P*-value***
Bothered by side effect				
Cycle 2 day 1	103	137	6.7 (3.9, 11.5)	< 0.001
Cycle 3 day 1	96	128	9.7 (5.3, 17.7)	< 0.001
Cycle 4 day 1	71	109	5.2 (2.8, 9.7)	< 0.001
Cycle 5 day 1	60	101	5.7 (3.0, 10.9)	< 0.001
Overall‡	112	146	7.6 (3.4, 16.7)	< 0.001

Data cutoff date: August 2, 2022. N = number of all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements. n = number of patients with observed data. Randomization stratification factors were number of prior lines of therapy in advanced disease (1 vs 2 vs > 2), race (Asian vs non-Asian), and history of CNS involvement (yes vs no). *OR, 95% CIs and *P*-values were estimated using a GEE model based on change from baseline as the dependent variable, and intercept, time, baseline score, treatment, treatment-by-time interaction, and randomization stratification factors as fixed effects. All post-baseline visits were considered excluding follow-up visits. †An OR > 1.0 indicates higher improvement in symptom scale for sotorasib relative to docetaxel. ‡Overall represents all post-baseline visits, including visits beyond cycle 5 day 1, excluding follow-up visits.
CI, confidence interval; CNS, central nervous system; FACT-G GP5, Functional Assessment of Cancer Therapy Tool General Form, single item “I am bothered by side effects of treatment”, rated on a 5-point Likert scale; GEE, generalized estimating equation; IV, intravenously; OR, odds ratio; PO, orally; Q3W, every 3 weeks, QD, daily.

Supplementary Table 3. Summary of FACT-G GP5 over time by original response

	Bothered by Side Effect	
	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	**Sotorasib 960 mg PO QD N = 147 n1 (%)**
Baseline		
n	112	146
Not at all	91 (81.3)	113 (77.4)
A little bit	14 (12.5)	18 (12.3)
Somewhat	4 (3.6)	9 (6.2)
Quite a bit	1 (0.9)	6 (4.1)
Very much	2 (1.8)	0 (0.0)
Cycle 2 day 1		
n	103	137
Not at all	33 (32.0)	96 (70.1)
A little bit	35 (34.0)	29 (21.2)
Somewhat	21 (20.4)	9 (6.6)
Quite a bit	11 (10.7)	3 (2.2)
Very much	3 (2.9)	0 (0.0)
Cycle 3 day 1		
n	96	128
Not at all	29 (30.2)	87 (68.0)
A little bit	21 (21.9)	28 (21.9)
Somewhat	26 (27.1)	10 (7.8)
Quite a bit	14 (14.6)	2 (1.6)
Very much	6 (6.3)	1 (0.8)
Cycle 4 day 1		
n	71	109
Not at all	20 (28.2)	68 (62.4)
A little bit	27 (38.0)	30 (27.5)
Somewhat	10 (14.1)	7 (6.4)
Quite a bit	13 (18.3)	3 (2.8)
Very much	1 (1.4)	1 (0.9)
Cycle 5 day 1		
n	60	101
Not at all	15 (25.0)	63 (62.4)
A little bit	22 (36.7)	24 (23.8)
Somewhat	13 (21.7)	9 (8.9)
Quite a bit	8 (13.3)	3 (3.0)
Very much	2 (3.3)	2 (2.0)
Cycle 6 day 1		

	Bothered by Side Effect	
	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	**Sotorasib 960 mg PO QD N = 147 n1 (%)**
n	49	88
Not at all	15 (30.6)	52 (59.1)
A little bit	15 (30.6)	18 (20.5)
Somewhat	13 (26.5)	16 (18.2)
Quite a bit	5 (10.2)	2 (2.3)
Very much	1 (2.0)	0 (0.0)
Cycle 7 day 1		
n	38	83
Not at all	14 (36.8)	55 (66.3)
A little bit	10 (26.3)	18 (21.7)
Somewhat	10 (26.3)	7 (8.4)
Quite a bit	4 (10.5)	3 (3.6)
Very much	0 (0.0)	0 (0.0)
Cycle 8 day 1		
n	37	75
Not at all	14 (37.8)	47 (62.7)
A little bit	8 (21.6)	19 (25.3)
Somewhat	6 (16.2)	7 (9.3)
Quite a bit	9 (24.3)	2 (2.7)
Very much	0 (0.0)	0 (0.0)
Cycle 9 day 1		
n	26	68
Not at all	10 (38.5)	49 (72.1)
A little bit	8 (30.8)	16 (23.5)
Somewhat	8 (30.8)	2 (2.9)
Quite a bit	0 (0.0)	1 (1.5)
Very much	0 (0.0)	0 (0.0)
Cycle 10 day 1		
n	20	64
Not at all	10 (50.0)	41 (64.1)
A little bit	6 (30.0)	16 (25.0)
Somewhat	2 (10.0)	4 (6.3)
Quite a bit	2 (10.0)	3 (4.7)
Very much	0 (0.0)	0 (0.0)
Cycle 11 day 1		
n	18	62
Not at all	5 (27.8)	47 (75.8)
A little bit	5 (27.8)	11 (17.7)
Somewhat	7 (38.9)	4 (6.5)
Quite a bit	1 (5.6)	0 (0.0)

	Bothered by Side Effect	
	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	**Sotorasib 960 mg PO QD N = 147 n1 (%)**
Very much	0 (0.0)	0 (0.0)
Cycle 12 day 1		
n	16	58
Not at all	7 (43.8)	39 (67.2)
A little bit	4 (25.0)	16 (27.6)
Somewhat	3 (18.8)	2 (3.4)
Quite a bit	2 (12.5)	1 (1.7)
Very much	0 (0.0)	0 (0.0)
Cycle 13 day 1		
n	14	57
Not at all	5 (35.7)	41 (71.9)
A little bit	3 (21.4)	14 (24.6)
Somewhat	3 (21.4)	1 (1.8)
Quite a bit	3 (21.4)	1 (1.8)
Very much	0 (0.0)	0 (0.0)
Cycle 14 day 1		
n	12	51
Not at all	5 (41.7)	32 (62.7)
A little bit	3 (25.0)	16 (31.4)
Somewhat	3 (25.0)	1 (2.0)
Quite a bit	1 (8.3)	1 (2.0)
Very much	0 (0.0)	1 (2.0)
Cycle 15 day 1		
n	10	49
Not at all	4 (40.0)	32 (65.3)
A little bit	3 (30.0)	16 (32.7)
Somewhat	2 (20.0)	1 (2.0)
Quite a bit	0 (0.0)	0 (0.0)
Very much	1 (10.0)	0 (0.0)

Data cutoff date: August 2, 2022. N = number of all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements. n = number of patients with evaluable data at the time point. n1 = number of patients with observed data per category. The analysis included baseline and all scheduled on-treatment visits, excluding follow-up visits. Proportions are based on the number of patients in each visit, treatment, and response category. FACT-G GP5, Functional Assessment of Cancer Therapy Tool General Form, single item “I am bothered by side effects of treatment”, rated on a 5-point Likert scale; IV, intravenously; PO, orally; Q3W, every 3 weeks, QD, daily.

Supplementary Table 4. GEE estimates of change from baseline for PRO-CTCAE severity by original response

	Docetaxel 75 mg/m^2 IV Q3W N = 113 n	Sotorasib 960 mg PO QD N = 148 n	OR*,† (95% CI)	*P*-value*
Pain				
Cycle 2 day 1	63	95	2.4 (1.3, 4.4)	0.007
Cycle 3 day 1	61	78	2.9 (1.5, 5.7)	0.002
Cycle 4 day 1	37	58	4.1 (1.7, 10.0)	0.002
Cycle 5 day 1	31	60	2.9 (1.2, 7.0)	0.014
Overall[‡]	79	111	12.4 (3.6, 43.0)	< 0.001
Aching muscles				
Cycle 2 day 1	33	54	1.0 (0.4, 2.9)	0.960
Cycle 3 day 1	25	45	3.1 (1.1, 8.2)	0.026
Cycle 4 day 1	20	35	1.6 (0.5, 4.6)	0.400
Cycle 5 day 1	16	40	4.4 (1.6, 12.4)	0.005
Overall‡	45	68	2.3 (1.1, 4.7)	0.021
Aching joints				
Cycle 2 day 1	42	53	1.5 (0.7, 3.6)	0.330
Cycle 3 day 1	34	44	0.8 (0.4, 1.9)	0.670
Cycle 4 day 1	24	41	2.2 (0.8, 6.3)	0.130
Cycle 5 day 1	21	44	4.2 (1.4, 12.2)	0.009
Overall‡	57	71	2.0 (0.8, 5.0)	0.120
Mouth or throat sores				
Cycle 2 day 1	103	138	9.1 (4.1, 20.4)	< 0.001
Cycle 3 day 1	96	128	5.0 (2.2, 11.3)	< 0.001
Cycle 4 day 1	71	109	4.1 (1.6, 10.9)	0.004
Cycle 5 day 1	60	101	4.3 (1.6, 11.5)	0.004
Overall‡	112	147	5.9 (2.2, 15.7)	< 0.001
Mouth cracking				
Cycle 2 day 1	103	138	7.9 (0, 837781352.9)	0.830
Cycle 3 day 1	96	128	2.8 (0, 41262.7)	0.830
Cycle 4 day 1	71	109	4.4 (0, 15531792.0)	0.850
Cycle 5 day 1	60	101	6.7 (0, 97873.0)	0.700
Overall‡	112	147	1.6 (0, 6322871.6)	0.950
Itchy skin				
Cycle 2 day 1	103	138	1.2 (0.7, 2.1)	0.540
Cycle 3 day 1	96	128	0.9 (0.5, 1.7)	0.700
Cycle 4 day 1	71	109	0.6 (0.3, 1.3)	0.210
Cycle 5 day 1	60	101	1.0 (0.5, 2.1)	0.990
Overall‡	112	147	0.8 (0.4, 1.5)	0.390

	Docetaxel 75 mg/m^2 IV Q3W N = 113 n	Sotorasib 960 mg PO QD N = 148 n	OR*,† (95% CI)	*P*-value*
Numbness				
Cycle 2 day 1	103	138	1.3 (0.8, 2.3)	0.270
Cycle 3 day 1	96	128	1.4 (0.8, 2.6)	0.220
Cycle 4 day 1	71	109	1.5 (0.8, 3.0)	0.200
Cycle 5 day 1	60	101	2.1 (1.0, 4.3)	0.050
Overall‡	112	147	10.0 (3.9, 25.8)	<0.001

Data cutoff date: August 2, 2022.
N = number of all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements. n = number of patients with observed data.
Randomization stratification factors were number of prior lines of therapy in advanced disease (1 vs 2 vs > 2), race (Asian vs non-Asian), and history of CNS involvement (yes vs no).
*OR, 95% CI, and *P*-value are estimated using a GEE model based on change from baseline as the dependent variable, and intercept, time, baseline score, treatment, treatment-by-time interaction, and randomization stratification factors as fixed effects. All post-baseline visits are considered excluding follow-up visits. †An OR > 1.0 indicates higher improvement in symptom scale for sotorasib relative to docetaxel. ‡Overall represents all post-baseline visits, including visits beyond cycle 5 day 1, excluding follow-up visits.
CI, confidence interval; GEE, generalized estimating equation; IV, intravenously; PO, orally; PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events; OR, odds ratio; QD, daily; Q3W, every 3 weeks.

