Sotorasib (NSCLC)

Addendum to Project A23-06 (dossier assessment)[1]

ADDENDUM

Project: A23-53 Version: 1.0 Status: 7 July 2023

[1] Translation of addendum A23-53 *Sotorasib (NSCLC) – Addendum zum Projekt A23-06 (Dossierbewertung)*. Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Sotorasib (NSCLC) – Addendum to Project A23-06

Commissioning agency

Federal Joint Committee

Commission awarded on

6 June 2023

Internal Project No.

A23-53

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Christina Frings
- Merlin Bittlinger
- Katharina Hirsch
- Ana Liberman
- Volker Vervölgyi

Keywords

Sotorasib, Carcinoma – Non-Small-Cell Lung, Benefit Assessment

Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BPI-SF	Brief Pain Inventory-Short Form
CNS	central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
FACT-G	Functional Assessment of Cancer Therapy-General
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GP5	General Population 5
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NSCLC	non-small cell lung cancer
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-LC13	Quality of Life Questionnaire – Lung Cancer 13
SMQ	Standardised MedDRA Query
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 6 June 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-06 (Sotorasib – Benefit assessment according to § 35a Social Code Book V) [1].

As commissioned, the total population of the CodeBreak 200 study was to be analysed, taking into account the information provided in the dossier [2].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The research question of benefit assessment A23-06 [1] was to assess the added benefit of sotorasib monotherapy in comparison with the appropriate comparator therapy (ACT) in adult patients with advanced non-small cell lung cancer (NSCLC) with Kirsten Rat Sarcoma Viral Oncogene Homologue (KRAS) G12C mutation (as per G-BA, KRAS p.G12C mutation) who have progressed after at least 1 prior line of systemic therapy using cytotoxic chemotherapy or a programmed cell death protein 1 (PD-1) / programmed cell death ligand 1 (PD-L1) antibody in combination with platinum-containing chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody and platinum-containing chemotherapy.

CodeBreak 200 study unsuitable for the benefit assessment

For research question 3, the company presents the CodeBreak 200 study (see Section 2.2 for a description of the study). The CodeBreak 200 study is a single-comparator study in which all comparator arm participants received docetaxel monotherapy. The CodeBreak 200 study did not implement the ACT defined by the G-BA for research question 3 (individualized therapy taking into account prior therapy and histology, selecting from afatinib, pemetrexed, erlotinib, docetaxel, docetaxel in combination with ramucirumab, docetaxel in combination with nintedanib, and vinorelbine).

More detailed reasoning can be found in A23-06 [1].

The CodeBreak 200 study is presented below as commissioned.

2.1 CodeBreak 200 study

The study presented in the following addendum was included in the present addendum.

Table 1: Study pool of the company – RCT, direct comparison: sotorasib vs. docetaxel

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
CodeBreak 200	No	Yes	No	Yes [3]	Yes [4,5]	Yes [6]

a. Study for which the company was sponsor.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

2.2 Study characteristics

Table 2 and Table 3 describe the CodeBreak 200 study presented by the company.

Table 2: Characteristics of the study included by the company – RCT, direct comparison: sotorasib versus docetaxel (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CodeBreak 200	RCT, open-label, parallel-group	Adult patients with locally advanced and unresectable or metastatic[b] NSCLC with a KRAS G12C mutation[c] with progression or recurrence after ≥ 1 prior systemic therapy with a platinum-based chemotherapy doublet and a checkpoint inhibitor in advanced or metastatic stage and ECOG-PS ≤ 1	Sotorasib (N = 171) Docetaxel (N = 174)	Screening: 28 days Treatment: until disease progression[d], intolerance, start of new cancer therapy, withdrawal of consent, lost to follow-up, or death Observation[e]: outcome-specific, at maximum until withdrawal of consent, lost-to-follow-up, or death (maximum 5 years after inclusion of the last patient)	148 study centres in: Australia, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Japan, Korea, Netherlands, Poland, Portugal, Russia, Spain, Sweden, Switzerland, United Kingdom, and the United States 06/2020–ongoing Data cut-off: 2/08/2022 (primary PFS analysis[f])	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 2: Characteristics of the study included by the company – RCT, direct comparison: sotorasib versus docetaxel (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this addendum. Secondary outcomes comprise exclusively data based on the information provided by the company's Module 4 A.
b. Patients with active brain metastases (untreated and/or symptomatic at the time of study entry) were excluded.
c. Diseases with other mutations (e.g. EGFR, ALK) were excluded, as were mixed small-cell lung cancer or mixed NSCLC histology.
d. Patients who, in the investigator's opinion, met certain criteria were allowed to receive continued treatment with sotorasib or docetaxel even after disease progression. Patients in the docetaxel arm were allowed to switch to sotorasib after progression if they met certain criteria, including not having started any other cancer therapy.
e. Outcome-specific information is described in Table 4.
f. The primary analysis was planned to occur after 230 PFS events or termination of recruitment and a six-week follow-up of the last randomised study participant, whichever is later. For overall survival, analyses were planned to be conducted after about 175 deaths and about 198 deaths. In light of the number of events reached, these analyses are already included in the present data cutoff. A final analysis is planned to be conducted after the last patient has completed long-term follow-up observation.

AE: adverse event; ALK: anaplastic lymphoma kinase; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: Epidermal Growth Factor Receptor; KRAS G12C: Kirsten Rat Sarcoma Viral Oncogene Homologue G12C; N: Number of randomised patients; NSCLC: non-small cell lung cancer; PFS: progression-free survival; RCT: randomised controlled trial

Table 3: Characteristics of the intervention – RCT, direct comparison: sotorasib versus docetaxel (multipage table)

Study	Intervention	Comparison
CodeBreak 200	Sotorasib 960 mg/day, orally	Docetaxel 75 mg/m^2 BSA, i.v., on day 1 of a 21-week cycle
	Dose adjustment and discontinuation of therapy ▪ Interruption of therapy: in case of severe AEs (CTCAE grade ≥ 3) and various hepatotoxic AEs, interruption until improvement to grade 1 or baseline severity for sotorasib or until normalisation of liver function for docetaxel, followed by reduced-dose therapy: up to 2 dose reductions possible: ▫ sotorasib to 480 and 240 mg/day, respectively ▫ docetaxel to 55 and to 37.5 mg/m^2 BSA, respectively ▪ Discontinuation of therapy: if toxicity has not improved after the 2nd dose reduction as well as ▫ sotorasib: for ILD/pneumonitis ▫ docetaxel: discontinuation of therapy: if toxicity has not improved after 4 weeks; in case of severe thrombocytopenia (CTCAE grade ≥ 3) associated with bleeding as well as in certain non-haematological severe AEs (CTCAE grade ≥ 3)	
	Required pretreatment ▪ At least 1 prior systemic therapy with a platinum-based chemotherapy doublet and a checkpoint inhibitor, either as one line of therapy or as individual lines of therapy (patients with a medical contraindication to any of the required therapies were allowed to be enrolled following approval by the study monitor). Prior lines of therapy may include: ▫ chemoradiotherapy for locally advanced and inoperable NSCLC in case of disease progression during or within 6 months after the end of therapy ▫ chemoradiotherapy followed by planned systemic therapy (including checkpoint inhibitor, also in reverse order) without documented progression between chemoradiotherapy and systemic therapy; counts as 1 line of therapy if disease progresses within 6 months after end of therapy ▫ adjuvant therapy counts as 1 line of therapy if the disease progresses within 6 months after the end of therapy ▫ any new systemic therapy for progressive locally advanced and inoperable or metastatic disease ▫ Maintenance therapy following a platinum-containing chemotherapy doublet or adjustment of a chemotherapy regimen due to intolerance is not deemed a separate line of therapy. ▫ Prior therapy with docetaxel in unresectable or metastatic disease (including in first-line metastatic disease) was excluded. Previous neoadjuvant or adjuvant therapy with docetaxel without progression within 6 months after the end of therapy was allowed.	

Table 3: Characteristics of the intervention – RCT, direct comparison: sotorasib versus docetaxel (multipage table)

Study	Intervention	Comparison
	Permitted pretreatment ▪ Bisphosphonates or anti-RANKL antibody therapy for the treatment of hypercalcaemia or for the prevention of skeletal-related events **Prohibited prior and concomitant treatment** ▪ CYP3A4-sensitive substrates with narrow therapeutic range, strong CYP3A4 inducers, or p-glycoprotein within 14 days or 5 half-lives of the active substance before study entry ▪ Antitumour therapy (chemotherapy, antibody therapy, molecular targeted therapy, retinoid therapy, hormone therapy[a], or investigational drugs) within 4 weeks prior to study entry ▪ Therapeutic or palliative radiotherapy within 2 weeks prior to study entry (associated toxicities must have improved to CTCAE grade ≤ 1, with the exception of alopecia, where any CTCAE grade was allowed) ▪ Prior treatment with sotorasib or other KRAS G12C inhibitor ▪ Warfarin ▪ Major elective surgery from 28 days before study entry to 28 days after last dose of study medication **Permitted concomitant treatment** ▪ Palliative radiotherapy[b] for pain control ▪ Supportive therapy at the investigator's discretion ▪ In the docetaxel arm: ▫ dexamethasone 8 mg twice daily, orally, for 3 days starting 1 day before docetaxel administration ▫ Antiemetic according to institutional guidelines on the day of docetaxel administration	

a. Except for patients with a history of completely resected breast cancer who have had no active disease for more than 3 years and who are receiving long-term adjuvant endocrine therapy.
b. During radiotherapy and 7 days thereafter, the study medication should be interrupted.

AE: adverse event; Anti-RANKL: Anti-Receptor Activator of Nuclear Factor Kappa Beta Ligand; BSA: body surface area; CTCAE: Common Terminology Criteria for Adverse Events; ILD: interstitial lung disease; i.v.: intravenous; KRAS G12C: Kirsten Rat Sarcoma Viral Oncogene Homologue G12C; RCT: randomised controlled trial

Study design

The CodeBreak 200 study is an ongoing, open-label study comparing sotorasib versus docetaxel. It enrolled adult patients with locally advanced and unresectable or metastatic NSCLC with a KRAS G12C mutation and progression or recurrence after at least 1 prior systemic therapy. This therapy had to involve a platinum-based chemotherapy doublet and a checkpoint inhibitor (either in 1 line of therapy or as individual lines of therapy). Patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1 at study entry.

A total of 345 patients were enrolled in the study. Participants were randomised in a 1:1 ratio, stratified by number of prior lines of therapy in advanced disease (1 versus 2 versus > 2),

ancestry (Asian versus non-Asian), and brain metastases at the time of randomisation (yes versus no).

Participants in the intervention arm were treated with a daily oral dose of 960 mg sotorasib. Docetaxel was administered intravenously at 75 mg/m^2 BSA on Day 1 of each 3-week cycle. In the event of certain AEs, both study arms provided for interruption of therapy, up to 2 dose reductions or, if necessary, discontinuation of therapy. Sotorasib treatment in the CodeBreak 200 study was in line with the SPC except that the study, unlike the SPC [7], allows a new dose of sotorasib if the participant vomited within 15 minutes. If a dose reduction is needed, the docetaxel SPC provides for a reduction of the docetaxel dose to 60 mg/kg BSA [8], whereas the study provides for a dose reduction to 55 mg/m^2 BSA and a second dose reduction to 37.5 mg/m^2 BSA if needed. Otherwise, the docetaxel treatment in the study was carried out according to the SPC [8].

The CodeBreak 200 study administers treatment with sotorasib or docetaxel until disease progression, intolerance, initiation of new cancer therapy, withdrawal of consent, lost to follow-up, or death. If certain criteria are met in the investigator's opinion, further treatment with sotorasib or docetaxel is allowed even after disease progression. Under certain conditions, a change of therapy from docetaxel to sotorasib is allowed at the physician's discretion (e.g. patients are not allowed to have started any other cancer therapy).

The study's primary outcome is progression-free survival (PFS). Patient-relevant outcomes are overall survival as well as outcomes on symptoms, health status, health-related quality of life, and side effects.

Data cutoffs

The CodeBreak 200 study is an ongoing study for which the primary data cut-off from 2 August 2022 is currently available. For PFS, the primary analysis was planned to occur after 230 PFS events or termination of recruitment and 6-week follow-up observation of the last randomised study participant, whichever is later. For overall survival, analyses were planned to be conducted after about 175 deaths and about 198 deaths. Due to the number of events reached, these analyses are already included in the present data cutoff. A final analysis is planned to be conducted after the last patient has completed long-term follow-up observation.

Planned duration of follow-up observation

Table 4 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 4: Planned duration of follow-up observation – RCT, direct comparison: sotorasib versus docetaxel

Study **Outcome category** **Outcome**	**Planned follow-up observation**
CodeBreak 200	
Mortality	
Overall survival	Until death, withdrawal of consent, lost-to-follow-up , or up to 5 years after inclusion of the last patient
Morbidity	
Symptoms (EORTC-QLQ-LC13, EORTC-QLQ-C30, BPI-SF), treatment-related burden (FACT-G GP5)	Until 30 days after treatment end
Health status (EQ-5D VAS)	Until 30 days after end of treatment and a further survey 5 years after inclusion of the last patient[a], withdrawal of consent, or lost-to-follow-up
Health status (PGI-C)	Until Day 1 of Cycle 5[b]
Health-related quality of life	
EORTC QLQ-C30	Until 30 days after treatment end
Side effects	
All outcomes in the side effects category	Until 30 days after treatment end

a. Not yet reached at the present data cutoff.
b. First surveyed on Day 1 of Cycle 3.

