IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Nintedanib – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Nintedanib – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 March 2015). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AJCC	American Joint Committee on Cancers
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
PFS	progression-free survival
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-LC13	Quality of Life Questionnaire-Lung Cancer 13
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug nintedanib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 2 January 2015.

Research question

The aim of this report is to assess the added benefit of nintedanib in combination with docetaxel in comparison with the appropriate comparator therapy (ACT) in adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.

The G-BA specified the ACT presented in Table 2.

Table 2: ACT for the benefit assessment of nintedanib

Therapeutic indication	**ACT**[a]
Combination therapy with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy	**Chemotherapy with docetaxel** or pemetrexed or gefitinib or erlotinib (only for patients with activating EGFR mutations) or crizotinib (only for patients with activating ALK mutations)
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer	

The present benefit assessment was conducted in comparison with the G-BA's ACT. The company followed the specification of the G-BA and, from the options mentioned, chose chemotherapy with docetaxel as comparator therapy.

The assessment was conducted based on patient-relevant outcomes and on the evidence provided by the company in the dossier.

Results

The LUME-Lung 1 study (approval study of nintedanib) was included in the assessment.

Study characteristics

The LUME-Lung 1 study is an ongoing, randomized, multicentre, double-blind approval study. Adult patients with locally advanced and/or metastatic NSCLC of stage IIIB or IV (according to American Joint Committee on Cancers [AJCC]) or recurrent NSCLC, in each case after first-line chemotherapy, were enrolled. Since nintedanib in combination with docetaxel is only approved for patients with adenocarcinoma histology, only the corresponding subpopulation of these patients was considered for the present benefit assessment.

The disease severity of the patients at baseline had to correspond to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. Patients with more than one prior chemotherapy regimen for advanced and/or metastatic or recurrent NSCLC were excluded from the study.

Patients were randomized in a ratio of 1:1 to treatment with nintedanib + docetaxel or to placebo + docetaxel. A total of 1314 patients were randomized (nintedanib + docetaxel: 655 patients; placebo + docetaxel: 659 patients). 658 (approximately 50%) of these patients had adenocarcinoma (nintedanib + docetaxel: 322 patients; placebo + docetaxel: 336 patients).

Nintedanib was administered at a dose of 200 mg twice daily on days 2 to 21 of each 21-day treatment cycle. Placebo administration in the comparator arm was analogous to the intervention arm. In both treatment groups, docetaxel was administered intravenously in a dosage of 75 mg/m^2 on day 1 of each 21-day treatment cycle.

Study medication was to be continued until unacceptable adverse events (AEs) occurred, disease progression was determined, or the physician or patient refused to continue treatment. In these cases, the patients could start other anticancer therapies on disease progression.

Progression-free survival (PFS) was the primary outcome of the LUME-Lung 1 study. The data of all patients were included in the analysis of overall survival also after ending the study medication. The recording of other data was conducted outcome-specific beyond the end of treatment. AEs were recorded up to 28 days after the end of treatment. Data on symptoms and quality of life were recorded up to the first follow-up visit at approximately 6 to 8 weeks after ending the study medication.

Risk of bias

The risk of bias at study level was rated as low for the LUME-Lung 1 study. At most indications, e.g. of an added benefit, could be derived from this study. Due to the different observation periods resulting from the different treatment durations between the nintedanib + docetaxel arm and the placebo + docetaxel arm (median treatment durations: 4.3 months in the nintedanib + docetaxel arm, and 3.0 months in the placebo + docetaxel arm) and the respective follow-up, the study results for all outcomes – except for overall survival – were assessed to have a high risk of bias.

Results

Mortality

A statistically significant difference in overall survival between nintedanib + docetaxel and placebo + docetaxel was shown in the LUME-Lung 1 study. In addition, there was an indication of an effect modification by the characteristic "presence of brain metastases". For patients without brain metastases, this results in an indication of an added benefit of nintedanib + docetaxel in comparison with the ACT. For patients with brain metastases, there is no hint of an added benefit, an added benefit is therefore not proven for these patients.