Supplementary Table 5. Summary of PRO-CTCAE severity over time by original response

	Pain		Aching Muscles		Aching Joints		Mouth or Throat Sores		Numbness		Mouth Cracking		Itchy Skin	
	Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)
Baseline														
n	80	113	51	75	61	77	112	147	112	147	112	147	112	147
None	4 (5.0)	2 (1.8)	3 (5.9)	0 (0.0)	5 (8.2)	4 (5.2)	104 (92.9)	132 (89.8)	76 (67.9)	96 (65.3)	105 (93.8)	135 (91.8)	81 (72.3)	112 (76.2)
Mild	34 (42.5)	44 (38.9)	25 (49.0)	41 (54.7)	25 (41.0)	35 (45.5)	6 (5.4)	12 (8.2)	25 (22.3)	39 (26.5)	6 (5.4)	11 (7.5)	22 (19.6)	26 (17.7)
Moderate	25 (31.3)	32 (28.3)	14 (27.5)	26 (34.7)	19 (31.1)	28 (36.4)	1 (0.9)	2 (1.4)	8 (7.1)	11 (7.5)	0 (0.0)	1 (0.7)	8 (7.1)	6 (4.1)
Severe	13 (16.3)	22 (19.5)	8 (15.7)	7 (9.3)	10 (16.4)	9 (11.7)	1 (0.9)	1 (0.7)	3 (2.7)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.9)	2 (1.4)
Very severe	4 (5.0)	13 (11.5)	1 (2.0)	1 (1.3)	2 (3.3)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.7)
Cycle 2 day 1														
n	74	104	51	71	54	66	103	138	103	138	103	138	103	138
None	2 (2.7)	4 (3.8)	6 (11.8)	6 (8.5)	2 (3.7)	4 (6.1)	70 (68.0)	129 (93.5)	63 (61.2)	87 (63.0)	78 (75.7)	131 (94.9)	65 (63.1)	92 (66.7)
Mild	26 (35.1)	49 (47.1)	19 (37.3)	34 (47.9)	22 (40.7)	31 (47.0)	21 (20.4)	7 (5.1)	25 (24.3)	38 (27.5)	16 (15.5)	5 (3.6)	25 (24.3)	27 (19.6)
Moderate	22 (29.7)	27 (26.0)	13 (25.5)	13 (18.3)	15 (27.8)	17 (25.8)	4 (3.9)	1 (0.7)	13 (12.6)	9 (6.5)	7 (6.8)	2 (1.4)	6 (5.8)	13 (9.4)
Severe	18 (24.3)	20 (19.2)	7 (13.7)	14 (19.7)	14 (25.9)	12 (18.2)	7 (6.8)	1 (0.7)	2 (1.9)	3 (2.2)	1 (1.0)	0 (0.0)	7 (6.8)	5 (3.6)
Very severe	6 (8.1)	4 (3.8)	6 (11.8)	4 (5.6)	1 (1.9)	2 (3.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.7)
Cycle 3 day 1														
n	72	96	45	64	43	62	96	128	96	128	96	128	96	128
None	4 (5.6)	4 (4.2)	7 (15.6)	5 (7.8)	3 (7.0)	4 (6.5)	63 (65.6)	111 (86.7)	49 (51.0)	67 (52.3)	82 (85.4)	119 (93.0)	59 (61.5)	74 (57.8)
Mild	24 (33.3)	51 (53.1)	18 (40.0)	38 (59.4)	21 (48.8)	33 (53.2)	25 (26.0)	15 (11.7)	29 (30.2)	42 (32.8)	10 (10.4)	9 (7.0)	20 (20.8)	27 (21.1)
Moderate	24 (33.3)	23 (24.0)	14 (31.1)	17 (26.6)	15 (34.9)	18 (29.0)	4 (4.2)	2 (1.6)	10 (10.4)	13 (10.2)	3 (3.1)	0 (0.0)	13 (13.5)	20 (15.6)
Severe	16 (22.2)	12 (12.5)	5 (11.1)	2 (3.1)	4 (9.3)	5 (8.1)	3 (3.1)	0 (0.0)	5 (5.2)	5 (3.9)	0 (0.0)	0 (0.0)	2 (2.1)	7 (5.5)
Very severe	4 (5.6)	6 (6.3)	1 (2.2)	2 (3.1)	0 (0.0)	2 (3.2)	1 (1.0)	0 (0.0)	3 (3.1)	1 (0.8)	1 (1.0)	0 (0.0)	2 (2.1)	0 (0.0)
Cycle 4 day 1														
n	46	67	33	50	34	62	71	109	71	109	71	109	71	109
None	4 (8.7)	1 (1.5)	2 (6.1)	4 (8.0)	2 (5.9)	3 (4.8)	56 (78.9)	101 (92.7)	37 (52.1)	60 (55.0)	59 (83.1)	103 (94.5)	47 (66.2)	65 (59.6)
Mild	12 (26.1)	36 (53.7)	18 (54.5)	27 (54.0)	16 (47.1)	32 (51.6)	12 (16.9)	7 (6.4)	20 (28.2)	35 (32.1)	9 (12.7)	5 (4.6)	15 (21.1)	27 (24.8)
Moderate	14 (30.4)	10 (14.9)	6 (18.2)	14 (28.0)	9 (26.5)	22 (35.5)	3 (4.2)	0 (0.0)	8 (11.3)	10 (9.2)	2 (2.8)	1 (0.9)	8 (11.3)	12 (11.0)
Severe	11 (23.9)	14 (20.9)	6 (18.2)	5 (10.0)	6 (17.6)	3 (4.8)	0 (0.0)	1 (0.9)	6 (8.5)	3 (2.8)	1 (1.4)	0 (0.0)	1 (1.4)	4 (3.7)
Very severe	5 (10.9)	6 (9.0)	1 (3.0)	0 (0.0)	1 (2.9)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Cycle 5 day 1														

	Pain		Aching Muscles		Aching Joints		Mouth or Throat Sores		Numbness		Mouth Cracking		Itchy Skin	
	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)
n	38	76	26	61	26	66	60	101	60	101	60	101	60	101
None	0 (0.0)	7 (9.2)	1 (3.8)	1 (1.6)	1 (3.8)	7 (10.6)	46 (76.7)	92 (91.1)	34 (56.7)	63 (62.4)	47 (78.3)	96 (95.0)	38 (63.3)	67 (66.3)
Mild	14 (36.8)	41 (53.9)	10 (38.5)	46 (75.4)	10 (38.5)	42 (63.6)	8 (13.3)	8 (7.9)	12 (20.0)	25 (24.8)	9 (15.0)	5 (5.0)	14 (23.3)	25 (24.8)
Moderate	15 (39.5)	15 (19.7)	7 (26.9)	9 (14.8)	7 (26.9)	11 (16.7)	5 (8.3)	1 (1.0)	7 (11.7)	11 (10.9)	3 (5.0)	0 (0.0)	5 (8.3)	8 (7.9)
Severe	6 (15.8)	8 (10.5)	6 (23.1)	3 (4.9)	7 (26.9)	4 (6.1)	1 (1.7)	0 (0.0)	7 (11.7)	1 (1.0)	1 (1.7)	0 (0.0)	3 (5.0)	1 (1.0)
Very severe	3 (7.9)	5 (6.6)	2 (7.7)	2 (3.3)	1 (3.8)	2 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 6 day 1														
n	34	62	21	46	22	48	49	88	49	88	49	88	49	88
None	1 (2.9)	2 (3.2)	1 (4.8)	3 (6.5)	0 (0.0)	4 (8.3)	42 (85.7)	86 (97.7)	20 (40.8)	54 (61.4)	44 (89.8)	85 (96.6)	27 (55.1)	56 (63.6)
Mild	17 (50.0)	26 (41.9)	9 (42.9)	26 (56.5)	9 (40.9)	21 (43.8)	4 (8.2)	2 (2.3)	15 (30.6)	28 (31.8)	5 (10.2)	2 (2.3)	16 (32.7)	24 (27.3)
Moderate	10 (29.4)	20 (32.3)	6 (28.6)	14 (30.4)	7 (31.8)	20 (41.7)	2 (4.1)	0 (0.0)	8 (16.3)	4 (4.5)	0 (0.0)	1 (1.1)	4 (8.2)	6 (6.8)
Severe	6 (17.6)	11 (17.7)	4 (19.0)	2 (4.3)	4 (18.2)	3 (6.3)	1 (2.0)	0 (0.0)	4 (8.2)	2 (2.3)	0 (0.0)	0 (0.0)	2 (4.1)	2 (2.3)
Very severe	0 (0.0)	3 (4.8)	1 (4.8)	1 (2.2)	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 7 day 1														
n	26	62	18	37	17	38	38	83	38	83	38	83	38	83
None	0 (0.0)	7 (11.3)	2 (11.1)	3 (8.1)	1 (5.9)	2 (5.3)	27 (71.1)	73 (88.0)	14 (36.8)	50 (60.2)	31 (81.6)	78 (94.0)	23 (60.5)	58 (69.9)
Mild	14 (53.8)	35 (56.5)	7 (38.9)	26 (70.3)	4 (23.5)	27 (71.1)	8 (21.1)	9 (10.8)	12 (31.6)	28 (33.7)	7 (18.4)	4 (4.8)	13 (34.2)	18 (21.7)
Moderate	7 (26.9)	10 (16.1)	6 (33.3)	6 (16.2)	8 (47.1)	5 (13.2)	1 (2.6)	1 (1.2)	10 (26.3)	3 (3.6)	0 (0.0)	1 (1.2)	2 (5.3)	7 (8.4)
Severe	3 (11.5)	5 (8.1)	1 (5.6)	2 (5.4)	2 (11.8)	3 (7.9)	2 (5.3)	0 (0.0)	2 (5.3)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Very severe	2 (7.7)	5 (8.1)	2 (11.1)	0 (0.0)	2 (11.8)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 8 day 1														
n	24	48	21	33	18	33	37	75	37	75	37	75	37	75
None	0 (0.0)	4 (8.3)	1 (4.8)	1 (3.0)	1 (5.6)	2 (6.1)	30 (81.1)	68 (90.7)	14 (37.8)	48 (64.0)	27 (73.0)	71 (94.7)	27 (73.0)	52 (69.3)
Mild	12 (50.0)	31 (64.6)	11 (52.4)	20 (60.6)	12 (66.7)	17 (51.5)	4 (10.8)	6 (8.0)	11 (29.7)	20 (26.7)	9 (24.3)	3 (4.0)	9 (24.3)	20 (26.7)
Moderate	10 (41.7)	7 (14.6)	8 (38.1)	9 (27.3)	4 (22.2)	11 (33.3)	2 (5.4)	1 (1.3)	9 (24.3)	5 (6.7)	1 (2.7)	1 (1.3)	0 (0.0)	3 (4.0)
Severe	1 (4.2)	6 (12.5)	0 (0.0)	3 (9.1)	0 (0.0)	3 (9.1)	1 (2.7)	0 (0.0)	2 (5.4)	1 (1.3)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)
Very severe	1 (4.2)	0 (0.0)	1 (4.8)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 9 day 1														
n	14	45	11	31	13	36	26	68	26	68	26	68	26	68
None	1 (7.1)	5 (11.1)	0 (0.0)	2 (6.5)	0 (0.0)	1 (2.8)	18 (69.2)	64 (94.1)	7 (26.9)	43 (63.2)	20 (76.9)	62 (91.2)	14 (53.8)	41 (60.3)
Mild	5 (35.7)	20 (44.4)	8 (72.7)	22 (71.0)	9 (69.2)	22 (61.1)	5 (19.2)	3 (4.4)	12 (46.2)	19 (27.9)	4 (15.4)	6 (8.8)	10 (38.5)	24 (35.3)
Moderate	6 (42.9)	15 (33.3)	1 (9.1)	3 (9.7)	2 (15.4)	10 (27.8)	2 (7.7)	1 (1.5)	4 (15.4)	5 (7.4)	2 (7.7)	0 (0.0)	1 (3.8)	3 (4.4)