BPI-SF: Brief Pain Inventory-Short Form; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACT-G GP5: Functional Assessment of Cancer Therapy-General General Population 5; PGI-C: Patient Global Impression of Change; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer Module 13; RCT: randomised controlled trial; VAS: visual analogue scale

In the CodeBreak 200 study, only the outcome of overall survival is surveyed until the end of the study (i.e. 5 years after the inclusion of the last patient). The observation times for the outcomes on symptoms, health status assessed by means of Patient Global Impression of Change (PGI-C), health-related quality of life as well as side effects are systematically shortened because they were recorded only for the period of treatment with the study medication (plus 30 days) or, in the case of the outcome of PGI-C, until Day 1 of Cycle 5. An additional survey at 5 years after the inclusion of the last patient is planned to be conducted only for health status (European Quality of Life Questionnaire – 5 Dimensions [EQ-5D] visual analogue scale [VAS]) – like for overall survival. In order to draw a reliable conclusion on the total study period or the time to patient death, however, it would be necessary to survey all outcomes over the total period, as was done for survival.

Patient characteristics

Table 5 shows the characteristics of the patients in the CodeBreak 200 study.

Table 5: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: sotorasib versus docetaxel (multipage table)

Study **Characteristic** **Category**	**Sotorasib** **N[a] = 171**	**Docetaxel** **N[a] = 174**
CodeBreak 200		
Age [years], mean (SD)	63 (10)	64 (9)
Sex [f/m], %	36/64	45/55
Family origin, n (%)		
Asian	21 (12)	22 (13)
Black or African American	2 (1)	0 (0)
White	142 (83)	144 (83)
Multiple	1 (< 1)	0 (0)
Other	4 (2)	7 (4)
Unknown	1 (< 1)	1 (< 1)
Smoking history, n (%)		
Never	5 (3)	8 (5)
Current	32 (19)	35 (20)
Former	134 (78)	131 (75)
ECOG-PS at screening, n (%)		
0	59 (35)	59 (34)
1	112 (66)	115 (66)
Number of previous lines of therapy in advanced disease stage, n (%)		
1	77 (45)	78 (45)
2	65 (38)	69 (40)
> 2	29 (17)	27 (16)
History of brain metastases[b], n (%)		
Yes	58 (34)	60 (35)
No	113 (66)	114 (66)
Histology type, n (%)		
Squamous	1 (< 1)	7 (4)
Non-squamous	169 (99)	165 (95)
Other	1 (< 1)	2 (1)
Disease stage, n (%)		
Locally advanced and inoperable	9 (5)	8 (5)
Metastatic	162 (95)	166 (95)
Disease duration: time between first diagnosis and randomization [months], median [min; max]	16.2 [2.3; 132.3]	16.9 [1.5; 227.3]

Table 5: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: sotorasib versus docetaxel (multipage table)

Study **Characteristic** **Category**	**Sotorasib** **N[a] = 171**	**Docetaxel** **N[a] = 174**
PD-L1 protein expression, n (%)		
< 1%	57 (33)	55 (32)
≥ 1% to < 50%	46 (27)	70 (40)
≥ 50%	60 (35)	40 (23)
Previous anti-cancer therapy, n (%)		
Platinum-containing chemotherapy	44 (26)	35 (20)
Non-platinum-containing chemotherapy	13 (8)	10 (6)
PD-1/PD-L1 inhibitor and platinum-containing chemotherapy	64 (37)	69 (40)
PD-1/PD-L1 inhibitor monotherapy	43 (25)	53 (31)
Other	7 (4)	7 (4)
Treatment discontinuation, n (%)[c]	147 (86)	143 (82)
Study discontinuation, n (%)[d]	121 (71)	126 (72)

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. Patients with active brain metastases at the time of randomisation were excluded from study participation unless they met certain criteria (e.g. neurological symptoms CTCAE grade ≤ 2).
c. Common reasons for patients discontinuing therapy in the sotorasib vs. docetaxel arm were: disease progression (103 vs. 95), AE (29 vs. 25), patient request (6 vs. 10).
d. Common reasons for patients dropping out of the study in the sotorasib vs. docetaxel arm were: withdrawal of consent (12 vs. 39), lost to follow-up (5 vs. 2), death (104 vs. 85).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; f: female; m: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation

Both treatment arms are largely similar in terms of the demographic and clinical characteristics of the patients in the CodeBreak 200 study. The mean age of patients was 63 to 64 years in both studies, and the majority (83%) was of White family origin. About 3/4 of the patients had smoked in the past, while about 1/5 were still actively smoking at the time of study inclusion. Most of the patients included (99% in the sotorasib arm vs. 95% in the docetaxel arm) had non-squamous cell carcinoma. Although the proportions of patients with treatment or study discontinuation are balanced at treatment discontinuation rates of 86% in the sotorasib arm versus 82% in the docetaxel arm as well as study discontinuation rates of 71% in the sotorasib arm vs. 72% in the docetaxel arm, the study arms differ (by 15 percentage points) in the proportion of patients with study discontinuation due to withdrawal of consent.

There were slight differences between treatment groups with regard to sex distribution and PD-L1 status: The proportion of women was 36% in the sotorasib arm and 45% in the docetaxel

arm. Furthermore, 27% of patients in the sotorasib arm had a PD-L1 protein expression of 1% to < 50%, compared to 40% in the docetaxel arm. Accordingly, PD-L1 protein expression of 50% or more was present in 35% of patients in the sotorasib arm and 23% in the docetaxel arm. However, the proportion of patients with PD-L1 protein expression below 1% was comparable in both study arms (33% in the sotorasib arm versus 32% in the docetaxel arm).

Treatment duration and observation period

Table 6 shows patients' mean and median treatment durations as well as the mean and median observation period for individual outcomes.

Table 6: Information on the course of the study – RCT, direct comparison: sotorasib versus docetaxel (multipage table)

Study **Duration of the study phase** **Outcome category**	**Sotorasib** **N = 171**	**Docetaxel** **N = 174**
CodeBreak 200		
Treatment duration [months][a]		
N	169	151
Median [min; max]	4.6 [0.1; 23.3]	2.8 [0.7; 23.2]
Mean (SD)	7.4 (6.3)	4.1 (4.1)
Observation period [months]		
Overall survival		
Median [95% CI][b]	17.7 [17.0; 19.2]	16.3 [16.1; 17.1]
min; max	0.8; 24.0	0.0; 24.1
Mean (SD)	ND	ND
Morbidity[c]		
Symptoms (EORTC QLQ-C30)		
N	160	130
Median [min; max]	5.4 [0.7; 20.7]	4.7 [0.7; 23.5]
Mean (SD)	7.7 (6.0)	6.9 (5.6)
Symptoms (EORTC QLQ-LC13)		
N	158	124
Median [min; max]	5.4 [0.7; 20.7]	4.9 [0.7; 23.5]
Mean (SD)	7.8 (6.0)	7.0 (5.5)
Health status (EQ-5D VAS)		
N	160	138
Median [min; max]	6.2 [0.2; 20.7]	5.7 [0.1; 23.5]
Mean (SD)	8.4 (6.2)	7.4 (6.2)

Table 6: Information on the course of the study – RCT, direct comparison: sotorasib versus docetaxel (multipage table)

Study **Duration of the study phase** **Outcome category**	**Sotorasib** **N = 171**	**Docetaxel** **N = 174**
Health status (PGI-C)		
N	143	110
Median [min; max]	2.8 [1.2; 4.9]	2.8 [1.3; 10.4]
Mean (SD)	2.5 (0.7)	2.7 (1.1)
Treatment-related burden (FACT-G GP5)		
N	147	113
Median [min; max]	5.5 [0.7; 20.7]	5.2 [0.7; 23.5]
Mean (SD)	7.9 (6.0)	7.0 (5.6)
Health-related quality of life[c]		
EORTC QLQ-C30		
N	160	130
Median [min; max]	5.4 [0.7; 20.7]	4.7 [0.7; 23.5]
Mean (SD)	7.7 (6.0)	6.9 (5.6)
EORTC QLQ-LC13		
N	158	124
Median [min; max]	5.4 [0.7; 20.7]	4.9 [0.7; 23.5]
Mean (SD)	7.8 (6.0)	7.0 (5.5)
Side effects		
N	169	151
Median [min; max]	5.72 [0.6; 23.7]	3.32 [0.2; 22.8]
Mean (SD)	8.26 (6.1)	4.72 (4.0)
PRO-CTCAE[c]		
N	148	113
Median [min; max]	5.4 [0.7; 20.7]	5.2 [0.7; 23.5]
Mean (SD)	7.9 (6.0)	7.0 (5.6)

a. The company's data are based on weeks, while the Institute's calculations are shown in months.
b. The observation period is calculated based on the inverse Kaplan-Meier method. The 95% CIs are estimated according to Klein and Moeschberger using log-log transformation.
c. The observation period per study participant equals the study day of the last answered question in the respective questionnaire. For all variables, the analysis included only study participants for whom values were available at baseline and at another observation time point.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACT-G GP5: Functional Assessment of Cancer Therapy-General General Population 5; max: maximum; min: minimum; N: number of patients evaluated; ND: no data; PGI-C: Patient Global Impression of Change; PGI-S: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer Module 13; RCT: randomised controlled trial; SD: standard deviation; VAS: visual analogue scale

The median treatment duration in the CodeBreak 200 study's docetaxel arm is markedly shortened, equalling approximately 61% of the median treatment duration in the sotorasib arm.

The median observation period for overall survival is 17.7 months in the sotorasib arm and 16.3 months in the docetaxel arm. For the morbidity, health-related quality of life, and side effects outcomes, whose observation durations were linked to treatment end (see Table 4), the observation durations were markedly shortened when compared to overall survival. For the morbidity outcome of health status (EQ-5D VAS) – like for overall survival – an additional survey is planned to occur 5 years after the inclusion of the last patient. As the study is still ongoing, this data collection point had not yet been reached at the time of this data cutoff. Thus, the median observation duration for health status (EQ-5D VAS) of 6.2 months in the sotorasib arm versus 5.7 months in the docetaxel arm is also markedly shorter compared to the observation duration for overall survival.

Subsequent therapies

Table 7 shows the subsequent antineoplastic therapies patients received after discontinuing the study medication.

Table 7: Information on subsequent antineoplastic therapies – RCT, direct comparison: sotorasib versus docetaxel

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)[a]**	
	Sotorasib **N = 171[b]**	**Docetaxel** **N = 174[b]**
CodeBreak 200		
Total (including cross-over to Sotorasib)	62 (36.3)	73 (42.0)
Chemotherapy	36 (21.1)	21 (12.1)
KRAS G12C inhibitor	6 (3.5)	59 (33.9)
Immunotherapy	16 (9.4)	10 (5.7)
Checkpoint inhibitor	14 (8.2)	10 (5.7)
Other	25 (14.6)	18 (10.3)

a. Based on all entries in the eCRF form for follow-up antineoplastic therapy and 46 patients who switched from docetaxel to sotorasib according to protocol, categorised under "KRAS G12C inhibitor".
b. Patients may have been counted under more than one category.

eCRF: electronic Case Report Form; KRAS G12C: Kirsten Rat Sarcoma Viral Oncogene Homologue G12C; n: number of patients with follow-up therapy; N: number of analysed patients; ND: no data; RCT: randomised controlled trial

According to the study protocol, the choice of the subsequent antineoplastic therapies was not restricted. In the CodeBreak 200 study, 36.3% of the patients in the sotorasib arm and 42.0% of the patients in the docetaxel arm received at least 1 subsequent antineoplastic

therapy. In the sotorasib arm, chemotherapy was used most frequently (21.1%), followed by immunotherapy with a checkpoint inhibitor (8.2%). In the docetaxel arm, follow-up antineoplastic therapy most often involved a KRAS G12C inhibitor (33.9%), followed by chemotherapy, which was used in 12.1% of cases. As per guidelines, if at least 1 systemic therapy fails, a switch to therapy with sotorasib is recommended [9-11]. The S3 guideline "Prevention, Diagnosis, Therapy and Follow-up of Lung Carcinoma" and the Onkopedia guideline "Lung Carcinoma, Non-Small Cell (NSCLC)" [9,10] provide no other recommendations for the further treatment of patients. According to the National Comprehensive Cancer Network (NCCN) guideline, switching to chemotherapy, targeted therapies, or best supportive care is recommended in the event of disease progression after therapy with sotorasib, depending on the patient's individual situation [11]. For the CodeBreak 200 study, no information is available on which specific agents were used in disease progression as part of follow-up therapy, but the drug classes used correspond to the recommendations of the NCCN guideline.

Risk of bias across outcomes (study level)

Table 8 shows the risk of bias across outcomes (risk of bias at study level).

Table 8: Risk of bias across outcomes (study level) – RCT, direct comparison: sotorasib versus docetaxel

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of additional aspects	Risk of bias at study level
			Patients	Treatment providers			
CodeBreak 200	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the CodeBreak 200 study.