Morbidity (symptoms)

The morbidity of the patients was recorded with the symptom scales of the disease-specific questionnaires European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30 (QLQ-C30) and EORTC Quality of Life Questionnaire-LC13 (QLQ-LC13).

For each of the outcomes **"diarrhoea"** and **"nausea and vomiting"**, there was a statistically significant difference in favour of placebo + docetaxel for the time to worsening of the symptom. For both symptoms, this results in a hint of lesser benefit of nintedanib + docetaxel in comparison with the ACT; however, due to effect modifications in nausea and vomiting, this hint only applies to patients with brain metastases.

For the outcome **"pain (arm/shoulder)"**, there was a statistically significant difference in favour of nintedanib + docetaxel for the time to worsening of symptoms. The extent of the effect in this non-serious/non-severe outcome was no more than marginal. There was no statistically significant difference between the treatment groups for each of the outcomes "**pain (chest)", "pain"**, and "**pain (other parts)**". Overall, no added benefit could be derived for any outcome from the category "pain" for nintedanib + docetaxel in comparison with the ACT.

There was no statistically significant difference between the treatment groups for the outcome **"appetite loss"**. However, there was proof of an effect modification by the characteristic "presence of brain metastases" for this outcome. For the group of patients with brain metastases at baseline, this results in a hint of lesser benefit of nintedanib + docetaxel in comparison with the ACT. For patients without brain metastases, there is no hint of an added benefit, an added benefit is therefore not proven for these patients.

There was no statistically significant difference between the treatment groups for the outcome **"constipation"**. However, there was proof of an effect modification by the characteristic "bevacizumab pretreatment" for this outcome. For patients with bevacizumab pretreatment, this results in a hint of an added benefit of nintedanib + docetaxel in comparison with the ACT. For patients without bevacizumab pretreatment, there is no hint of an added benefit, an added benefit is therefore not proven for these patients.

There was no statistically significant difference between the treatment options for any of the following outcomes: **dyspnoea, fatigue, insomnia, haemoptysis, alopecia, cough, sore mouth, peripheral neuropathy** and **dysphagia**. This results in no hint of an added benefit of nintedanib + docetaxel in comparison with the ACT, an added benefit for these outcomes is therefore not proven.

Morbidity (health status)

Health status was determined with the visual analogue scale (VAS) for self-assessment of the current health status from the European Quality of Life-5 Dimensions (EQ-5D). There was no statistically significant difference between the treatment groups. This results in no hint of an added benefit of nintedanib + docetaxel in comparison with the ACT, an added benefit is therefore not proven.

Health-related quality of life

The patients' health-related quality of life was recorded with the symptom scales of the disease-specific EORTC QLQ-LC13 questionnaire. The time to worsening of health-related quality of life was analysed. There was no statistically significant difference between the treatment groups for any of the following outcomes: **global health status, emotional functioning, cognitive functioning, physical functioning, role functioning** and **social functioning**. This results in no hint of an added benefit of nintedanib + docetaxel in comparison with the ACT, an added benefit for these outcomes is therefore not proven.

Adverse events

There was no statistically significant difference between the treatment groups regarding the outcomes **"serious AEs (SAEs)"** and **"discontinuation due to AEs"**. This results in no hint of greater or lesser harm of nintedanib + docetaxel in comparison with the ACT for these outcomes, an added benefit is therefore not proven.

There was no statistically significant difference between the treatment groups for the outcome **"severe AEs"** (CTCAE grade ≥ 3). However, there was proof of an effect modification by the characteristic "sex" for this outcome. For the group of female patients, this results in a hint of greater harm from treatment with nintedanib + docetaxel in comparison with the ACT. For male patients, this results in no hint of greater or lesser harm of nintedanib + docetaxel in comparison with the ACT, an added benefit is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

In the overall assessment, there are positive and negative effects of different certainty of results and extent, partly for different subgroups. There are positive effects for patients without brain metastases in the outcome category "mortality" and – for patients with bevacizumab pretreatment – in the outcome category "non-serious/non-severe symptoms". Negative effects were shown for different subgroups in the outcome categories "non-serious/non-severe symptoms" and "serious/severe AEs".