	Pain		Aching Muscles		Aching Joints		Mouth or Throat Sores		Numbness		Mouth Cracking		Itchy Skin	
	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)
Severe	1 (7.1)	3 (6.7)	1 (9.1)	3 (9.7)	1 (7.7)	2 (5.6)	0 (0.0)	0 (0.0)	3 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)
Very severe	1 (7.1)	2 (4.4)	1 (9.1)	1 (3.2)	1 (7.7)	1 (2.8)	1 (3.8)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 10 day 1														
n	11	44	6	34	7	31	20	64	20	64	20	64	20	64
None	0 (0.0)	5 (11.4)	1 (16.7)	5 (14.7)	0 (0.0)	0 (0.0)	16 (80.0)	63 (98.4)	8 (40.0)	39 (60.9)	16 (80.0)	60 (93.8)	17 (85.0)	44 (68.8)
Mild	1 (9.1)	22 (50.0)	2 (33.3)	21 (61.8)	3 (42.9)	21 (67.7)	2 (10.0)	0 (0.0)	5 (25.0)	19 (29.7)	3 (15.0)	4 (6.3)	3 (15.0)	17 (26.6)
Moderate	6 (54.5)	11 (25.0)	1 (16.7)	6 (17.6)	2 (28.6)	8 (25.8)	0 (0.0)	1 (1.6)	2 (10.0)	5 (7.8)	1 (5.0)	0 (0.0)	0 (0.0)	3 (4.7)
Severe	2 (18.2)	5 (11.4)	0 (0.0)	2 (5.9)	1 (14.3)	2 (6.5)	1 (5.0)	0 (0.0)	5 (25.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Very severe	2 (18.2)	1 (2.3)	2 (33.3)	0 (0.0)	1 (14.3)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 11 day 1														
n	12	41	8	31	7	30	18	62	18	62	18	62	18	62
None	0 (0.0)	3 (7.3)	0 (0.0)	4 (12.9)	0 (0.0)	1 (3.3)	13 (72.2)	56 (90.3)	4 (22.2)	39 (62.9)	14 (77.8)	60 (96.8)	12 (66.7)	43 (69.4)
Mild	6 (50.0)	26 (63.4)	4 (50.0)	19 (61.3)	5 (71.4)	21 (70.0)	4 (22.2)	5 (8.1)	10 (55.6)	16 (25.8)	2 (11.1)	2 (3.2)	6 (33.3)	16 (25.8)
Moderate	3 (25.0)	5 (12.2)	3 (37.5)	3 (9.7)	1 (14.3)	6 (20.0)	0 (0.0)	1 (1.6)	2 (11.1)	6 (9.7)	2 (11.1)	0 (0.0)	0 (0.0)	3 (4.8)
Severe	2 (16.7)	5 (12.2)	0 (0.0)	4 (12.9)	0 (0.0)	2 (6.7)	1 (5.6)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Very severe	1 (8.3)	2 (4.9)	1 (12.5)	1 (3.2)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 12 day 1														
n	11	40	9	30	8	29	16	58	16	58	16	58	16	58
None	0 (0.0)	4 (10.0)	1 (11.1)	0 (0.0)	0 (0.0)	2 (6.9)	13 (81.3)	54 (93.1)	7 (43.8)	34 (58.6)	14 (87.5)	56 (96.6)	11 (68.8)	44 (75.9)
Mild	3 (27.3)	21 (52.5)	2 (22.2)	19 (63.3)	4 (50.0)	18 (62.1)	1 (6.3)	3 (5.2)	4 (25.0)	20 (34.5)	1 (6.3)	1 (1.7)	5 (31.3)	10 (17.2)
Moderate	5 (45.5)	8 (20.0)	3 (33.3)	7 (23.3)	2 (25.0)	4 (13.8)	2 (12.5)	1 (1.7)	1 (6.3)	4 (6.9)	1 (6.3)	1 (1.7)	0 (0.0)	4 (6.9)
Severe	2 (18.2)	7 (17.5)	1 (11.1)	4 (13.3)	1 (12.5)	5 (17.2)	0 (0.0)	0 (0.0)	3 (18.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Very severe	1 (9.1)	0 (0.0)	2 (22.2)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 13 day 1														
n	10	36	7	28	6	24	14	57	14	57	14	57	14	57
None	1 (10.0)	1 (2.8)	1 (14.3)	1 (3.6)	0 (0.0)	0 (0.0)	11 (78.6)	56 (98.2)	4 (28.6)	38 (66.7)	12 (85.7)	52 (91.2)	10 (71.4)	36 (63.2)
Mild	4 (40.0)	16 (44.4)	3 (42.9)	16 (57.1)	3 (50.0)	14 (58.3)	1 (7.1)	1 (1.8)	4 (28.6)	17 (29.8)	1 (7.1)	4 (7.0)	4 (28.6)	17 (29.8)
Moderate	3 (30.0)	13 (36.1)	1 (14.3)	7 (25.0)	2 (33.3)	9 (37.5)	1 (7.1)	0 (0.0)	4 (28.6)	2 (3.5)	1 (7.1)	1 (1.8)	0 (0.0)	3 (5.3)
Severe	2 (20.0)	6 (16.7)	1 (14.3)	3 (10.7)	0 (0.0)	1 (4.2)	1 (7.1)	0 (0.0)	2 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)
Very severe	0 (0.0)	0 (0.0)	1 (14.3)	1 (3.6)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	Pain		Aching Muscles		Aching Joints		Mouth or Throat Sores		Numbness		Mouth Cracking		Itchy Skin	
	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	Sotorasib 960 mg PO QD N = 148 n1 (%)
Cycle 14 day 1														
n	7	35	6	29	5	31	12	51	12	51	12	51	12	51
None	0 (0.0)	4 (11.4)	0 (0.0)	2 (6.9)	0 (0.0)	2 (6.5)	10 (83.3)	47 (92.2)	5 (41.7)	33 (64.7)	9 (75.0)	48 (94.1)	7 (58.3)	33 (64.7)
Mild	4 (57.1)	15 (42.9)	4 (66.7)	15 (51.7)	3 (60.0)	20 (64.5)	0 (0.0)	4 (7.8)	3 (25.0)	15 (29.4)	1 (8.3)	1 (2.0)	5 (41.7)	14 (27.5)
Moderate	1 (14.3)	9 (25.7)	1 (16.7)	9 (31.0)	1 (20.0)	6 (19.4)	2 (16.7)	0 (0.0)	1 (8.3)	3 (5.9)	1 (8.3)	2 (3.9)	0 (0.0)	3 (5.9)
Severe	1 (14.3)	4 (11.4)	0 (0.0)	2 (6.9)	0 (0.0)	3 (9.7)	0 (0.0)	0 (0.0)	3 (25.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (2.0)
Very severe	1 (14.3)	3 (8.6)	1 (16.7)	1 (3.4)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 15 day 1														
n	5	31	4	26	5	28	10	49	10	49	10	49	10	49
None	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)	8 (80.0)	44 (89.8)	3 (30.0)	31 (63.3)	8 (80.0)	45 (91.8)	10 (100.0)	32 (65.3)
Mild	2 (40.0)	17 (54.8)	3 (75.0)	16 (61.5)	3 (60.0)	13 (46.4)	0 (0.0)	5 (10.2)	5 (50.0)	15 (30.6)	0 (0.0)	3 (6.1)	0 (0.0)	14 (28.6)
Moderate	1 (20.0)	9 (29.0)	1 (25.0)	8 (30.8)	2 (40.0)	12 (42.9)	1 (10.0)	0 (0.0)	1 (10.0)	2 (4.1)	1 (10.0)	1 (2.0)	0 (0.0)	3 (6.1)
Severe	1 (20.0)	5 (16.1)	0 (0.0)	2 (7.7)	0 (0.0)	2 (7.1)	1 (10.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Very severe	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data cutoff date: August 2, 2022. N = number of all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements. n = number of patients with evaluable data at the time point. n1 = number of patients with observed data per category. The analysis included baseline and all scheduled on-treatment visits, excluding follow-up visits. Proportions are based on the number of patients in each visit, treatment, and response category. IV, intravenously; PO, orally; PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events; Q3W, every 3 weeks, QD, daily.