Transferability of the study results to the German health care context

In the company's view, the characteristics of CodeBreak 200 participants correspond to the characteristics of patients with NSCLC treated in Germany. In addition, the second-line treatment of these patients was reportedly carried out according to international NSCLC guidelines as well as NSCLC guidelines valid in Germany. Therefore, the results of the CodeBreak 200 study are reportedly fully transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.3 Study results

2.3.1 Presented outcomes

This addendum presents the following patient-relevant outcomes for the CodeBreak 200 study:

- Mortality
  - overall survival
- Morbidity
  - symptoms surveyed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30)
  - symptoms surveyed with the EORTC QLQ – Lung Cancer Module 13 (LC13)
  - worst pain (Brief Pain Inventory – Short Form [BPI-SF] Item 3)
  - pain interference (BPI-SF items 9a–g)
  - health status (PGI-C)
  - health status (EQ-5D VAS)
  - treatment-related burden as measured by the Functional Assessment of Cancer Therapy Tool General form (FACT-G) General Population 5 (GP5)
- Health-related quality of life
  - health-related quality of life (EORTC QLQ-C30)
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - hepatic disorders (Standardised Medical Dictionary for Regulatory Activities [MedDRA] query [Standardised MedDRA Query, SMQ], severe AEs [CTCAE grade ≥ 3])
  - interstitial lung disease (SMQ, severe AEs [CTCAE grade ≥ 3])
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that taken by the company, which used further outcomes in the dossier (Module 4 A).

Table 9 shows the outcomes for which data were available in the CodeBreak 200 study.

Table 9: Matrix of outcomes – RCT, direct comparison: sotorasib versus docetaxel

Study	Outcomes														
	Overall survival	Symptoms (EORTC QLQ-LC13)	Symptoms (EORTC QLQ-C30)	Worst pain (BPI-SF Item 3)	Pain interference (BPI-SF items 9a–g)	Health status (PGI-C)	Health status (EQ-5D VAS)	Treatment-related burden (FACT-G GP5)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Diseases of the liver (SMQ, severe AEs[a])	Interstitial lung disease (SMQ, severe AEs[a])	Further specific AEs[a, b]
CodeBreak 200	Yes	No[c]	No[c]	No[c]	No[c]	No[c]	Yes	No[c]	No[c]	Yes	Yes	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are taken into account (coded according to MedDRA version 24.0 or later versions): stomatitis (PT, AE), chest pain (PT, AE), peripheral oedema (PT, AE), fever (PT, AE), peripheral neuropathy (PT, AE), alopecia (PT, AE), blood and lymphatic system disorders (SOC, severe AEs), diarrhoea (PT, severe AE), fatigue (PT, severe AE), infections and infestations (SOC, severe AE).
c. No suitable data available; for the reasoning, see the following sections of the present addendum.

AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and Treatment of Cancer; FACT-G GP5: Functional Assessment of Cancer Therapy Tool General form General Population 5; MedDRA: Medical Dictionary for Regulatory Activities; PGI-C: Patient Global Impression of Change; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire–Core 30; QLQ-LC13: Quality of Life Questionnaire–Lung Cancer 13; RCT: randomised controlled trial; SAE: serious adverse event; SMQ: standardised MedDRA query; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

Overall survival

To investigate the possible influence of treatment switching (from docetaxel to sotorasib), the company presented sensitivity analyses based on the rank preserving structural failure time (RPFST), inverse probability of censoring weights (IPCW) and 2-stage models as sensitivity analyses for the outcome of overall survival. The presented sensitivity analyses are irrelevant for the present addendum because these analyses are based on unverifiable assumptions and insufficient information is available on the concrete implementation of these methods [12].

PGI-C and PGI-S

The CodeBreak 200 study surveyed the change in physical condition at the respective survey time compared to baseline for the symptoms of cough, chest pain, and shortness of breath in the form of individual items of the PGI-C questionnaire. In addition, the Patient Global Impression of Severity (PGI-S) questionnaire was used to determine how the surveyed patients rated the severity of the symptoms of cough, chest pain, and shortness of breath in the past week. As per study protocol, the results of the PGI-S questionnaire were analysed only descriptively; likewise, the company did not present any evaluations of the PGI-S in Module 4 A. For the outcome of PGI-C, the effect estimates predefined in the study protocol are available, but the treatment arms differed by > 15 percentage points in the proportion of patients included in the evaluation of PGI-C. Therefore, these analyses are not suitable for use in the present addendum.

Treatment-related burden (FACT-G GP5)

The assessment of treatment-related burden, collected by the single item GP5 ("I am bothered by side effects of treatment") from the questionnaire FACT-G, is deemed a patient-relevant outcome. However, the treatment arms differed by > 15 percentage points in the proportion of patients included in the analysis. Therefore, these analyses are not suitable for use in the present addendum.

Progression of central nervous system (CNS) metastases

CNS metastases are of special significance in the present therapeutic indication. The outcome of CNS progression was defined as the time from randomisation to radiological evidence of CNS disease progression (outcome assessment only for patients who already had CNS disease at study inclusion). The outcome of progression of CNS metastases was assessed by contrast-enhanced magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CT) scan. Disease progression was assessed by a blinded independent central committee using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria (version 1.1). Thus, the assessment was based exclusively on imaging techniques and did not take into account any symptoms perceived by patients. Thus, the outcome is not directly patient-relevant for the present addendum and is not presented. In addition, only patients who already had CNS disease at the time of enrolment were included in the analysis. Patients without previous CNS disease or with first-time occurrence of CNS metastases were excluded from the analysis.

Other patient-reported outcomes (EORTC QLQ-C30, EORTC QLQ-LC13, BPI-SF)

The patient-reported outcomes on symptoms and health-related quality of life rated using the EORTC QLQ-C30, EORTC QLQ-LC13, and BPI-SF are patient-relevant, but the treatment arms differ by > 15 percentage points in the proportion of patients included in the analysis for all outcomes listed. Therefore, each of these analyses are unsuitable for the present addendum.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, unlike other side effects outcomes, Module 4 A presents analyses which contain events assessed by the company as progression of the underlying disease. This is not appropriate. However, the included System Organ Class (SOCs) and Preferred Term (PT) data show discontinuation due to progression events in 6 out of 28 patients in the sotorasib arm and 2 out of 24 patients in the docetaxel arm (see Table 16). This had no consequence for the present addendum.

Patient-Reported Outcome – Common Terminology Criteria for Adverse Events (PRO-CTCAE)

In the CodeBreak 200 study, side effects were also recorded with the PRO-CTCAE instrument. Overall, the PRO-CTCAE system represents a valuable addition to the usual survey and analysis of AEs. The system comprises a total of 78 symptomatic AEs of the CTCAE system, which are compiled into a questionnaire adapted to the respective study situation. The selection process should be planned a priori and conducted transparently. The individual symptomatic AEs must be transparently selected, e.g. each important potential AE of the active substances in the intervention and control arms must be surveyed. For a detailed description of the PRO-CTCAE system, see the corresponding explanations in benefit assessment A20-87 [13]. According to the study protocol, the following symptomatic AEs from the PRO-CTCAE were recorded in the CodeBreak 200 study:

- cracking at the corners of the mouth
- hives
- mouth/throat sores
- numbness and tingling in hands and feet
- general pain
- muscle pain
- joint pain

It is unclear whether the following events are included in the survey; while predefined by the study protocol, they are not specified in the company's Module 4 A under the description of the operationalization:

- nail loss
- nail ridging
- nail discolouration

The available documents do not show on what basis the events from the PRO-CTCAE system were selected. The company does not provide more detailed information on its approach – e.g. on its search. On the basis of the information provided by the company, it is thus impossible to determine whether the company implemented the approaches described in A20-87 [13] for a selection of items as per Tolstrup [14] or Taarnhøj [15]. It is also impossible to determine whether the side effects of sotorasib and docetaxel have been mapped adequately. Overall, the outcome of PRO-CTCAE is disregarded due to intransparencies regarding the selection process as well as the selection of items to represent the symptomatic AEs of sotorasib.

Irrespective of the PRO-CTCAE operationalization, the treatment arms differ by > 15 percentage points in the proportion of patients included in the analysis. Notwithstanding the operationalization's suitability, the analyses of PRO-CTCAE are unsuitable for the present addendum.

2.3.2 Risk of bias

Table 10 describes the risk of bias for the results of the relevant outcomes.

Table 10: Risk of bias on the study and outcomes levels – RCT, direct comparison: sotorasib versus docetaxel

Study		Outcomes														
	Study level	Overall survival	Symptoms (EORTC QLQ-LC13)	Symptoms (EORTC QLQ-C30)	Worst pain (BPI-SF Item 3)	Pain interference (BPI-SF Item 9a–g)	Health status (PGIC)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	Treatment-related burden (FACT-G GP5)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Diseases of the liver (SMQ, severe AEs[a])	Interstitial lung disease (SMQ, severe AEs[a])	Further specific AEs[a, b]
CodeBreak 200	L	H[c, d]	–[e]	–[e]	–[e]	–[e]	–[e]	H[f, g, h]	–[e]	–[e]	H[g, i]	H[g, i]	H[i, j]	H[g, i]	H[g, i]	H[g, h, i]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are taken into account (coded according to MedDRA version 24.0 or later versions): stomatitis (PT, AE), chest pain (PT, AE), peripheral oedema (PT, AE), fever (PT, AE), peripheral neuropathy (PT, AE), alopecia (PT, AE), blood and lymphatic system disorders (SOC, severe AE), diarrhoea (PT, severe AE), fatigue (PT, severe AE), infections and infestations (SOC, severe AE).
c. A high proportion of patients switched from the docetaxel arm to the sotorasib arm in the course of the study (26.4%); no information available on the timing of the switches.
d. A high proportion of patients was censored at baseline.
e. No suitable data available; see Section 2.3.1 of the present addendum for reasoning.
f. Large difference in the proportion of patients included in the analysis (93.6% in the sotorasib arm vs. 79.3% in the docetaxel arm)
g. Incomplete observations for potentially informative reasons.
h. Lack of blinding in the presence of subjective outcome recording; for specific AEs, in non-severe and non-severe AEs.
i. Large difference in the proportion of patients included in the analysis due to not having received the randomized study medication (98.8% in the sotorasib arm vs. 86.8% in the docetaxel arm).
j. Lack of blinding in the presence of subjective decision on treatment discontinuation.

AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and Treatment of Cancer; FACT-G GP5: Functional Assessment of Cancer Therapy Tool General form General Population 5; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PGIC-C: Patient Global Impression of Change; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomised controlled trial; SAE: serious adverse event; SMQ: standardised MedDRA query; SOC: System Organ Class; VAS: visual analogue scale

Concurring with the company, the risk of bias of the results for the outcomes of overall survival and health status (EQ-5D VAS) is deemed high. For overall survival, this is due to the high proportion of patients who switched from the docetaxel arm to the sotorasib arm in the course of the study (26.4%); no information was available on the time points of switching. In

addition, the proportion of patients who were censored at the beginning of the study is unclear. If patients were censored at study start, they de facto contributed no times to the analysis, and they were thus disregarded. The high risk of bias for the results on health status (EQ-5D VAS) is due to (a) the large difference in the proportion of patients included in the analysis (93.6% in the sotorasib arm versus 79.3% in the docetaxel arm), (b) the incomplete observation for potentially informative reasons, and (c) the lack of blinding in the presence of subjective outcome survey.

Unlike the company, this assessment rates the risk of bias for the outcomes of SAEs, severe AEs, and discontinuation due to AEs as high. The following were presented as specific AEs: hepatic disorders (SMQ, severe AEs), interstitial lung disease (SMQ, severe AEs), stomatitis (PT, AE), chest pain (PT, AE), peripheral oedema (PT, AE), fever (PT, AE), peripheral neuropathy (PT, AE), alopecia (PT, AE), blood and lymphatic system disorders (SOC, severe AE), diarrhoea (PT, severe AE [CTCAE grade ≥ 3]), fatigue (PT, severe AE [CTCAE grade ≥ 3]), infections and infestations (SOC, severe AE [CTCAE grade ≥ 3]). The company has not estimated the risk of bias for the specific AEs, which is likewise estimated to be high. In the respective treatment arms, different numbers of patients received the randomly allocated treatment (98.8% in the sotorasib arm versus 86.8% in the docetaxel arm). This results in a large difference (12 percentage points) in the proportion of patients who are included in the analyses of the side effects outcomes. In addition, the observations are incomplete for potentially informative reasons for SAEs and severe AEs, including the corresponding specific AEs. In the case of discontinuation due to AEs, lack of blinding in the presence of subjective decision to discontinue therapy additionally contributes to the high risk of bias. Lack of blinding in the presence of subjective recording of outcomes is also part of the reasoning for the high risk of bias for non-serious and non-severe specific AEs.

2.3.3 Results

Table 11 summarizes the results on the comparison of sotorasib versus docetaxel in NSCLC patients.

Kaplan-Meier curves for time-to-event analyses can be found in Appendix A, while results for common AEs are in Appendix B.

Table 11: Results (overall survival, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sotorasib versus docetaxel (multipage table)

Study Outcome category Outcome	Sotorasib N	Sotorasib Median time to event in months [95% CI] Patients with event n (%)	Docetaxel N	Docetaxel Median time to event in months [95% CI] Patients with event n (%)	Sotorasib vs. docetaxel HR [95% CI]; p-value
CodeBreak 200					
Mortality					
Overall survival	171	10.64 [8.94; 13.96] 109 (63.7)	174	11.30 [9.00; 14.85] 94 (54.0)	1.010 [0.77; 1.33]; 0.94[a]
Morbidity					
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)		No suitable data[b]			
Worst pain (BPI-SF Item 3)		No suitable data[b]			
Pain interference (BPI-SF Item 9a–g)		No suitable data[b]			
Treatment-related burden (FACT-G GP5)		No suitable data[b]			
Health status (PGI-C)		No suitable data[b]			
Health status (EQ-5D VAS)[c]	160	5.2 [3.6; 10.4] 83 (51.9)	138	1.6 [1.0; 3.3] 83 (60.1)	0.55 [0.40; 0.76]; < 0.001[a]
Health-related quality of life					
Functioning scales (EORTC QLQ-C30)		No suitable data[b]			
Side effects					
AEs[d] (supplementary information)	169	0.72 [0.49; 0.82] 165 (97.6)	151	0.16 [0.13; 0.20] 148 (98.0)	–
SAEs[d]	169	9.86 [7.29; 15.34] 82 (48.5)	151	7.10 [3.68; NR] 66 (43.7)	0.73 [0.52; 1.01]; 0.061[e]
Severe AEs[f,d]	169	3.35 [2.53; 4.73] 114 (67.5)	151	2.96 [1.38; 4.14] 90 (59.6)	0.80 [0.61; 1.06]; 0.13[e]
Discontinuation due to AEs	169	NR 28 (16.6)	151	NR [13.40; NC] 24 (15.9)	0.79 [0.45; 1.39]; 0.40[e]
Hepatic disorders (SMQ, severe AEs[f])	169	NR33 (19.5)	151	NR2 (1.3)	13.92 [3.3; 58.76]; < 0.001[e]
Interstitial lung disease (SMQ, severe AEs[f])	169	NR2 (1.2)	151	NR 4 (2.6)	0.31 [0.06; 1.55]; 0.17[e]
Stomatitis (PT, AE)	169	NR 3 (1.8)	151	NR 19 (12.6)	0.13 [0.04; 0.41]; < 0.001[e]
Chest pain (PT, AE)	169	NR 15 (8.9)	151	NR 2 (1.3)	4.3 [0.91; 20.30]; 0.038[e,h]

Table 11: Results (overall survival, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sotorasib versus docetaxel (multipage table)

Study Outcome category Outcome	Sotorasib N	Sotorasib Median time to event in months [95% CI] Patients with event n (%)	Docetaxel N	Docetaxel Median time to event in months [95% CI] Patients with event n (%)	Sotorasib vs. docetaxel HR [95% CI]; p-value
Peripheral oedema (PT, AE)	169	NR 5 (3.0)	151	NR [16.53; NR] 19 (12.6)	0.14 [0.05; 0.40]; < 0.001[e]
Fever (PT, AE)	169	NR 11 (6.5)	151	NR 20 (13.2)	0.32 [0.15; 0.67]; 0.002[e]
Peripheral neuropathy (PT, AE)	169	NR 1 (0.6)	151	NR 16 (10.6)	0.03 [0; 0.29]; < 0.001[e]
Alopecia (PT, AE)	169	NR 3 (1.8)	151	NR 35 (23.2)	0.06 [0.02; 0.21]; < 0.001[e]
Blood and lymphatic system disorders (SOC, severe AEs[f])	169	NR 10 (5.9)	151	NR 27 (17.9)	0.25 [0.13; 0.50]; < 0.001[e]
Infections and infestations (SOC, severe AEs[f])	169	NR 10 (5.9)	151	18.37 [18.37; NR] 27 (17.9)	0.20 [0.10; 0.40]; < 0.001[e]
Diarrhoea (PT, severe AE[f])	169	NR 23 (13.6)	151	4 (2.6)	4.75 [1.65; 13.69]; 0.002[e]
Fatigue (PT, severe AE[f])	169	NR 4 (2.4)	151	9 (6.0)	0.31 [0.10; 1.05]; 0.043[e]

a. Effect and CI from stratified Cox proportional hazards model; p-value from stratified log-rank test; each stratified by number of previous lines of therapy for advanced disease (1 vs. 2 vs. > 2), ethnicity (Asian vs. non-Asian), and history of CNS involvement (yes vs. no).
b. Large difference between treatment arms (> 15%) in the proportion of patients included in the analysis; see Section 2.3.1 of this addendum for reasoning.
c. Time to deterioration by ≥ 15 points (excluding death).
d. Excluding events which were rated by the company as progression of the underlying disease (any PTs containing the terms metastasis/metastases, tumour pain, NSCLC/non-small cell lung cancer or adenocarcinoma of the lung).
e. Effect and CI from Cox proportional hazards model; p-value from log-rank test; each unstratified.
f. Operationalized as CTCAE grade ≥ 3.
g. SMQ broad scope.
h. Discrepancy between p-value and CI due to different calculation methods.

AE: adverse event; BPI:-SF: Brief Pain Inventory – Short Form; CNS: central nervous system; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Lung Cancer 13; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACT-G GP5: Functional Assessment of Cancer Therapy Tool General Form General Population 5; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; PGIC: Patient Global Impression of Change; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: standardized MedDRA query; SOC: System Organ Class; VAS: visual analogue scale

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. This results in no advantages or disadvantages of sotorasib compared to docetaxel.

Morbidity

Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13), worst pain (BPI-SF item 3), impairment due to pain (BPI-SF items 9a–g), treatment-related burden (FACT-G GP5), and PGI-C

No suitable data are available for the symptoms assessed using the symptom scales of the cancer-specific instrument EORTC QLQ-C30 and the lung cancer-specific instrument EORTC QLQ-LC13 or for the outcomes of worst pain (BPI-SF item 3), impairment due to pain (BPI-SF items 9a–g), treatment-related burden (FACT-G GP5), or PGI-C of the morbidity category (see Section 2.3.1). This results in no advantages or disadvantages of sotorasib compared to docetaxel for any of them.

EQ-5D VAS

The CodeBreak 200 study surveyed the outcome of health status using the EQ-5D VAS in the form of time to deterioration by ≥ 15 points (excluding death). For this outcome, a statistically significant difference was found in favour of sotorasib versus docetaxel.

Health-related quality of life

Health-related quality of life (EORTC QLQ-C30)

No suitable data are available for health-related quality of life, surveyed with the functioning scales of the cancer-specific instrument EORTC QLQ-C30 (see Section 2.3.1).

Side effects

SAEs, severe AEs, discontinuation due to AEs, and interstitial lung disease (severe AEs)

No statistically significant differences between treatment groups were found for any of the outcomes of SAEs, severe AEs, discontinuation due to AEs, or the specific AE of interstitial lung disease (severe AEs). This results in no advantages or disadvantages of sotorasib compared to docetaxel for any of them.

Hepatic disorders (severe AEs)

The CodeBreak 200 study surveyed the specific AE of hepatic disorders (severe AEs) as time to event. A statistically significant difference to the disadvantage of sotorasib versus docetaxel was found.

Further specific AEs

Stomatitis (PT, AE), peripheral oedema (AE), peripheral neuropathy (AE), alopecia (AE), blood and lymphatic system disorders (AE), and fatigue (AE)

The CodeBreak 200 study surveyed the specific AEs of stomatitis (AE), peripheral oedema (AE), peripheral neuropathy (AE), alopecia (AE), blood and lymphatic system disorders (AE), and fatigue (AE) using time-to-event data. Each of them exhibited a statistically significant difference in favour of sotorasib over docetaxel.

Chest pain (PT, AE) and diarrhoea (AE)

The CodeBreak 200 study surveyed the specific AEs of chest pain (AEs) and diarrhoea (AEs) using time-to-event data. Each of them exhibited a statistically significant difference to the disadvantage of sotorasib compared to docetaxel.

Fever (AE)

The CodeBreak 200 study surveyed the specific AE of fever (AE) using time-to-event data. It found a statistically significant difference in favour of sotorasib versus docetaxel. There was an effect modification by the attribute of age. For patients < 65 years of age, there is a statistically significant difference in favour of sotorasib, whereas for patients ≥ 65 years of age, there is no statistically significant difference between the treatment groups (see Section 2.3.4).

Infections and infestations (AEs)

The CodeBreak 200 study surveyed the specific AE of infections and infestations (AEs) using time-to-event data. It found a statistically significant difference in favour of sotorasib versus docetaxel. There was an effect modification by the attribute of age. For patients ≥ 65 years of age, there is a statistically significant difference in favour of sotorasib, whereas for patients < 65 years of age, there is no statistically significant difference between the treatment groups (see Section 2.3.4).

2.3.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account for the present addendum:

- sex (female/male)
- age (< 65 years / > 65 years)
- brain metastases at the time of randomisation (yes/no)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Table 12 shows the results of the subgroup analyses. Kaplan-Meier curves on the time-to-event analyses for the subgroups are presented in Appendix A.

Table 12: Subgroups (overall survival, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sotorasib versus docetaxel

Study Outcome Characteristic Subgroup	Sotorasib N	Sotorasib Median time to event in months [95% CI] Patients with event n (%)	Docetaxel N	Docetaxel Median time to event in months [95% CI] Patients with event n (%)	Sotorasib vs. docetaxel HR [95% CI][a]	Sotorasib vs. docetaxel p-value[b]
CodeBreak 200						
Fever (AE, PT)						
Age						
< 65 years	91	NR 1 (1.1)	85	NR [8.48; NC] 12 (14.1)	0.05 [0.01; 0.3]	< 0.001
≥ 65 years	78	NR 10 (12.8)	66	NR 8 (12.1)	0.71 [0.28; 1.81]	0.49
Total					Interaction[c]:	0.021
Infections and infestations (SOC, severe AE[d])						
Age						
< 65 years	91	NR 8 (8.8)	85	NR 12 (14.1)	0.43 [0.19; 0.98]	0.061
≥ 65 years	78	NR 2 (2.6)	66	18.4 [7.10; NC] 15 (22.7)	0.05 [0.01; 0.22]	< 0.001
Total					Interaction[c]:	0.037

a. Unstratified Cox proportional hazards model with subgroup, treatment, and interaction between treatment and subgroup as covariates.
b. Log-rank test.
c. Interaction term from Cox proportional hazards model.
d. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NR: not reached; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Side effects

Fever (AE)

For the specific AE of fever (AE), there was an effect modification by the attribute of age. For patients < 65 years of age, a statistically significant difference was shown in favour of sotorasib. However, no statistically significant difference between treatment groups was found for patients ≥ 65 years.

Infections and infestations (AE)

For the specific AE of infections and infestations (AE), there was an effect modification by the characteristic of age. For patients < 65 years of age, a statistically significant difference was shown in favour of sotorasib. However, no statistically significant difference between treatment groups was found for patients ≥ 65 years.

2.4 Summary

The present addendum results in no changes to the conclusion on the added benefit of sotorasib arrived at in dossier assessment A23-06.

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Sotorasib (NSCLC); Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung); Dossierbewertung [online]. 2023 [Accessed: 03.05.2023]. URL: https://www.iqwig.de/download/a23-06_sotorasib_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Amgen. Sotorasib (LUMYKRAS); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2023 [Accessed: 10.05.2023]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/918/#dossier.

3. Amgen. A Phase 3 Multicenter, Randomized, Open Label, Active-controlled, Study of AMG 510 Versus Docetaxel for the Treatment of Previously Treated Locally Advanced and Unresectable or Metastatic NSCLC Subjects With Mutated KRAS p.G12C; Clinical Study Report [unpublished]. 2022.

4. Amgen. Study to Compare AMG 510 "Proposed INN Sotorasib" With Docetaxel in Non Small Cell Lung Cancer (NSCLC) (CodeBreak 200) [online]. 2022 [Accessed: 17.02.2023]. URL: https://ClinicalTrials.gov/show/NCT04303780.

5. Amgen. A Phase 3 Multicenter, Randomized, Open Label, Active-controlled, Study of AMG 510 Versus Docetaxel for the Treatment of Previously Treated Locally Advanced and Unresectable or Metastatic NSCLC Subjects With Mutated KRAS p.G12C [online]. [Accessed: 17.02.2023]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-003582-18.

6. de Langen AJ, Johnson ML, Mazieres J et al. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRASG12C mutation: a randomised, open-label, phase 3 trial. Lancet 2023; 401(10378): 733-746. https://dx.doi.org/10.1016/S0140-6736(23)00221-0.

7. Amgen. LUMYKRAS 120 mg Filmtabletten [online]. 2022 [Accessed: 12.06.2023]. URL: https://www.fachinfo.de.

8. Sanofi. TAXOTERE 20mg/1 ml, TAXOTERE 80mg/4 ml, TAXOTERE 160mg/8 ml [online]. 2022 [Accessed: 12.06.2023]. URL: https://www.fachinfo.de.

9. Leitlinienprogramm Onkologie. Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms; Version 2.1; Leilinie (Langversion) [online]. 2022 [Accessed: 03.07.2023]. URL: https://register.awmf.org/assets/guidelines/020-007OLl_S3_Praevention-Diagnostik-Therapie-Nachsorge-Lungenkarzinom_2022-12.pdf.

10. Onkopedia. Onkopedia Leitlinien: Lungenkarzinom, nicht-kleinzellig (NSCLC) [online]. 2022 [Accessed: 03.07.2023]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/lungenkarzinom-nicht-kleinzellig-nsclc/@@guideline/html/index.html.

11. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer; NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines); Version 3.2023 [online]. 2023 [Accessed: 03.07.2023]. URL: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

12. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Treatment Switching in onkologischen Studien; Arbeitspapier [online]. 2018 [Accessed: 10.12.2018]. URL: https://www.iqwig.de/download/GA14-04_Treatment-Switching-in-onkologischen-Studien_Arbeitspapier_V1-0.pdf.

13. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Durvalumab (kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2020 [Accessed: 16.04.2021]. URL: https://www.iqwig.de/download/a20-87_durvalumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

14. Tolstrup LK, Bastholt L, Zwisler AD et al. Selection of patient reported outcomes questions reflecting symptoms for patients with metastatic melanoma receiving immunotherapy. J Patient Rep Outcomes 2019; 3(1): 19. https://dx.doi.org/10.1186/s41687-019-0111-8.

15. Taarnhøj G, Lindberg H, Johansen C et al. Patient-reported outcomes item selection for bladder cancer patients in chemo- or immunotherapy. J Patient Rep Outcomes 2019; 3(1): 56. https://dx.doi.org/10.1186/s41687-019-0141-2.

Appendix A Kaplan-Meier curves on results of the CodeBreak 200 study

A.1 Mortality

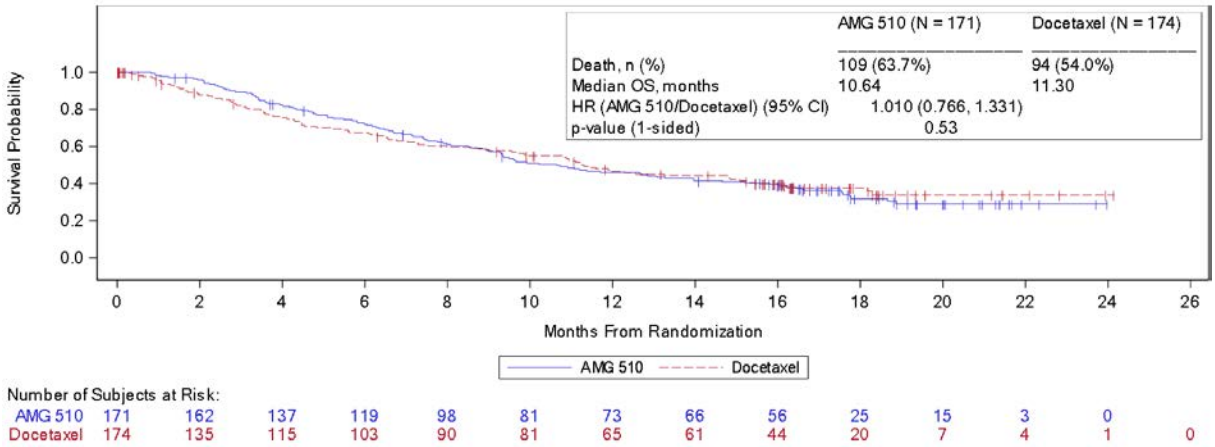

Figure 1: Kaplan-Meier curve for the outcome of overall survival

A.2 Morbidity

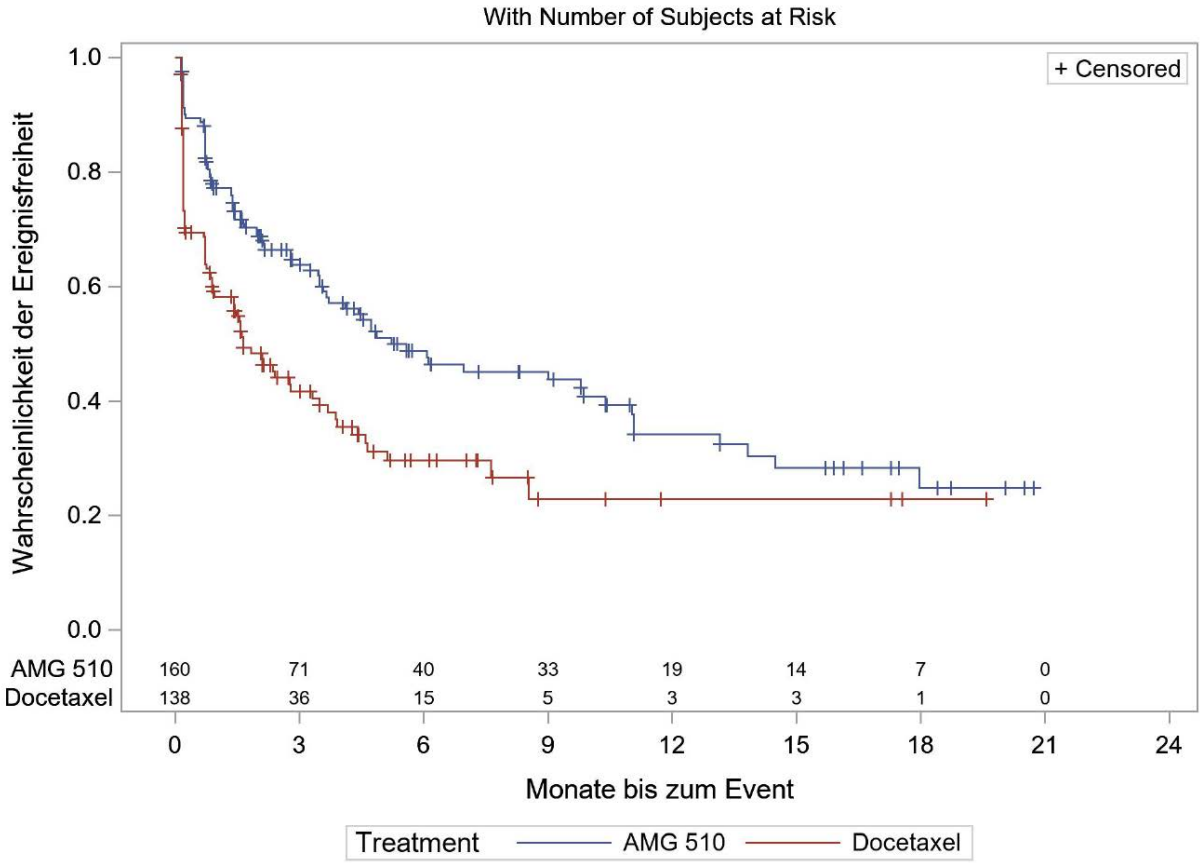

Figure 2: Kaplan-Meier curves on the outcome of EQ-5D VAS – time to deterioration by ≥ 15 points

A.3 Side effects

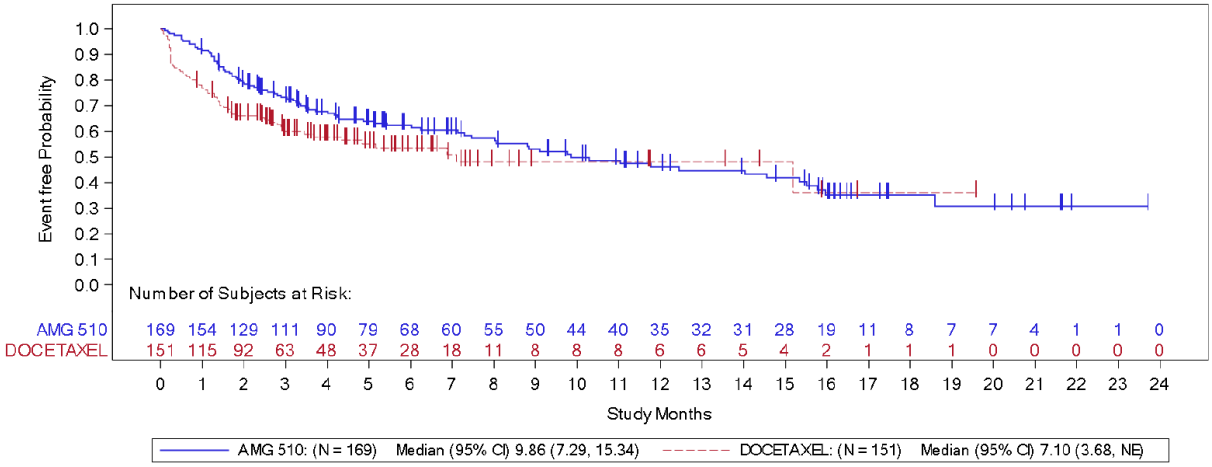

Figure 3: Kaplan-Meier curves on the outcome of SAEs (excluding disease progression events)

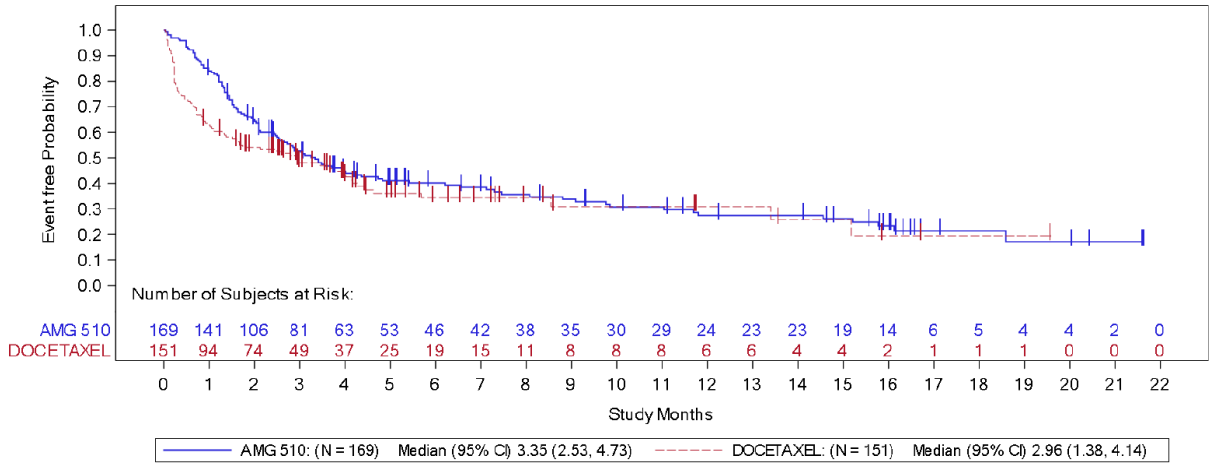

Figure 4: Kaplan-Meier curves on the outcome of severe AEs (excluding disease progression events)

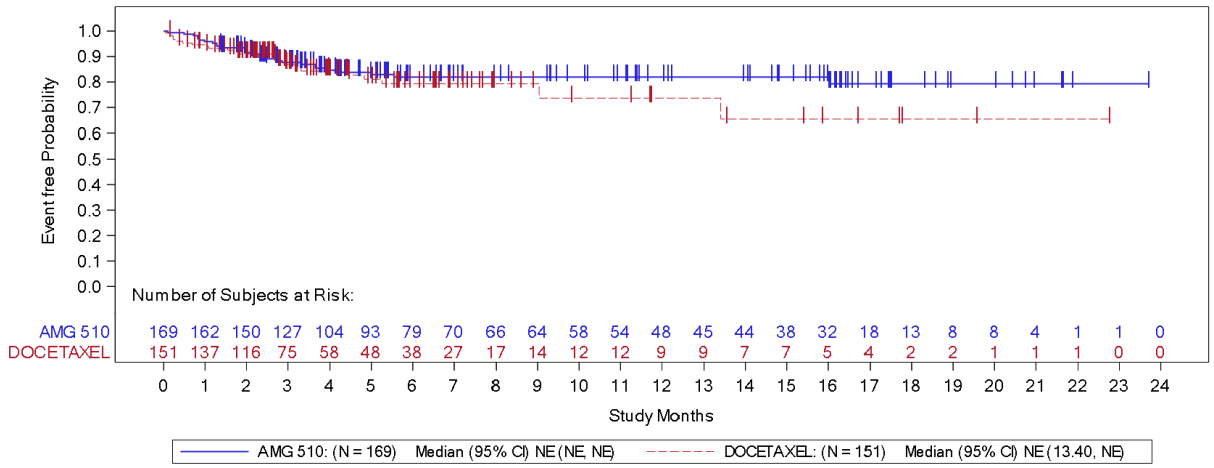

Figure 5: Kaplan-Meier curves on the outcome of discontinuation due to AEs

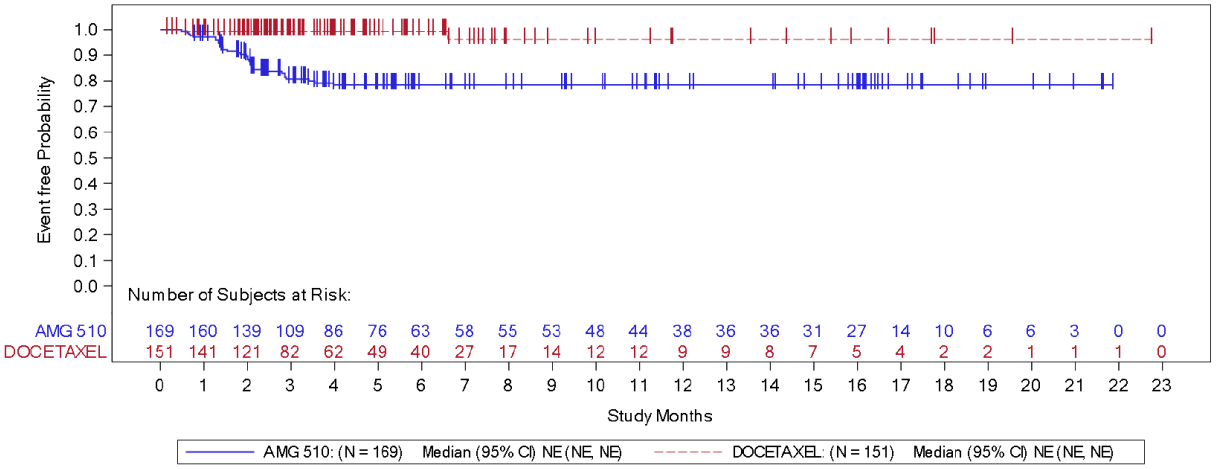

Figure 6: Kaplan-Meier curves on hepatic disorders (SMQ, severe AEs)