Supplementary Table 6. PRO-CTCAE severity by worst response at baseline or all scheduled on-treatment visits

	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	**Sotorasib 960 mg PO QD N = 148 n1 (%)**
Pain		
n	102	143
None	0 (0.0)	4 (2.8)
Mild	24 (23.5)	32 (22.4)
Moderate	30 (29.4)	36 (25.2)
Severe	30 (29.4)	42 (29.4)
Very severe	18 (17.6)	29 (20.3)
Aching muscles		
n	91	122
None	3 (3.3)	3 (2.5)
Mild	29 (31.9)	43 (35.2)
Moderate	32 (35.2)	36 (29.5)
Severe	16 (17.6)	28 (23.0)
Very severe	11 (12.1)	12 (9.8)
Aching joints		
n	89	124
None	3 (3.4)	2 (1.6)
Mild	35 (39.3)	41 (33.1)
Moderate	23 (25.8)	39 (31.5)
Severe	23 (25.8)	32 (25.8)
Very severe	5 (5.6)	10 (8.1)
Mouth or throat sores		
n	112	147
None	52 (46.4)	106 (72.1)
Mild	38 (33.9)	30 (20.4)
Moderate	9 (8.0)	8 (5.4)
Severe	10 (8.9)	3 (2.0)
Very severe	3 (2.7)	0 (0.0)
Mouth cracking		
n	112	147
None	69 (61.6)	107 (72.8)
Mild	27 (24.1)	32 (21.8)
Moderate	12 (10.7)	8 (5.4)
Severe	2 (1.8)	0 (0.0)
Very severe	2 (1.8)	0 (0.0)
Itchy skin		
n	112	147
None	42 (37.5)	54 (36.7)

	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	**Sotorasib 960 mg PO QD N = 148 n1 (%)**
Mild	34 (30.4)	42 (28.6)
Moderate	21 (18.8)	32 (21.8)
Severe	13 (11.6)	16 (10.9)
Very severe	2 (1.8)	3 (2.0)
Numbness		
n	112	147
None	29 (25.9)	51 (34.7)
Mild	38 (33.9)	53 (36.1)
Moderate	22 (19.6)	25 (17.0)
Severe	14 (12.5)	15 (10.2)
Very severe	9 (8.0)	3 (2.0)

Data cutoff date: August 2, 2022. N = number of all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements. n = number of patients with observed data. n1 = number of patients with outcome. The analysis presents the number and proportion of patients according to the “worst” response at baseline or all scheduled on-treatment visits, excluding follow-up visits. Proportions are based on the number of patients in each treatment and response category.
IV, intravenously; PO, orally; PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events; Q3W, every 3 weeks, QD, daily.

Supplementary Table 7. GEE estimates of change from baseline for PRO-CTCAE interference by original response

	Docetaxel 75 mg/m^2 IV Q3W N = 113 n	Sotorasib 960 mg PO QD N = 148 n	OR*,† (95% CI)	*P*-value*
Pain				
Cycle 2 day 1	59	92	2.7 (1.5, 5.0)	0.002
Cycle 3 day 1	54	75	1.9 (0.9, 3.8)	0.087
Cycle 4 day 1	30	57	2.9 (1.2, 7.1)	0.023
Cycle 5 day 1	29	57	3.2 (1.2, 8.3)	0.018
Overall‡	74	109	NE (NE, NE)	NE
Aching muscles				
Cycle 2 day 1	28	51	1.9 (0.7, 5.0)	0.200
Cycle 3 day 1	19	40	2.8 (0.8, 9.3)	0.094
Cycle 4 day 1	17	32	2.1 (0.7, 6.4)	0.200
Cycle 5 day 1	14	40	3.9 (1.1, 13.6)	0.033
Overall‡	41	67	1.4 (0.7, 2.6)	0.360
Aching joints				
Cycle 2 day 1	38	49	2.0 (0.9, 4.7)	0.094
Cycle 3 day 1	32	41	1.5 (0.6, 3.8)	0.340
Cycle 4 day 1	21	39	3.5 (1.3, 9.7)	0.017
Cycle 5 day 1	20	40	10.7 (3.4, 33.4)	< 0.001
Overall‡	53	65	1.5 (0.6, 3.8)	0.440
Mouth or throat sores				
Cycle 2 day 1	3	4	0.3 (0, 12.9)	0.530
Cycle 3 day 1	4	8	0.4 (0, 63.2)	0.690
Cycle 4 day 1	3	4	0.0 (0.0, 5.0)	0.150
Cycle 5 day 1	2	5	101.2 (0.5, 21353.8)	0.091
Overall‡	7	11	NE (NE, NE)	NE
Numbness				
Cycle 2 day 1	25	39	1.5 (0.5, 4.3)	0.460
Cycle 3 day 1	24	39	0.9 (0.3, 2.6)	0.770
Cycle 4 day 1	18	28	1.9 (0.5, 7.0)	0.330
Cycle 5 day 1	13	28	1.3 (0.2, 7.1)	0.800
Overall‡	33	46	NE (NE, NE)	NE

Data cutoff date: August 2, 2022. N = number of all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements. n = number of patients with observed data. *OR, 95% CIs, and *P*-values are estimated using a GEE model based on change from baseline as the dependent variable, intercept, time, baseline score, treatment, treatment-by-time interaction, and randomization stratification factors as fixed effects. All post-baseline visits are considered excluding follow-up visits. †An OR > 1.0 indicates higher improvement in symptom scale for sotorasib relative to docetaxel. ‡Overall represents all post-baseline visits, including visits beyond cycle 5 day 1, excluding follow-up visits. CI, confidence interval; GEE, generalized estimating equation; IV, intravenously; NE, not

estimable; OR, odds ratio; PO, orally; PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events; Q3W, every 3 weeks; QD, daily.

Supplementary Table 8. Summary of PRO-CTCAE interference over time by original response

	Pain		Aching Muscles		Aching Joints		Mouth or Throat Sores		Numbness	
	Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**
Baseline										
n	76	111	48	75	56	73	8	15	36	51
Not at all	12 (15.8)	32 (28.8)	11 (22.9)	28 (37.3)	15 (26.8)	20 (27.4)	6 (75.0)	6 (40.0)	12 (33.3)	27 (52.9)
A little bit	34 (44.7)	34 (30.6)	18 (37.5)	23 (30.7)	20 (35.7)	29 (39.7)	1 (12.5)	9 (60.0)	20 (55.6)	21 (41.2)
Somewhat	12 (15.8)	20 (18.0)	11 (22.9)	18 (24.0)	10 (17.9)	13 (17.8)	1 (12.5)	0 (0.0)	2 (5.6)	3 (5.9)
Quite a bit	15 (19.7)	18 (16.2)	7 (14.6)	5 (6.7)	7 (12.5)	9 (12.3)	0 (0.0)	0 (0.0)	2 (5.6)	0 (0.0)
Very much	3 (3.9)	7 (6.3)	1 (2.1)	1 (1.3)	4 (7.1)	2 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 2 day 1										
n	72	100	45	65	52	62	33	9	40	51
Not at all	10 (13.9)	34 (34.0)	12 (26.7)	16 (24.6)	7 (13.5)	15 (24.2)	10 (30.3)	4 (44.4)	17 (42.5)	28 (54.9)
A little bit	27 (37.5)	36 (36.0)	10 (22.2)	30 (46.2)	20 (38.5)	28 (45.2)	11 (33.3)	3 (33.3)	18 (45.0)	16 (31.4)
Somewhat	21 (29.2)	14 (14.0)	13 (28.9)	9 (13.8)	15 (28.8)	9 (14.5)	6 (18.2)	0 (0.0)	3 (7.5)	6 (11.8)
Quite a bit	12 (16.7)	12 (12.0)	7 (15.6)	8 (12.3)	8 (15.4)	8 (12.9)	5 (15.2)	2 (22.2)	2 (5.0)	0 (0.0)
Very much	2 (2.8)	4 (4.0)	3 (6.7)	2 (3.1)	2 (3.8)	2 (3.2)	1 (3.0)	0 (0.0)	0 (0.0)	1 (2.0)
Cycle 3 day 1										
n	68	92	38	59	40	58	33	17	47	61
Not at all	13 (19.1)	24 (26.1)	8 (21.1)	12 (20.3)	8 (20.0)	16 (27.6)	14 (42.4)	9 (52.9)	17 (36.2)	28 (45.9)
A little bit	30 (44.1)	44 (47.8)	19 (50.0)	33 (55.9)	22 (55.0)	33 (56.9)	13 (39.4)	6 (35.3)	21 (44.7)	27 (44.3)
Somewhat	11 (16.2)	14 (15.2)	5 (13.2)	11 (18.6)	4 (10.0)	5 (8.6)	4 (12.1)	2 (11.8)	7 (14.9)	5 (8.2)
Quite a bit	13 (19.1)	8 (8.7)	6 (15.8)	2 (3.4)	6 (15.0)	3 (5.2)	1 (3.0)	0 (0.0)	1 (2.1)	0 (0.0)
Very much	1 (1.5)	2 (2.2)	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.7)	1 (3.0)	0 (0.0)	1 (2.1)	1 (1.6)
Cycle 4 day 1										
n	42	66	31	46	32	59	15	8	34	49
Not at all	4 (9.5)	16 (24.2)	7 (22.6)	13 (28.3)	5 (15.6)	12 (20.3)	6 (40.0)	3 (37.5)	14 (41.2)	30 (61.2)
A little bit	19 (45.2)	29 (43.9)	11 (35.5)	23 (50.0)	15 (46.9)	32 (54.2)	6 (40.0)	4 (50.0)	10 (29.4)	11 (22.4)