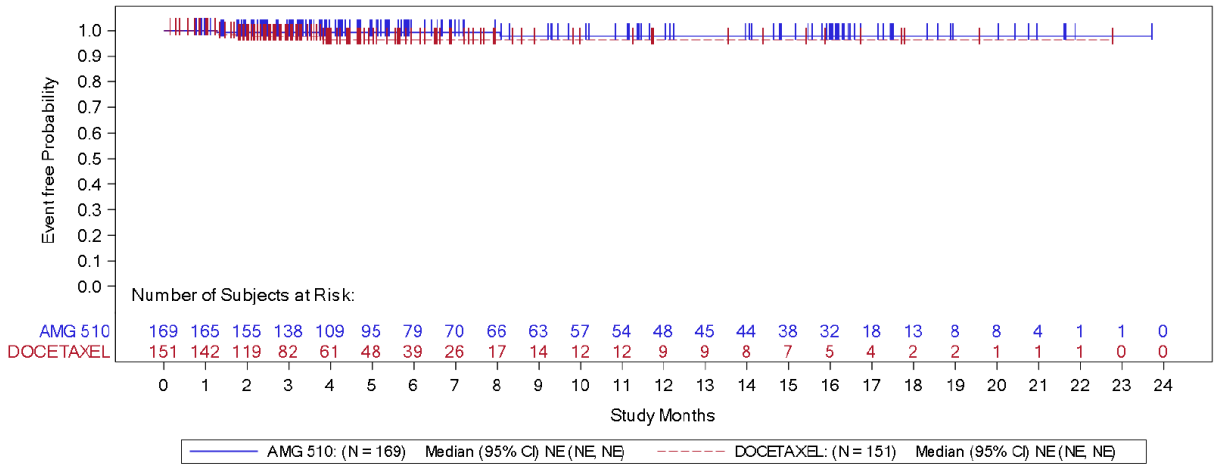

Figure 7: Kaplan-Meier curves on interstitial lung disease (SMQ, severe AEs)

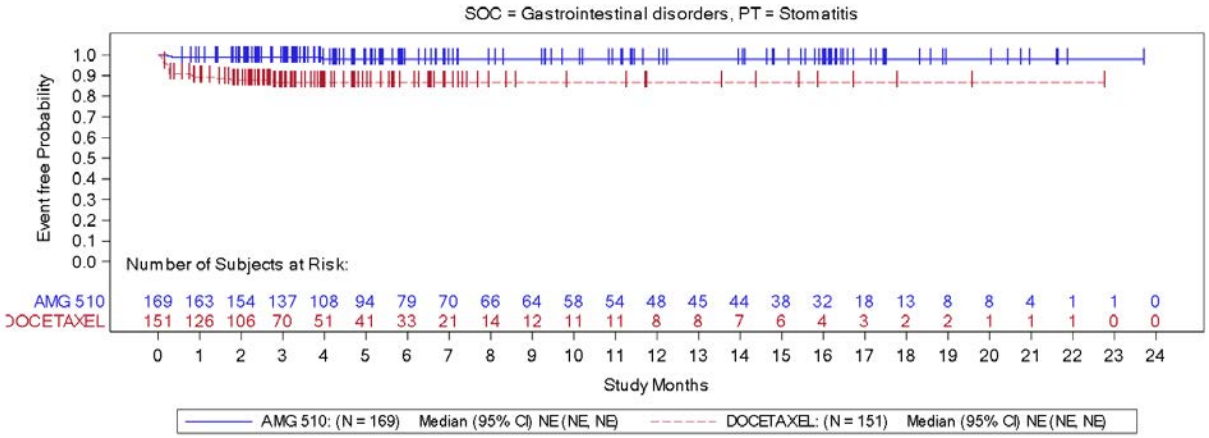

Figure 8: Kaplan-Meier curves on stomatitis (PT, AE)

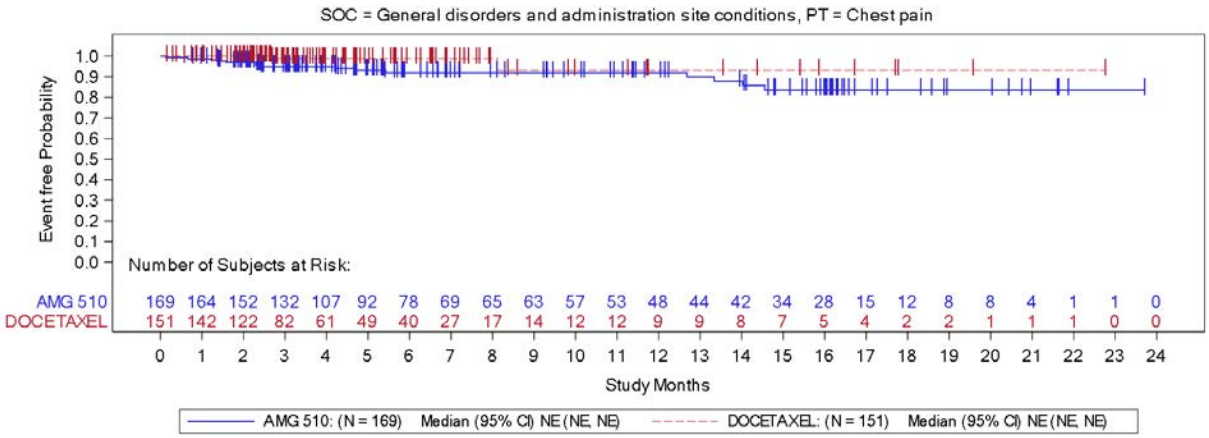

Figure 9: Kaplan-Meier curves on chest pain (PT, AE)

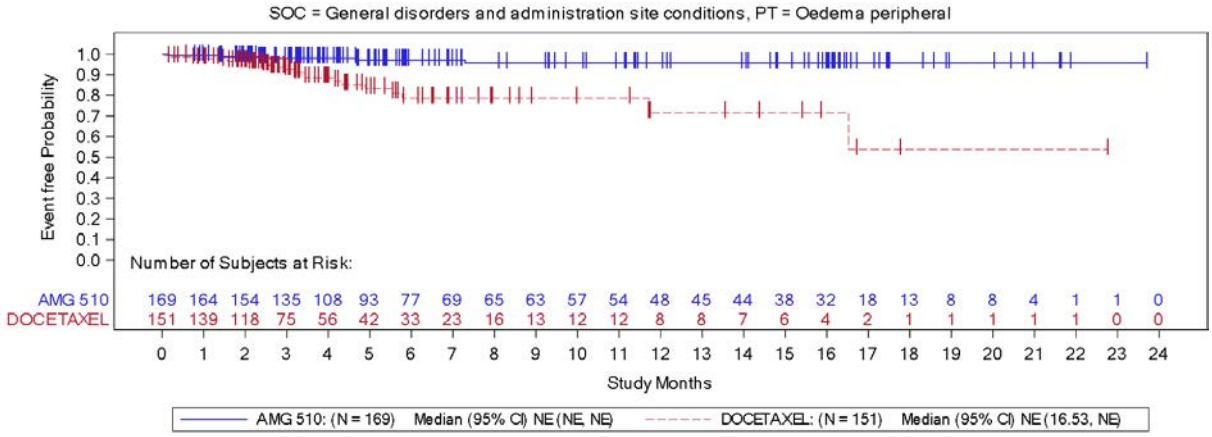

Figure 10: Kaplan-Meier curves on peripheral oedema (PT, AE)

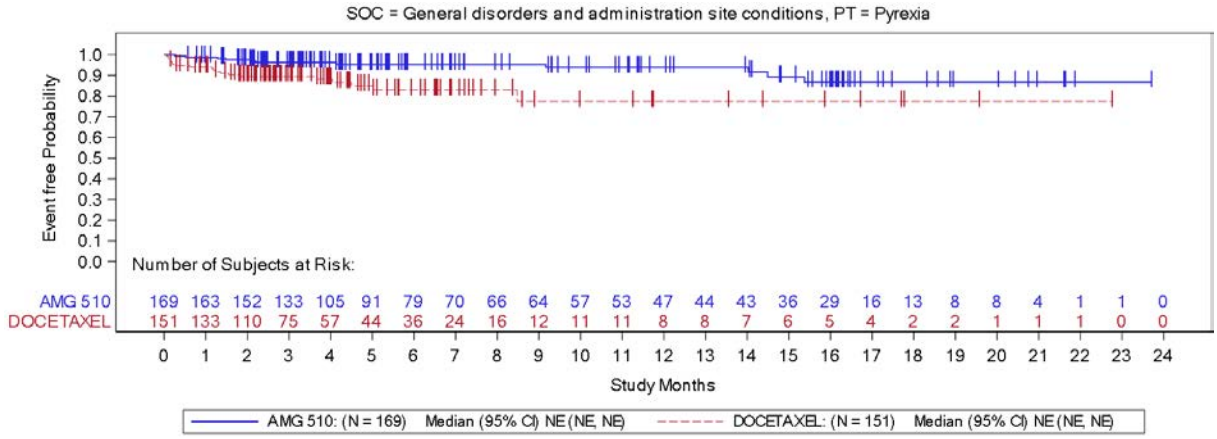

Figure 11: Kaplan-Meier curves on fever (PT, AE)

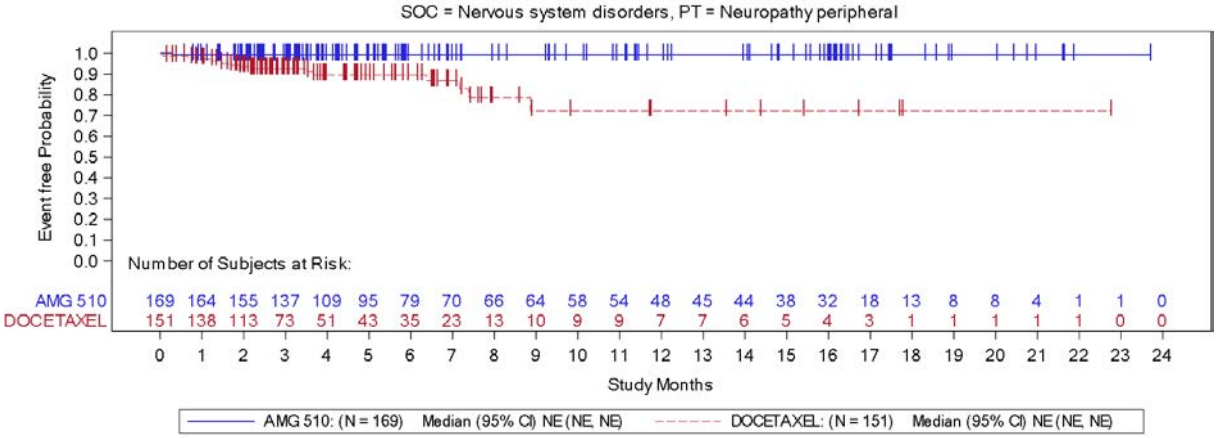

Figure 12: Kaplan-Meier curves on peripheral neuropathy (PT, AE)

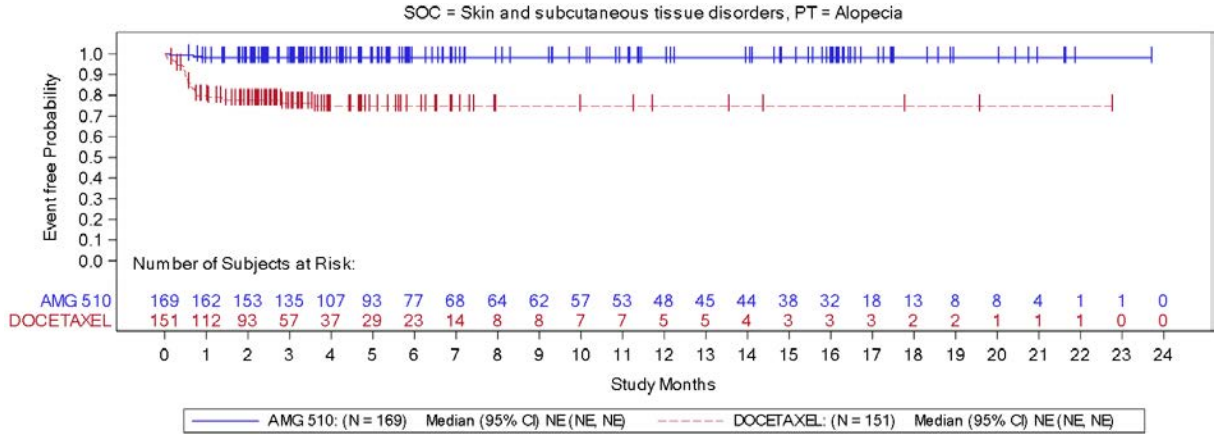

Figure 13: Kaplan-Meier curves on alopecia (PT, AE)