	Pain		Aching Muscles		Aching Joints		Mouth or Throat Sores		Numbness	
	Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**
Somewhat	7 (16.7)	11 (16.7)	8 (25.8)	7 (15.2)	6 (18.8)	12 (20.3)	2 (13.3)	1 (12.5)	7 (20.6)	7 (14.3)
Quite a bit	8 (19.0)	8 (12.1)	3 (9.7)	3 (6.5)	4 (12.5)	3 (5.1)	1 (6.7)	0 (0.0)	2 (5.9)	1 (2.0)
Very much	4 (9.5)	2 (3.0)	2 (6.5)	0 (0.0)	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Cycle 5 day 1										
n	38	69	25	60	25	59	14	9	27	38
Not at all	7 (18.4)	23 (33.3)	5 (20.0)	20 (33.3)	5 (20.0)	17 (28.8)	3 (21.4)	6 (66.7)	11 (40.7)	15 (39.5)
A little bit	11 (28.9)	30 (43.5)	8 (32.0)	32 (53.3)	6 (24.0)	34 (57.6)	4 (28.6)	3 (33.3)	6 (22.2)	16 (42.1)
Somewhat	9 (23.7)	7 (10.1)	6 (24.0)	5 (8.3)	7 (28.0)	4 (6.8)	3 (21.4)	0 (0.0)	4 (14.8)	7 (18.4)
Quite a bit	8 (21.1)	5 (7.2)	5 (20.0)	2 (3.3)	6 (24.0)	2 (3.4)	4 (28.6)	0 (0.0)	6 (22.2)	0 (0.0)
Very much	3 (7.9)	4 (5.8)	1 (4.0)	1 (1.7)	1 (4.0)	2 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 6 day 1										
n	33	60	20	43	22	44	7	2	29	34
Not at all	5 (15.2)	16 (26.7)	2 (10.0)	11 (25.6)	3 (13.6)	5 (11.4)	1 (14.3)	2 (100.0)	9 (31.0)	16 (47.1)
A little bit	16 (48.5)	23 (38.3)	8 (40.0)	24 (55.8)	8 (36.4)	26 (59.1)	3 (42.9)	0 (0.0)	13 (44.8)	14 (41.2)
Somewhat	7 (21.2)	15 (25.0)	5 (25.0)	7 (16.3)	6 (27.3)	11 (25.0)	1 (14.3)	0 (0.0)	3 (10.3)	3 (8.8)
Quite a bit	4 (12.1)	6 (10.0)	4 (20.0)	1 (2.3)	4 (18.2)	1 (2.3)	2 (28.6)	0 (0.0)	4 (13.8)	1 (2.9)
Very much	1 (3.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (4.5)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 7 day 1										
n	26	55	16	34	16	36	11	10	24	33
Not at all	7 (26.9)	16 (29.1)	4 (25.0)	12 (35.3)	2 (12.5)	7 (19.4)	6 (54.5)	4 (40.0)	6 (25.0)	12 (36.4)
A little bit	8 (30.8)	24 (43.6)	6 (37.5)	17 (50.0)	6 (37.5)	23 (63.9)	3 (27.3)	6 (60.0)	11 (45.8)	18 (54.5)
Somewhat	4 (15.4)	11 (20.0)	3 (18.8)	3 (8.8)	4 (25.0)	3 (8.3)	0 (0.0)	0 (0.0)	4 (16.7)	2 (6.1)
Quite a bit	5 (19.2)	3 (5.5)	3 (18.8)	2 (5.9)	2 (12.5)	3 (8.3)	2 (18.2)	0 (0.0)	3 (12.5)	0 (0.0)
Very much	2 (7.7)	1 (1.8)	0 (0.0)	0 (0.0)	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)

	Pain		Aching Muscles		Aching Joints		Mouth or Throat Sores		Numbness	
	Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**
Cycle 8 day 1										
n	24	44	20	32	17	31	7	7	23	27
Not at all	6 (25.0)	14 (31.8)	6 (30.0)	8 (25.0)	4 (23.5)	8 (25.8)	3 (42.9)	2 (28.6)	3 (13.0)	13 (48.1)
A little bit	12 (50.0)	22 (50.0)	7 (35.0)	18 (56.3)	9 (52.9)	17 (54.8)	2 (28.6)	5 (71.4)	13 (56.5)	12 (44.4)
Somewhat	2 (8.3)	5 (11.4)	5 (25.0)	4 (12.5)	2 (11.8)	4 (12.9)	2 (28.6)	0 (0.0)	6 (26.1)	1 (3.7)
Quite a bit	3 (12.5)	3 (6.8)	1 (5.0)	2 (6.3)	1 (5.9)	2 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Very much	1 (4.2)	0 (0.0)	1 (5.0)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	1 (3.7)
Cycle 9 day 1										
n	13	40	11	29	13	35	8	4	19	25
Not at all	2 (15.4)	14 (35.0)	4 (36.4)	14 (48.3)	5 (38.5)	9 (25.7)	2 (25.0)	1 (25.0)	9 (47.4)	12 (48.0)
A little bit	6 (46.2)	20 (50.0)	5 (45.5)	11 (37.9)	5 (38.5)	19 (54.3)	5 (62.5)	2 (50.0)	8 (42.1)	12 (48.0)
Somewhat	2 (15.4)	2 (5.0)	0 (0.0)	1 (3.4)	1 (7.7)	5 (14.3)	1 (12.5)	1 (25.0)	1 (5.3)	0 (0.0)
Quite a bit	2 (15.4)	3 (7.5)	1 (9.1)	2 (6.9)	1 (7.7)	1 (2.9)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)
Very much	1 (7.7)	1 (2.5)	1 (9.1)	1 (3.4)	1 (7.7)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)
Cycle 10 day 1										
n	11	39	5	29	7	31	4	1	12	25
Not at all	3 (27.3)	12 (30.8)	1 (20.0)	10 (34.5)	3 (42.9)	5 (16.1)	2 (50.0)	0 (0.0)	2 (16.7)	12 (48.0)
A little bit	3 (27.3)	17 (43.6)	2 (40.0)	14 (48.3)	1 (14.3)	21 (67.7)	1 (25.0)	1 (100.0)	5 (41.7)	12 (48.0)
Somewhat	3 (27.3)	6 (15.4)	0 (0.0)	4 (13.8)	1 (14.3)	5 (16.1)	0 (0.0)	0 (0.0)	3 (25.0)	0 (0.0)
Quite a bit	0 (0.0)	4 (10.3)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (4.0)
Very much	2 (18.2)	0 (0.0)	2 (40.0)	0 (0.0)	2 (28.6)	0 (0.0)	1 (25.0)	0 (0.0)	1 (8.3)	0 (0.0)
Cycle 11 day 1										
n	12	38	8	27	7	29	5	6	14	23
Not at all	3 (25.0)	13 (34.2)	2 (25.0)	12 (44.4)	1 (14.3)	9 (31.0)	0 (0.0)	5 (83.3)	5 (35.7)	7 (30.4)
A little bit	5 (41.7)	17 (44.7)	3 (37.5)	9 (33.3)	4 (57.1)	16 (55.2)	5 (100.0)	1 (16.7)	8 (57.1)	13 (56.5)
Somewhat	3 (25.0)	2 (5.3)	2 (25.0)	5 (18.5)	1 (14.3)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.7)

	Pain		Aching Muscles		Aching Joints		Mouth or Throat Sores		Numbness	
	Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m² IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**
Quite a bit	0 (0.0)	6 (15.8)	0 (0.0)	1 (3.7)	0 (0.0)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)
Very much	1 (8.3)	0 (0.0)	1 (12.5)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)
Cycle 12 day 1										
n	11	36	8	30	8	27	3	4	9	24
Not at all	2 (18.2)	11 (30.6)	1 (12.5)	9 (30.0)	2 (25.0)	6 (22.2)	0 (0.0)	3 (75.0)	2 (22.2)	8 (33.3)
A little bit	3 (27.3)	13 (36.1)	4 (50.0)	14 (46.7)	2 (25.0)	16 (59.3)	1 (33.3)	0 (0.0)	2 (22.2)	16 (66.7)
Somewhat	3 (27.3)	9 (25.0)	1 (12.5)	5 (16.7)	2 (25.0)	5 (18.5)	1 (33.3)	1 (25.0)	1 (11.1)	0 (0.0)
Quite a bit	2 (18.2)	3 (8.3)	0 (0.0)	2 (6.7)	1 (12.5)	0 (0.0)	1 (33.3)	0 (0.0)	4 (44.4)	0 (0.0)
Very much	1 (9.1)	0 (0.0)	2 (25.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 13 day 1										
n	9	35	6	27	6	24	3	1	10	19
Not at all	2 (22.2)	8 (22.9)	3 (50.0)	8 (29.6)	3 (50.0)	6 (25.0)	1 (33.3)	1 (100.0)	3 (30.0)	8 (42.1)
A little bit	2 (22.2)	19 (54.3)	1 (16.7)	13 (48.1)	2 (33.3)	12 (50.0)	1 (33.3)	0 (0.0)	5 (50.0)	11 (57.9)
Somewhat	3 (33.3)	6 (17.1)	0 (0.0)	5 (18.5)	0 (0.0)	6 (25.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)
Quite a bit	2 (22.2)	2 (5.7)	1 (16.7)	1 (3.7)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (10.0)	0 (0.0)
Very much	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data cutoff date: August 2, 2022. N = number of all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements. n = number of patients with evaluable data at the time point. n1 = number of patients with observed data per category. The analysis included baseline and all scheduled on-treatment visits, excluding follow-up visits. Proportions are based on the number of patients in each visit, treatment, and response category. IV, intravenously; PO, orally; PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events; Q3W, every 3 weeks, QD, daily.

Supplementary Table 9. PRO-CTCAE interference by worst response at baseline or all scheduled on-treatment visits

	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	**Sotorasib 960 mg PO QD N = 148 n1 (%)**
Pain		
n	102	139
Not at all	7 (6.9)	11 (7.9)
A little bit	30 (29.4)	44 (31.7)
Somewhat	15 (14.7)	31 (22.3)
Quite a bit	34 (33.3)	32 (23.0)
Very much	16 (15.7)	21 (15.1)
Aching muscles		
n	88	119
Not at all	8 (9.1)	15 (12.6)
A little bit	28 (31.8)	44 (37.0)
Somewhat	24 (27.3)	28 (23.5)
Quite a bit	20 (22.7)	25 (21.0)
Very much	8 (9.1)	7 (5.9)
Aching joints		
n	86	122
Not at all	10 (11.6)	12 (9.8)
A little bit	33 (38.4)	52 (42.6)
Somewhat	18 (20.9)	25 (20.5)
Quite a bit	17 (19.8)	24 (19.7)
Very much	8 (9.3)	9 (7.4)
Mouth or throat sores		
n	60	41
Not at all	14 (23.3)	14 (34.1)
A little bit	24 (40.0)	20 (48.8)
Somewhat	9 (15.0)	5 (12.2)
Quite a bit	10 (16.7)	2 (4.9)
Very much	3 (5.0)	0 (0.0)
Numbness		
n	83	96
Not at all	18 (21.7)	23 (24.0)
A little bit	34 (41.0)	49 (51.0)
Somewhat	13 (15.7)	21 (21.9)
Quite a bit	13 (15.7)	2 (2.1)
Very much	5 (6.0)	1 (1.0)

Data cutoff date: August 2, 2022. N = number of all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements. n = number of patients with evaluable data at the time point. n1 = number of patients with observed data per category. The analysis presents

the number and proportion of patients according to the “worst” response at baseline or all scheduled on-treatment visits, excluding follow-up visits. Proportions are based on the number of patients in each treatment and response category. IV, intravenously; PO, orally; PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events; Q3W, every 3 weeks, QD, daily.

Supplementary Table 10. GEE estimates of change from baseline for PRO-CTCAE frequency by original response

	Docetaxel 75 mg/m^2 IV Q3W N = 113 n	Sotorasib 960 mg PO QD N = 148 n	OR*,† (95% CI)	*P*-value*
Pain				
Cycle 2 day 1	103	138	1.4 (0.9, 2.3)	0.180
Cycle 3 day 1	96	128	1.2 (0.7, 2.0)	0.440
Cycle 4 day 1	71	109	2.0 (1.1, 3.7)	0.026
Cycle 5 day 1	60	101	1.2 (0.7, 2.3)	0.520
Overall§	112	147	3.1 (1.7, 5.9)	< 0.001
Aching muscles				
Cycle 2 day 1	103	138	1.0 (0.6, 1.6)	0.850
Cycle 3 day 1	96	128	1.1 (0.6, 1.9)	0.710
Cycle 4 day 1	71	109	1.4 (0.8, 2.5)	0.260
Cycle 5 day 1	60	101	0.9 (0.5, 1.8)	0.850
Overall§	112	147	2.1 (1.3, 3.6)	0.003
Aching joints				
Cycle 2 day 1	103	138	1.7 (1.0, 2.8)	0.056
Cycle 3 day 1	96	128	1.0 (0.6, 1.6)	0.950
Cycle 4 day 1	71	109	0.7 (0.4, 1.4)	0.330
Cycle 5 day 1	60	101	0.6 (0.3, 1.1)	0.076
Overall§	112	147	1.6 (0.9, 2.8)	0.094

Data cutoff date: August 2, 2022. N = number of all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements. n = number of patients with observed data. *OR, 95% CIs, and *P*-values are estimated using a GEE model based on change from baseline as the dependent variable, intercept, time, baseline score, treatment, treatment-by-time interaction and randomization stratification factors as fixed effects. All post-baseline visits are considered, excluding follow-up visits. †An OR > 1.0 indicates higher improvement in symptom scale for sotorasib relative to docetaxel. ‡Overall represents all post-baseline visits, including visits beyond cycle 5 day 1, excluding follow-up visits. CI, confidence interval; GEE, generalized estimating equation; IV, intravenously; PO, orally; PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events; OR, odds ratio; Q3W, every 3 weeks, QD, daily.

Supplementary Table 11. Summary of PRO-CTCAE frequency over time by original response

	Pain		Aching Muscles		Aching Joints	
	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**
Baseline						
n	112	147	112	147	112	147
Never	32 (28.6)	34 (23.1)	61 (54.5)	72 (49.0)	51 (45.5)	70 (47.6)
Rarely	30 (26.8)	28 (19.0)	25 (22.3)	36 (24.5)	25 (22.3)	31 (21.1)
Occasionally	19 (17.0)	36 (24.5)	18 (16.1)	25 (17.0)	20 (17.9)	29 (19.7)
Frequently	19 (17.0)	36 (24.5)	5 (4.5)	13 (8.8)	11 (9.8)	16 (10.9)
Almost constantly	12 (10.7)	13 (8.8)	3 (2.7)	1 (0.7)	5 (4.5)	1 (0.7)
Cycle 2 day 1						
n	103	138	103	138	103	138
Never	29 (28.2)	34 (24.6)	52 (50.5)	67 (48.6)	49 (47.6)	72 (52.2)
Rarely	18 (17.5)	38 (27.5)	21 (20.4)	27 (19.6)	10 (9.7)	26 (18.8)
Occasionally	25 (24.3)	35 (25.4)	17 (16.5)	22 (15.9)	25 (24.3)	20 (14.5)
Frequently	24 (23.3)	14 (10.1)	8 (7.8)	18 (13.0)	14 (13.6)	14 (10.1)
Almost constantly	7 (6.8)	17 (12.3)	5 (4.9)	4 (2.9)	5 (4.9)	6 (4.3)
Cycle 3 day 1						
n	96	128	96	128	96	128
Never	24 (25.0)	32 (25.0)	51 (53.1)	64 (50.0)	53 (55.2)	66 (51.6)
Rarely	28 (29.2)	40 (31.3)	19 (19.8)	26 (20.3)	14 (14.6)	23 (18.0)
Occasionally	21 (21.9)	26 (20.3)	18 (18.8)	29 (22.7)	20 (20.8)	28 (21.9)
Frequently	17 (17.7)	21 (16.4)	6 (6.3)	6 (4.7)	7 (7.3)	8 (6.3)
Almost constantly	6 (6.3)	9 (7.0)	2 (2.1)	3 (2.3)	2 (2.1)	3 (2.3)
Cycle 4 day 1						
n	71	109	71	109	71	109
Never	25 (35.2)	42 (38.5)	38 (53.5)	60 (55.0)	37 (52.1)	47 (43.1)
Rarely	12 (16.9)	25 (22.9)	17 (23.9)	23 (21.1)	14 (19.7)	21 (19.3)
Occasionally	16 (22.5)	21 (19.3)	7 (9.9)	20 (18.3)	10 (14.1)	32 (29.4)

	Pain		Aching Muscles		Aching Joints	
	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**
Frequently	9 (12.7)	16 (14.7)	7 (9.9)	5 (4.6)	6 (8.5)	8 (7.3)
Almost constantly	9 (12.7)	5 (4.6)	2 (2.8)	1 (0.9)	4 (5.6)	1 (0.9)
Cycle 5 day 1						
n	60	101	60	101	60	101
Never	22 (36.7)	25 (24.8)	34 (56.7)	40 (39.6)	34 (56.7)	35 (34.7)
Rarely	10 (16.7)	37 (36.6)	10 (16.7)	37 (36.6)	11 (18.3)	34 (33.7)
Occasionally	14 (23.3)	20 (19.8)	10 (16.7)	21 (20.8)	8 (13.3)	27 (26.7)
Frequently	6 (10.0)	11 (10.9)	1 (1.7)	3 (3.0)	5 (8.3)	3 (3.0)
Almost constantly	8 (13.3)	8 (7.9)	5 (8.3)	0 (0.0)	2 (3.3)	2 (2.0)
Cycle 6 day 1						
n	49	88	49	88	49	88
Never	15 (30.6)	26 (29.5)	28 (57.1)	42 (47.7)	27 (55.1)	40 (45.5)
Rarely	9 (18.4)	17 (19.3)	7 (14.3)	24 (27.3)	5 (10.2)	21 (23.9)
Occasionally	10 (20.4)	23 (26.1)	9 (18.4)	17 (19.3)	10 (20.4)	18 (20.5)
Frequently	12 (24.5)	19 (21.6)	2 (4.1)	5 (5.7)	4 (8.2)	7 (8.0)
Almost constantly	3 (6.1)	3 (3.4)	3 (6.1)	0 (0.0)	3 (6.1)	2 (2.3)
Cycle 7 day 1						
n	38	83	38	83	38	83
Never	13 (34.2)	21 (25.3)	20 (52.6)	46 (55.4)	21 (55.3)	45 (54.2)
Rarely	9 (23.7)	28 (33.7)	6 (15.8)	22 (26.5)	7 (18.4)	20 (24.1)
Occasionally	9 (23.7)	20 (24.1)	8 (21.1)	13 (15.7)	5 (13.2)	14 (16.9)
Frequently	3 (7.9)	12 (14.5)	2 (5.3)	2 (2.4)	3 (7.9)	3 (3.6)
Almost constantly	4 (10.5)	2 (2.4)	2 (5.3)	0 (0.0)	2 (5.3)	1 (1.2)
Cycle 8 day 1						
n	37	75	37	75	37	75
Never	13 (35.1)	28 (37.3)	16 (43.2)	42 (56.0)	19 (51.4)	42 (56.0)

	Pain		Aching Muscles		Aching Joints	
	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**
Rarely	8 (21.6)	22 (29.3)	8 (21.6)	16 (21.3)	9 (24.3)	12 (16.0)
Occasionally	11 (29.7)	13 (17.3)	10 (27.0)	13 (17.3)	7 (18.9)	18 (24.0)
Frequently	2 (5.4)	9 (12.0)	2 (5.4)	4 (5.3)	1 (2.7)	3 (4.0)
Almost constantly	3 (8.1)	3 (4.0)	1 (2.7)	0 (0.0)	1 (2.7)	0 (0.0)
Cycle 9 day 1						
n	26	68	26	68	26	68
Never	12 (46.2)	23 (33.8)	15 (57.7)	37 (54.4)	13 (50.0)	32 (47.1)
Rarely	6 (23.1)	23 (33.8)	7 (26.9)	19 (27.9)	7 (26.9)	17 (25.0)
Occasionally	4 (15.4)	13 (19.1)	2 (7.7)	6 (8.8)	4 (15.4)	15 (22.1)
Frequently	2 (7.7)	5 (7.4)	1 (3.8)	5 (7.4)	1 (3.8)	3 (4.4)
Almost constantly	2 (7.7)	4 (5.9)	1 (3.8)	1 (1.5)	1 (3.8)	1 (1.5)
Cycle 10 day 1						
n	20	64	20	64	20	64
Never	9 (45.0)	20 (31.3)	14 (70.0)	30 (46.9)	13 (65.0)	33 (51.6)
Rarely	1 (5.0)	23 (35.9)	3 (15.0)	23 (35.9)	1 (5.0)	18 (28.1)
Occasionally	6 (30.0)	10 (15.6)	1 (5.0)	7 (10.9)	4 (20.0)	6 (9.4)
Frequently	2 (10.0)	10 (15.6)	0 (0.0)	4 (6.3)	1 (5.0)	7 (10.9)
Almost constantly	2 (10.0)	1 (1.6)	2 (10.0)	0 (0.0)	1 (5.0)	0 (0.0)
Cycle 11 day 1						
n	18	62	18	62	18	62
Never	6 (33.3)	21 (33.9)	10 (55.6)	31 (50.0)	11 (61.1)	32 (51.6)
Rarely	3 (16.7)	21 (33.9)	1 (5.6)	21 (33.9)	1 (5.6)	16 (25.8)
Occasionally	3 (16.7)	10 (16.1)	5 (27.8)	5 (8.1)	5 (27.8)	9 (14.5)
Frequently	4 (22.2)	6 (9.7)	1 (5.6)	4 (6.5)	0 (0.0)	4 (6.5)
Almost constantly	2 (11.1)	4 (6.5)	1 (5.6)	1 (1.6)	1 (5.6)	1 (1.6)