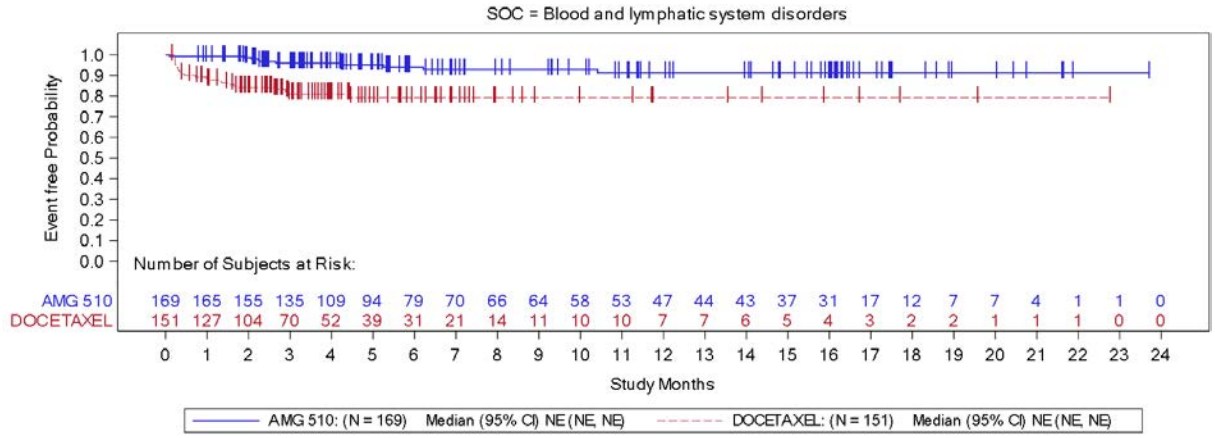

Figure 14: Kaplan-Meier curves on blood and lymphatic system disorders (SOC, AE)

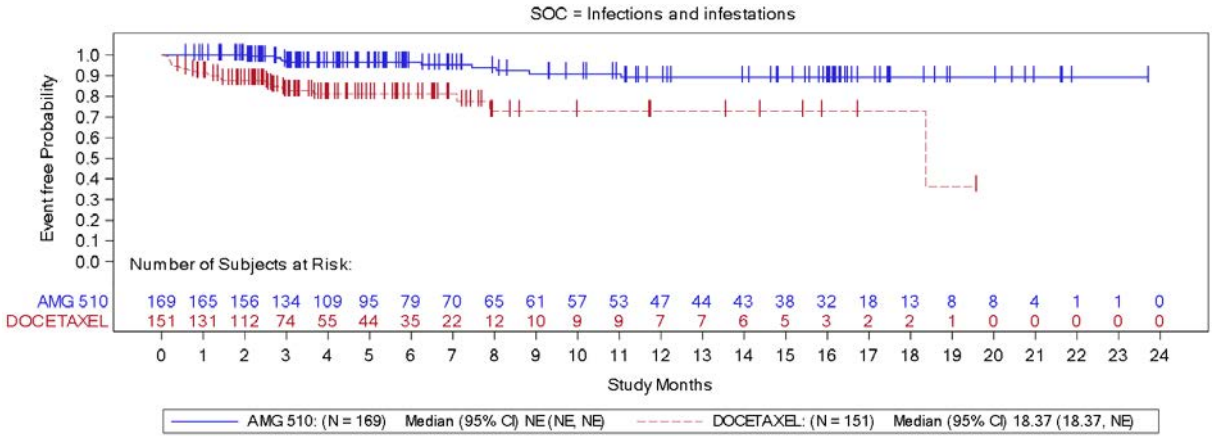

Figure 15: Kaplan-Meier curves on infections and infestations (SOC, AE)

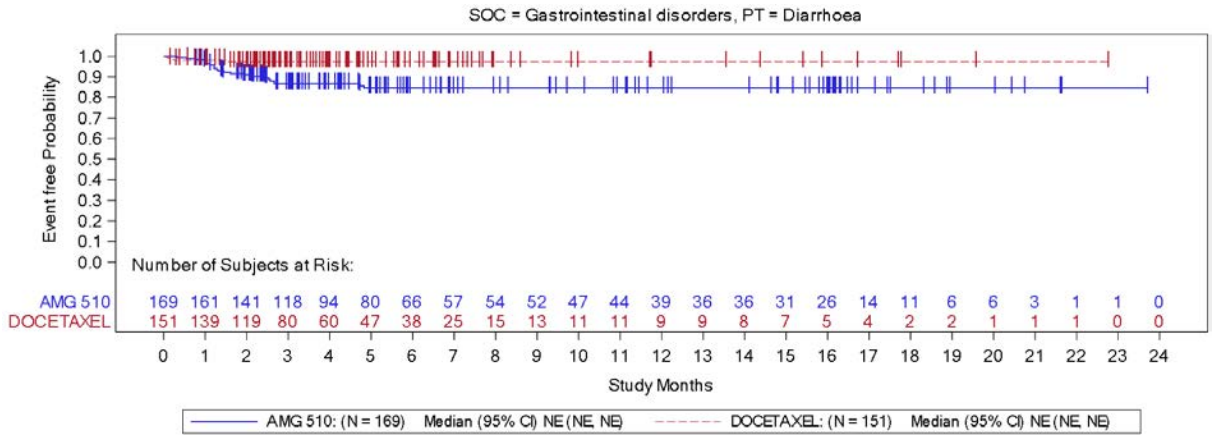

Figure 16: Kaplan-Meier curves on diarrhoea (PT, severe AE)

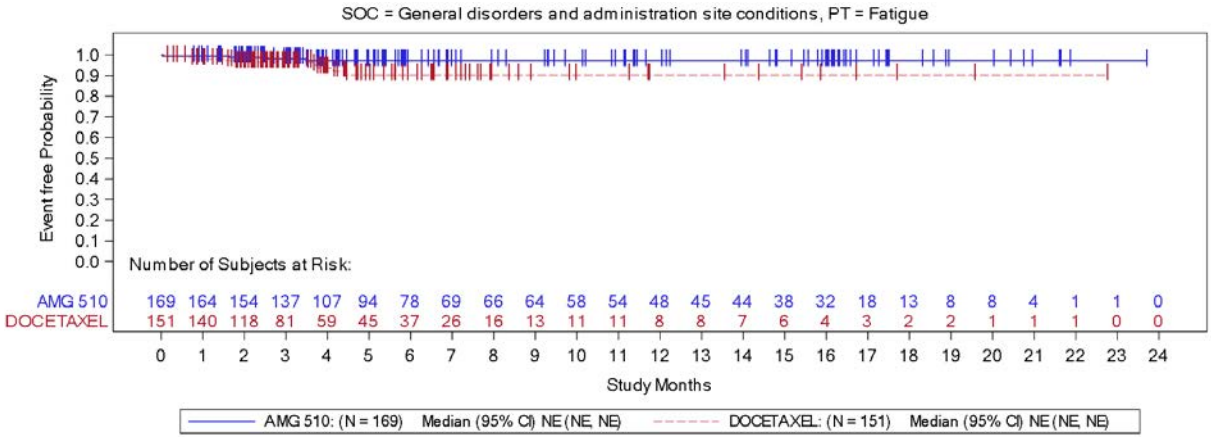

Figure 17: Kaplan-Meier curves on results on subgroups

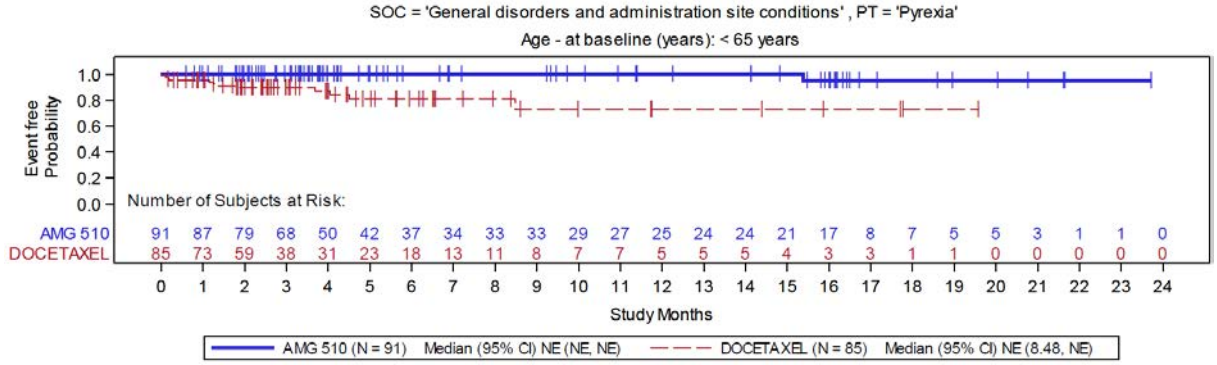

Figure 18: Kaplan-Meier curves on fever (PT, AE), subgroup of age (< 65 years)

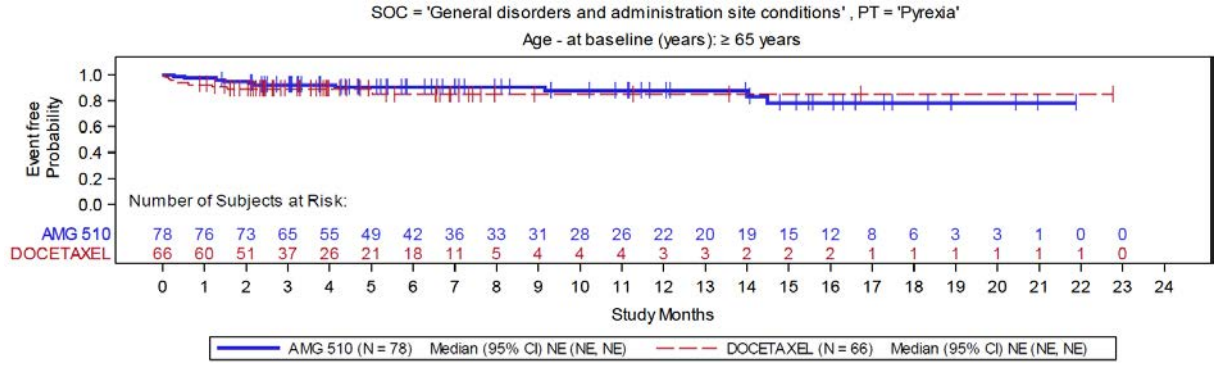

Figure 19: Kaplan-Meier curves on fever (PT, AE), subgroup of age (≥ 65 years)

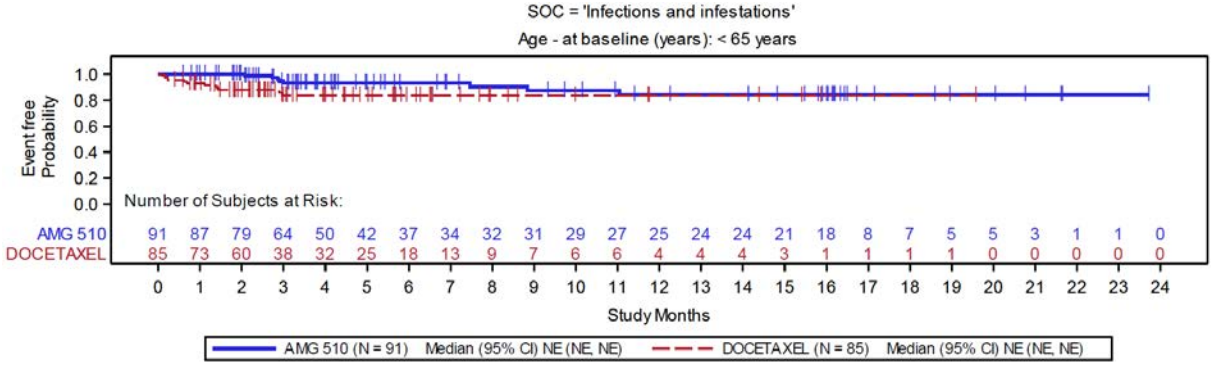

Figure 20: Kaplan-Meier curves on infections and infestations (SOC, severe AE), subgroup of age (< 65 years)

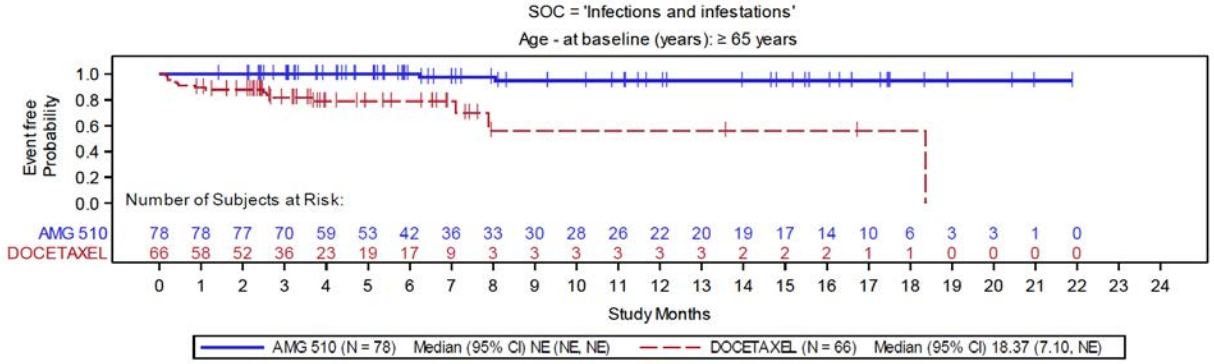

Figure 21: Kaplan-Meier curves on infections and infestations (SOC, severe AE), subgroup of age (≥ 65 years)

Appendix B Results on side effects

For the overall rates of AEs, SAEs, and severe AEs (CTCAE grade ≥ 3), the following tables present events for SOCs and PTs according to MedDRA, each on the basis of the following criteria:

- overall rate of AEs (irrespective of severity): events which occurred in at least 10% of patients in 1 study arm
- overall rates of severe AEs (CTCAE grade ≥ 3) and SAEs: events which occurred in at least 5% of the patients in 1 study arm
- in addition, for all events irrespective of severity grade: events which occurred in at least 10 patients and in at least 1% of patients in 1 study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) which resulted in discontinuation is provided.