	Pain		Aching Muscles		Aching Joints	
	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**
Cycle 12 day 1						
n	16	58	16	58	16	58
Never	5 (31.3)	18 (31.0)	7 (43.8)	28 (48.3)	8 (50.0)	29 (50.0)
Rarely	3 (18.8)	19 (32.8)	3 (18.8)	17 (29.3)	1 (6.3)	16 (27.6)
Occasionally	2 (12.5)	10 (17.2)	4 (25.0)	7 (12.1)	5 (31.3)	9 (15.5)
Frequently	4 (25.0)	9 (15.5)	0 (0.0)	6 (10.3)	1 (6.3)	3 (5.2)
Almost constantly	2 (12.5)	2 (3.4)	2 (12.5)	0 (0.0)	1 (6.3)	1 (1.7)
Cycle 13 day 1						
n	14	57	14	57	14	57
Never	4 (28.6)	21 (36.8)	7 (50.0)	29 (50.9)	8 (57.1)	33 (57.9)
Rarely	5 (35.7)	11 (19.3)	3 (21.4)	14 (24.6)	2 (14.3)	9 (15.8)
Occasionally	2 (14.3)	15 (26.3)	2 (14.3)	7 (12.3)	3 (21.4)	14 (24.6)
Frequently	2 (14.3)	6 (10.5)	1 (7.1)	7 (12.3)	0 (0.0)	1 (1.8)
Almost constantly	1 (7.1)	4 (7.0)	1 (7.1)	0 (0.0)	1 (7.1)	0 (0.0)
Cycle 14 day 1						
n	12	51	12	51	12	51
Never	5 (41.7)	16 (31.4)	6 (50.0)	22 (43.1)	7 (58.3)	20 (39.2)
Rarely	3 (25.0)	17 (33.3)	5 (41.7)	16 (31.4)	2 (16.7)	18 (35.3)
Occasionally	1 (8.3)	9 (17.6)	0 (0.0)	10 (19.6)	2 (16.7)	9 (17.6)
Frequently	1 (8.3)	6 (11.8)	0 (0.0)	3 (5.9)	0 (0.0)	3 (5.9)
Almost constantly	2 (16.7)	3 (5.9)	1 (8.3)	0 (0.0)	1 (8.3)	1 (2.0)
Cycle 15 day 1						
n	10	49	10	49	10	49
Never	5 (50.0)	18 (36.7)	6 (60.0)	23 (46.9)	5 (50.0)	21 (42.9)
Rarely	2 (20.0)	13 (26.5)	3 (30.0)	16 (32.7)	3 (30.0)	14 (28.6)
Occasionally	1 (10.0)	11 (22.4)	1 (10.0)	5 (10.2)	2 (20.0)	13 (26.5)
Frequently	2 (20.0)	6 (12.2)	0 (0.0)	4 (8.2)	0 (0.0)	1 (2.0)

	Pain		Aching Muscles		Aching Joints	
	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**	**Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)**	**Sotorasib 960 mg PO QD N = 148 n1 (%)**
Almost constantly	0 (0.0)	1 (2.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)

Data cutoff date: August 2, 2022. N = number of all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements. n = number of patients with evaluable data at the time point. n1 = number of patients with observed data per category. The analysis included baseline and all scheduled on-treatment visits, excluding follow-up visits. Proportions are based on the number of patients in each visit, treatment, and response category. IV, intravenously; PO, orally; PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events; Q3W, every 3 weeks, QD, daily.

Supplementary Table 12. PRO-CTCAE interference by worst response at baseline or all scheduled on-treatment visits

	Docetaxel 75 mg/m^2 IV Q3W N = 113 n1 (%)	**Sotorasib 960 mg PO QD N = 148 n1 (%)**
Pain		
n	112	147
Never	10 (8.9)	4 (2.7)
Rarely	16 (14.3)	14 (9.5)
Occasionally	20 (17.9)	43 (29.3)
Frequently	37 (33.0)	41 (27.9)
Almost constantly	29 (25.9)	45 (30.6)
Aching muscles		
n	112	147
Never	21 (18.8)	25 (17.0)
Rarely	19 (17.0)	25 (17.0)
Occasionally	40 (35.7)	47 (32.0)
Frequently	19 (17.0)	38 (25.9)
Almost constantly	13 (11.6)	12 (8.2)
Aching joints		
n	112	147
Never	23 (20.5)	23 (15.6)
Rarely	22 (19.6)	24 (16.3)
Occasionally	32 (28.6)	46 (31.3)
Frequently	21 (18.8)	37 (25.2)
Almost constantly	14 (12.5)	17 (11.6)

Data cutoff date: August 2, 2022. N = number of all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements. n = number of patients with evaluable data at the time point. n1 = number of patients with observed data per category. The analysis presents the number and proportion of patients according to the “worst” response at baseline or all scheduled on-treatment visits, excluding follow-up visits. Proportions are based on the number of patients in each treatment and response category. IV, intravenously; PO, orally; PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events; Q3W, every 3 weeks, QD, daily.

Supplementary Table 13. GEE estimates of change from baseline to week 12 for EQ-5D-5L

Dimension	OR (95% CI)*, †	*P*-value*
EQ-5D-5L		
Questionnaire		
Mobility	2.8 (1.4, 5.4)	0.003
Self-care	2.9 (1.4, 6.3)	0.006
Usual activities	1.9 (1.0, 3.6)	0.043
Pain/discomfort	1.6 (0.8, 3.1)	0.150
Anxiety/depression	1.0 (0.5, 1.8)	0.920

Data cutoff date: August 2, 2022. *OR, 95% CIs, and *P*-values were estimated using a GEE model based on change from baseline as the dependent variable, intercept, time, baseline score, treatment, treatment-by-time interaction and randomization stratification factors as fixed effects. The randomization stratification factors were number of prior lines of therapy in advanced disease (1 vs 2 vs > 2), race (Asian vs non-Asian), and history of CNS involvement (yes vs no). All post-baseline visits are considered excluding follow-up visits. †An OR > 1.0 indicates higher improvement in dimension for sotorasib relative to docetaxel. CI, confidence interval; EQ-5D-5L, 5-level European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire 5 dimensions; GEE, generalized estimating equation; OR, odds ratio.

Supplementary Table 14. Mean change from baseline in EQ-5D-5L VAS over time

Change from baseline to:	Docetaxel 75 mg/m^2 IV Q3W N = 138 Mean (SD) VAS [n]	Sotorasib 960 mg PO QD N = 160 Mean (SD) VAS [n]
Cycle 1 day 5	–8.4 (20.8) [122]	1.5 (15.9) [142]
Cycle 2 day 1	–1.0 (18.5) [110]	3.4 (20.4) [147]
Cycle 2 day 5	–5.1 (18.6) [108]	3.8 (18.2) [126]
Cycle 3 day 1	–3.7 (17.3) [106]	4.1 (18.3) [134]
Cycle 3 day 5	–6.6 (21.1) [81]	3.9 (16.5) [103)
Cycle 4 day 1	–5.4 (20.6) [81]	3.8 (15.2) [115]
Cycle 5 day 1	–5.8 (18.2) [67]	2.2 (15.6) [105]
Cycle 6 day 1	–7.3 (18.7) [55]	1.1 (16.5 [92]
Cycle 7 day 1	–2.1 (19.5) [40]	1.5 (15.4) [88]
Cycle 8 day 1	–3.8 (21.4) [39]	1.2 (16.6) [79]
Cycle 9 day 1	1.5 (16.8) [28]	1.8 (14.9) [70]
Cycle 10 day 1	1.0 (17.3) [21]	1.2 (13.8) [66]
Cycle 11 day 1	1.1 (16.4) [20]	2.8 (15.0) [65]
Cycle 12 day 1	–2.3 (15.0) [18]	2.8 (14.8) [59]
Cycle 13 day 1	1.4 (12.3 [14]	4.0 (15.9 [59]
Cycle 14 day 1	4.5 (13.8) [12]	2.1 (16.8) [54]
Cycle 15 day 1	7.0 (10.7) [10]	4.2 (13.8) [52]
Cycle 16 day 1	6.7 (12.8) [9]	3.4 (16.0) [49]
Cycle 17 day 1	3.0 (19.5) [8]	1.4 (15.4) [45]
Cycle 18 day 1	7.1 (14.3) [8]	2.1 (12.1) [40]
Cycle 19 day 1	–9.3 (25.3) [7]	2.1 (14.2) [41]
Cycle 20 day 1	–0.2 (24.9) [6]	2.8 (15.5) [39]
Cycle 21 day 1	8.8 (15.7) [5]	1.2 (15.3) [33]
Cycle 22 day 1	14.0 (13.1) [4]	2.0 (13.3) [31]
Cycle 23 day 1	10.5 (6.5) [4]	–0.3 (16.9) [28]
Cycle 24 day 1	10.0(15.5) [4]	5.1 (12.1) [20]
Cycle 25 day 1	14.0 (18.4) [3]	6.5 (10.3) [14]
Cycle 26 day 1	16.0 (19.8) [2]	5.5 (8.0) [13]
Cycle 27 day 1	15.5 (20.5) [2]	1.9 (15.7) [11]
Cycle 28 day 1	17.0 (22.6) [2]	8.0 (9.8) [8]
Cycle 29 day 1	0 (0) [1]	5.1 (9.1) [7]
Cycle 30 day 1	5.0 (0) [1]	5.1 (9.4) [7]

Data cutoff date: August 2, 2022. N = number of all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements. n = number of patients with observed data. The analysis included baseline and all scheduled on-treatment visits, excluding follow-up visits. EQ-5D-5L, 5-level European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire 5 dimensions; IV, intravenous; SD, standard deviation; PO, orally; Q3W, every 3 weeks; QD, daily; VAS, visual analog scale.

Supplementary Table 15. Change of BPI-SF over time

	Pain at its Worst	
	Docetaxel 75 mg/m² IV Q3W N = 122	**Sotorasib 960 mg PO QD N = 157**
Change from baseline to:	**Mean (SD) [n]**	**Mean (SD) [n]**
Cycle 2 day 1	0.3 (2.5) [111]	–0.6 (2.7) [147]
Cycle 3 day 1	0.3 (3.1) [107]	–0.4 (2.9) [134]
Cycle 4 day 1	0.9 (2.8) [81]	–0.4 (3.1) [116]
Cycle 5 day 1	0.3 (2.6) [67]	–0.3 (2.8) [105]
Cycle 6 day 1	0.6 (3.0) [55]	–0.3 (2.8) [92]
Cycle 7 day 1	–0.7 (2.7) [40]	–0.1 (3.1) [89]
Cycle 8 day 1	0.2 (2.3) [39]	–0.3 (2.8) [79]
Cycle 9 day 1	0.5 (3.2) [28]	–0.1 (3.2) [70]
Cycle 10 day 1	1.0 (3.7) [21]	0 (3.2) [66]
Cycle 11 day 1	1.1 (2.9) [20]	–0.1 (3.0) [65]
Cycle 12 day 1	1.2 (2.7) [18]	–0.5 (2.3) [59]
Cycle 13 day 1	0.5 (1.7) [14]	–0.3 (2.7) [59]
Cycle 14 day 1	0.8 (2.7) [12]	0.1 (2.9) [54]
Cycle 15 day 1	–0.1 (1.8) [10]	–0.2 (2.9) [52]
Cycle 16 day 1	0.9 (2.7) [9]	0.3 (2.6) [49]
Cycle 17 day 1	–0.1 (1.8) [8]	0 (2.8) [45]
Cycle 18 day 1	0.8 (2.4) [8]	0.7 (2.8) [40]
Cycle 19 day 1	2.0 (2.4) [7]	0.2 (2.5) [41]
Cycle 20 day 1	2.0 (3.1) [6]	0.1 (2.9) [39]
Cycle 21 day 1	2.0 (2.1) [5]	–0.3 (3.0) [33]
Cycle 22 day 1	–0.5 (1.3) [4]	0.3 (2.4) [31]
Cycle 23 day 1	2.3 (2.1) [4]	0.1 (2.5) [28]
Cycle 24 day 1	1.8 (1.5) [4]	0.1 (2.1) [20]
Cycle 25 day 1	5.0 (4.6) [3]	0.4 (2.3) [14]
Cycle 26 day 1	3.0 (2.8) [2]	0.5 (2.4) [13]
Cycle 27 day 1	0.5 (2.1) [2]	–0.1 (1.9) [11]
Cycle 28 day 1	1.0 (0) [2]	–0.4 (1.2) [8]
Cycle 29 day 1	4.0 (0) [1]	–0.6 (1.6) [7]
Cycle 30 day 1	–2.0 (0) [1]	–0.6 (2.1) [7]

Data cutoff date: August 2, 2022. N = number of all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements. n = number of patients with observed data. The analysis included baseline and all scheduled on-treatment visits, excluding follow-up visits. BPI-SF, Brief Pain Inventory-Short Form; IV, intravenous; SD, standard deviation; PO, orally; Q3W, every 3 weeks; QD, daily; VA, visual analog scale.

Supplementary Table 16. Summary of responders by change from baseline for BPI-SF over time

	Docetaxel 75 mg/m^2 IV Q3W N = 122 Pain at its Worst n (%), [n1]	**Sotorasib 960 mg PO QD N = 157 Pain at its Worst n (%) [n1]**
Cycle 2 day 1		
Improved (2 or more lower than baseline)	16 (14.4) [111]	49 (33.3) [147]
Stable (between 1 lower and 1 higher than baseline)	72 (64.9) [111]	68 (46.3) [147]
Worsening (2 or more higher than baseline)	23 (20.7) [111]	30 (20.4) [147]
Cycle 3 day 1		
Improved (2 or more lower than baseline)	26 (24.3) [107]	42 (31.3) [134]
Stable (between 1 lower and 1 higher than baseline)	52 (48.6) [107]	61 (45.5) [134]
Worsening (2 or more higher than baseline)	29 (27.1) [107]	31 (23.1) [134]
Cycle 4 day 1		
Improved (2 or more lower than baseline)	12 (14.8) [81]	30 (25.9) [116]
Stable (between 1 lower and 1 higher than baseline)	43 (53.1) [81]	60 (51.7) [116]
Worsening (2 or more higher than baseline)	26 (32.1) [81]	26 (22.4) [116]
Cycle 5 day 1		
Improved (2 or more lower than baseline)	12 (17.9) [67]	30 (28.6) [105]
Stable (between 1 lower and 1 higher than baseline)	41 (61.2) [67]	52 (49.5) [105]
Worsening (2 or more higher than baseline)	14 (20.9) [67]	23 (21.9) [105]
Cycle 6 day 1		
Improved (2 or more lower than baseline)	9 (16.4) [55]	26 (28.3) [92]
Stable (between 1 lower and 1 higher than baseline)	32 (58.2) [55]	43 (46.7) [92]
Worsening (2 or more higher than baseline)	14 (25.5) [55]	23 (25.0) [92]
Cycle 7 day 1		
Improved (2 or more lower than baseline)	11 (27.5) [40]	22 (24.7) [89]
Stable (between 1 lower and 1 higher than baseline)	24 (60.0) [40]	46 (51.7) [89]
Worsening (2 or more higher than baseline)	5 (12.5) [40]	21 (23.6) [89]
Cycle 8 day 1		
Improved (2 or more lower than baseline)	6 (15.4) [39]	22 (27.8) [79]
Stable (between 1 lower and 1 higher than baseline)	24 (61.5) [39]	39 (49.4) [79]
Worsening (2 or more higher than baseline)	9 (23.1) [39]	18 (22.8) [79]
Cycle 9 day 1		
Improved (2 or more lower than baseline)	3 (10.7) [28]	20 (28.6) [70]
Stable (between 1 lower and 1 higher than baseline)	17 (60.7) [28]	32 (45.7) [70]
Worsening (2 or more higher than baseline)	8 (28.6) [28]	18 (25.7) [70]
Cycle 10 day 1		
Improved (2 or more lower than baseline)	4 (19.0) [21]	17 (25.8) [66]
Stable (between 1 lower and 1 higher than baseline)	7 (33.3) [21]	34 (51.5) [66]
Worsening (2 or more higher than baseline)	10 (47.6) [21]	15 (22.7) [66]
Cycle 11 day 1		
Improved (2 or more lower than baseline)	2 (10.0) [20]	15 (23.1) [65]

	Docetaxel 75 mg/m^2 IV Q3W N = 122 Pain at its Worst n (%), [n1]	Sotorasib 960 mg PO QD N = 157 Pain at its Worst n (%) [n1]
Stable (between 1 lower and 1 higher than baseline)	13 (65.0) [20	35 (53.8) [65]
Worsening (2 or more higher than baseline)	5 (25.0) [20]	15 (23.1) [65]
Cycle 12 day 1		
Improved (2 or more lower than baseline)	2 (11.1) [18]	15 (25.4) [59]
Stable (between 1 lower and 1 higher than baseline)	10 (55.6) [18]	35 (59.3) [59]
Worsening (2 or more higher than baseline)	6 (33.3) [18]	9 (15.3) [59]
Cycle 13 day 1		
Improved (2 or more lower than baseline)	2 (14.3) [14]	17 (28.8) [59]
Stable (between 1 lower and 1 higher than baseline)	9 (64.3) [14]	31 (52.5) [59]
Worsening (2 or more higher than baseline)	3 (21.4) [14]	11 (18.6) [59]
Cycle 14 day 1		
Improved (2 or more lower than baseline)	2 (16.7) [12]	12 (22.2) [54]
Stable (between 1 lower and 1 higher than baseline)	8 (66.7) [12]	32 (59.3) [54]
Worsening (2 or more higher than baseline)	2 (16.7) [12]	10 (18.5) [54]
Cycle 15 day 1		
Improved (2 or more lower than baseline)	3 (30.0) [10]	15 (28.8) [52]
Stable (between 1 lower and 1 higher than baseline)	4 (40.0) [10]	22 (42.3) 52]
Worsening (2 or more higher than baseline)	3 (30.0) [10]	15 (28.8) [52]

Data cutoff date: August 2, 2022. N = number of all randomized patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements. n = number of patients with observed data. n1 = total number of patients with data for the outcome. The analysis included baseline and all scheduled on-treatment visits, excluding follow-up visits. Proportions are based on the number of patients in each visit, treatment, and response category. BPI-SF, Brief Pain Inventory-Short Form; IV, intravenous; SD, standard deviation; PO, orally; Q3W, every 3 weeks; QD, daily.

Supplementary Table 17. Early dropout: covariate-adjusted PRO analysis supports primary results

	Original Analysis	**Covariate-Adjusted Analysis***
Side effect bother		
OR	5.7 (3.0, 10.9)	6.2 (3.2, 11.9)
Key secondary endpoints		
Score difference (MMRM)		
Dyspnea	–10.1 (–13.4, –6.8)	–10.2 (–13.5, –6.8)
Global health status/QOL	6.9 (3.7, 10.2)	7.1 (3.9, 10.4)
Physical functioning	8.8 (5.4, 12.2)	9.0 (5.6, 12.4)
OR (GEE)		
Cough	3.2 (1.6, 6.7)	3.7 (1.8, 7.7)
Chest pain	1.6 (0.8, 3.0)	1.6 (0.8, 3.1)
Time to deterioration		
Hazard ratio		
Global health status/QOL	0.7 (0.5, 0.9)	0.7 (0.5, 0.9)
Physical functioning	0.7 (0.5, 0.9)	0.7 (0.5, 0.9)
Dyspnea	0.6 (0.5, 0.8)	0.6 (0.5, 0.8)
Cough	0.6 (0.4, 0.8)	0.5 (0.3, 0.7)
Chest pain	0.8 (0.6, 1.2)	0.8 (0.6, 1.1)

Data cutoff date: August 2, 2022. *Additional variables chosen for clinical importance and ≥ 10% prelevance: liver metastasis (yes, no), baseline tumor median (> median, ≤ median), ECOG performance status (0, 1), age < 65 years, ≥ 65 years), and North America (yes, no). ECOG, Eastern Cooperative Oncology Group; GEE, generalized estimating equation; MMRM, mixed model for repeated measurement; OR, odds ratio; PRO, patient-reported outcome; QOL, quality of life.