Table 13: Common AEs[a] – RCT, direct comparison: sotorasib versus docetaxel (multipage table)

Study	Patients with event n (%)	
SOC[b] **PT[b]**	**Sotorasib** **N = 169**	**Docetaxel** **N = 151**
CodeBreak 200		
Overall rate of AEs[c]	165 (97.6)	148 (98.0)
Blood and lymphatic system disorders	36 (21.3)	49 (32.5)
Anaemia	29 (17.2)	35 (23.2)
Neutropenia	3 (1.8)	15 (9.9)
Cardiac disorders	13 (7.7)	8 (5.3)
Eye disorders	12 (7.1)	11 (7.3)
Gastrointestinal disorders	88 (58.3)	118 (69.8)
Constipation	22 (13.0)	29 (19.2)
Stomatitis	3 (1.8)	19 (12.6)
Diarrhoea	70 (41.4)	39 (25.8)
Nausea	44 (26.0)	37 (24.5)
Vomiting	22 (13.0)	15 (9.9)
Abdominal pain	20 (11.8)	9 (6.0)
Abdominal pain upper	11 (6.5)	5 (3.3)
General disorders and administration site conditions	76 (45.0)	98 (64.9)
Asthenia	17 (10.1)	21 (13.9)
Chest pain	15 (8.9)	2 (1.3)
Fatigue	27 (16.0)	45 (29.8)
Malaise	4 (2.4)	10 (6.6)
Mucosal inflammation	1 (0.6)	11 (7.3)
Peripheral oedema	5 (3.0)	19 (12.6)
Fever	11 (6.5)	20 (13.2)
Hepatobiliary disorders	21 (12.4)	3 (2.0)
Injury, poisoning and procedural complications	16 (9.5)	9 (6.0)
Infections and infestations	52 (30.8)	58 (38.4)
Pneumonia	5 (3.0)	14 (9.3)
Investigations	56 (33.1)	30 (19.9)
Increased ALT	18 (10.7)	1 (0.7)
Increased AST	18 (10.7)	1 (0.7)
Blood alkaline phosphatase increased	13 (7.7)	3 (2.0)
Metabolism and nutrition disorders	74 (43.8)	53 (35.1)
Decreased appetite	39 (23.1)	29 (19.2)
Hypokalaemia	13 (7.7)	4 (2.6)

Table 13: Common AEs[a] – RCT, direct comparison: sotorasib versus docetaxel (multipage table)

Study	Patients with event n (%)	
SOC[b] **PT[b]**	**Sotorasib** **N = 169**	**Docetaxel** **N = 151**
Musculoskeletal and connective tissue disorders	74 (43.8)	57 (37.7)
Myalgia	9 (5.3)	15 (9.9)
Arthralgia	26 (15.4)	21 (13.9)
Back pain	23 (13.6)	16 (10.6)
Pain in extremity	12 (7.1)	8 (5.3)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	33 (19.5)	14 (9.3)
Non-small cell lung cancer	18 (10.7)	6 (4.0)
Nervous system disorders	47 (27.8)	57 (37.7)
Dysgeusia	4 (2.4)	14 (9.3)
Peripheral neuropathy	1 (0.6)	16 (10.6)
Headache	12 (7.1)	13 (8.6)
Dizziness	10 (5.9)	7 (4.6)
Psychiatric disorders	21 (12.4)	14 (9.3)
Renal and urinary disorders	24 (14.2)	6 (4.0)
Respiratory, thoracic and mediastinal disorders	71 (42.0)	65 (43.0)
Cough	22 (13.0)	25 (16.6)
Dyspnoea	32 (18.9)	27 (17.9)
Skin and subcutaneous tissue disorders	41 (24.3)	57 (37.7)
Alopecia	3 (1.8)	35 (23.2)
Pruritus	15 (8.9)	7 (4.6)
Vascular disorders	17 (10.1)	15 (9.9)

a. Events which occurred in ≥ 10 patients in at least 1 study arm.
b. As per SAP [3] MedDRA version 24.0 or later; SOC and PT notation taken from Module 4 A without adaptation or, if taken from Module 4 A Annex 4-G, SOC and PT notation taken from MedDRA version 25.0 without adaptation.
c. Excluding events which were rated by the company as progression of the underlying disease (any PTs containing the terms metastasis/metastases, tumour pain, NSCLC/non-small cell lung cancer or adenocarcinoma of the lung).

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAP: statistical analysis plan; SOC: System Organ Class

Table 14: Common SAEs[a] – RCT, direct comparison: sotorasib versus docetaxel

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Sotorasib** **N = 169**	**Docetaxel** **N = 151**
CodeBreak 200		
Overall rate of SAEs[c]	82 (48.5)	66 (43.7)
Blood and lymphatic system disorders	2 (1.2)	12 (7.9)
Gastrointestinal disorders	14 (8.3)	9 (6.0)
General disorders and administration site conditions	11 (6.5)	9 (6.0)
Infections and infestations	11 (6.5)	25 (16.6)
Pneumonia	1 (0.6)	10 (6.6)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	31 (18.3)	7 (4.6)
Non-small cell lung cancer	18 (10.7)	5 (3.3)
Nervous system disorders	11 (6.5)	6 (4.0)
Respiratory, thoracic, and mediastinal disorders	14 (8.3)	19 (12.6)

a. Events which occurred in ≥ 5% of patients in at least 1 study arm.
b. As per SAP [3] MedDRA version 24.0 or later; SOC and PT notation taken from Module 4 A without adaptation or, if taken from Module 4 A Annex 4-G, SOC and PT notation taken from MedDRA version 25.0 without adaptation.
c. Excluding events which were rated by the company as progression of the underlying disease (any PTs containing the terms metastasis/metastases, tumour pain, NSCLC/non-small cell lung cancer or adenocarcinoma of the lung).

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SAP: statistical analysis plan; SOC: System Organ Class

Table 15: Common severe AEs[a] – RCT, direct comparison: sotorasib versus docetaxel

Study	Patients with event n (%)	
SOC[b] **PT[b]**	**Sotorasib** **N = 169**	**Docetaxel** **N = 151**
CodeBreak 200		
Overall rate of severe AEs (CTCAE grade ≥ 3)[c]	114 (67.5)	90 (59.6)
Blood and lymphatic system disorders	10 (5.9)	27 (17.9)
Anaemia	8 (4.7)	10 (6.6)
Neutropenia	0 (0)	13 (8.6)
Febrile neutropenia	0 (0)	8 (5.3)
Gastrointestinal disorders	35 (20.7)	11 (7.3)
Diarrhoea	23 (13.6)	4 (2.6)
General disorders and administration site conditions	18 (10.7)	22 (14.6)
Fatigue	4 (2.4)	9 (6.0)
Hepatobiliary disorders	14 (8.3)	0 (0)
Infections and infestations	10 (5.9)	27 (17.9)
Pneumonia	1 (0.6)	9 (6.0)
Investigations	25 (14.8)	10 (6.6)
Alanine aminotransferase increased	14 (8.3)	0 (0)
Aspartate aminotransferase increased	10 (5.9)	0 (0)
Metabolism and nutrition disorders	15 (8.9)	6 (4.0)
Musculoskeletal and connective tissue disorders	8 (4.7)	9 (6.0)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	30 (17.8)	7 (4.6)
Non-small cell lung cancer	17 (10.1)	5 (3.3)
Nervous system disorders	13 (7.7)	8 (5.3)
Respiratory, thoracic and mediastinal disorders	18 (10.7)	22 (14.6)

a. Events which occurred in ≥ 5% of patients in at least 1 study arm.
b. As per SAP [3] MedDRA version 24.0 or later; SOC and PT notation taken from Module 4 A without adaptation or, if taken from Module 4 A Annex 4-G, SOC and PT notation taken from MedDRA version 25.0 without adaptation.
c. Excluding events which were rated by the company as progression of the underlying disease (any PTs containing the terms metastasis/metastases, tumour pain, NSCLC/non-small cell lung cancer or adenocarcinoma of the lung).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAP: statistical analysis plan; SOC: System Organ Class

Table 16: Discontinuation due to AEs – RCT, direct comparison: sotorasib versus docetaxel (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Sotorasib** **N = 169**	**Docetaxel** **N = 151**
CodeBreak 200		
Overall rate of discontinuations due to AEs[b, c]	28 (16.6)	24 (15.9)
Blood and lymphatic system disorders	1 (0.6)	4 (2.6)
Disseminated intravascular coagulation	1 (0.6)	0 (0)
Anaemia	0 (0)	2 (1.3)
Febrile neutropenia	0 (0)	2 (1.3)
Cardiac disorders	0 (0)	1 (0.7)
Pericarditis	0 (0)	1 (0.7)
Gastrointestinal disorders	2 (1.2)	2 (1.3)
Diarrhoea	1 (0.6)	0 (0)
Pancreatitis	1 (0.6)	0 (0)
Nausea	0 (0)	1 (0.7)
Stomatitis	0 (0)	1 (0.7)
Vomiting	0 (0)	1 (0.7)
General disorders and administration site conditions	2 (1.2)	6 (4.0)
Asthenia	2 (1.2)	1 (0.7)
Fatigue	0 (0)	3 (2.0)
Malaise	0 (0)	1 (0.7)
Multiple organ dysfunction syndrome	0 (0)	1 (0.7)
Hepatobiliary disorders	4 (2.4)	0 (0)
Drug-induced liver damage	2 (1.2)	0 (0)
Gall bladder inflammation	1 (0.6)	0 (0)
Hepatic failure	1 (0.6)	0 (0)
Hepatitis	1 (0.6)	0 (0)
Immune system disorders	0 (0)	1 (0.7)
Anaphylactic reaction	0 (0)	1 (0.7)
Infections and infestations	1 (0.6)	3 (2.0)
Hepatitis non-A, non-B	1 (0.6)	0 (0)
Clostridium difficile colitis	0 (0)	1 (0.7)
Pneumonia	0 (0)	1 (0.7)
Aspiration pneumonia	0 (0)	1 (0.7)
Investigations	8 (4.7)	1 (0.7)
Increased ALT	6 (3.6)	0 (0)
Blood bilirubin increased	4 (2.4)	0 (0)
Increased AST	2 (1.2)	0 (0)

Table 16: Discontinuation due to AEs – RCT, direct comparison: sotorasib versus docetaxel (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Sotorasib** **N = 169**	**Docetaxel** **N = 151**
Blood alkaline phosphatase increased	2 (1.2)	0 (0)
AST	1 (0.6)	0 (0)
Increased transaminase	1 (0.6)	0 (0)
Decreased neutrophil count	0 (0)	1 (0.7)
Musculoskeletal and connective tissue disorders	0 (0)	1 (0.7)
Muscular weakness	0 (0)	1 (0.7)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	6 (3.6)	2 (1.3)
NSCLC	5 (3.0)	2 (1.3)
Spinal metastases	1 (0.6)	0 (0)
Nervous system disorders	2 (1.2)	3 (2.0)
Polyneuropathy	1 (0.6)	1 (0.7)
Paraplegia	1 (0.6)	0 (0)
Cerebrovascular accident	0 (0)	1 (0.7)
Transient ischaemic attack	0 (0)	1 (0.7)
Renal and urinary disorders	2 (1.2)	0 (0)
Acute kidney injury	1 (0.6)	0 (0)
Chronic kidney disease	1 (0.6)	0 (0)
Respiratory, thoracic and mediastinal disorders	3 (1.8)	5 (3.3)
Dyspnoea	1 (0.6)	0 (0)
Interstitial lung disease	1 (0.6)	0 (0)
Pneumothorax	1 (0.6)	0 (0)
Aspiration	0 (0)	1 (0.7)
Dyspnoea, exertional	0 (0)	1 (0.7)
Pleural effusion	0 (0)	1 (0.7)
Pneumonitis	0 (0)	1 (0.7)
Respiratory failure	0 (0)	1 (0.7)
Skin and subcutaneous tissue disorders	0 (0)	1 (0.7)
Mucocutaneous rash	0 (0)	1 (0.7)

a. As per SAP [3], MedDRA version 24.0 or later; SOC and PT notation taken from Module 4 A without adaptation or, if taken from Module 4 A Annex 4-G, SOC and PT notation taken from MedDRA version 25.0 without adaptation.
b. Discontinuation due to AEs including events caused by progression of the underlying disease.
c. AEs which led to discontinuation of sotorasib or docetaxel.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SAP: statistical analysis plan; SOC: System Organ Class