Below, balancing of the positive and negative effects is conducted separately for patients with and without brain metastases at baseline.

Patients without brain metastases

There is an indication of minor added benefit of nintedanib + docetaxel for the outcome "overall survival" for patients without brain metastases. This is decisive because of the outcome category "mortality" and the greater certainty of results for this patient group on the side of positive results. On the negative side, this is offset to an important degree by a hint of lesser benefit with the extent "considerable" for the outcome "diarrhoea" (outcome category "non-serious/non-severe symptoms"). Due to the certainty of results, the negative effects cannot raise doubts about the positive effects so that overall there is an indication of minor added benefit of nintedanib + docetaxel in comparison with the ACT for patients without brain metastases.

Patients with brain metastases

There are several negative effects of the same certainty of results (hint) for patients with brain metastases. Due to the extent, the hint of lesser benefit with the extent "considerable" is decisive. On the positive side, this is offset by a hint of a minor added benefit (outcome category "non-severe/non-serious symptoms), which only applies to the subgroup of patients with bevacizumab pretreatment, however. For this reason, the positive effect is unsuitable to outweigh the negative effects so that there is a hint of lesser benefit of nintedanib + docetaxel in comparison with the ACT for patients with brain metastases.

Table 3 presents a summary of the extent and probability of the added benefit of nintedanib + docetaxel.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

Table 3: Nintedanib + docetaxel – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Subgroup**	**Extent and probability of added benefit**
Combination therapy with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy	**Chemotherapy with docetaxel** or pemetrexed or gefitinib or erlotinib (only for patients with activating EGFR) or crizotinib (only for patients with activating ALK)	Patients without brain metastases	Indication of a minor added benefit
		Patients with brain metastases	Hint of lesser benefit
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer			

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is to assess the added benefit of nintedanib + docetaxel in comparison with the ACT in adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy.

The G-BA specified the ACT presented in Table 4.

Table 4: ACT for the benefit assessment of nintedanib

Therapeutic indication	**ACT**[a]
Combination therapy with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy	**Chemotherapy with docetaxel** or pemetrexed or gefitinib or erlotinib (only for patients with activating EGFR mutations) or crizotinib (only for patients with activating ALK mutations)
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer	

The present benefit assessment was conducted in comparison with the G-BA's ACT. The company followed the specification of the G-BA and, from the options mentioned, chose chemotherapy with docetaxel as comparator therapy.

The assessment was conducted based on patient-relevant outcomes and on the evidence provided by the company in the dossier.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on nintedanib (studies completed up to 16 October 2014)
- bibliographical literature search on nintedanib (last search on 16 October 2014)
- search in trial registries for studies on nintedanib (last search on 16 October 2014)

To check the completeness of the study pool:

- search in trial registries for studies on nintedanib (last search on 19 January 2015)

No additional relevant study was identified from the check.

2.3.1 Studies included

The LUME-Lung 1 study [3] listed in the following Table 5 was included in the benefit assessment of nintedanib. Only the subpopulation of patients with adenocarcinoma histology is relevant for the present benefit assessment. This concurs with the company's approach.

Table 5: Study pool – RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	**Sponsored study[a] (yes/no)**	**Third-party study (yes/no)**
LUME-Lung 1	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

Section 2.6 contains a reference list for the study included.

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
LUME-Lung 1	RCT, double-blind, parallel	Adult patients with locally advanced and/or metastatic NSCLC of stage IIIB or IV (according to AJCC) or recurrent NSCLC, in each case after first-line chemotherapy[b]	Nintedanib + docetaxel (N = 655) placebo + docetaxel (N = 659) Relevant subpopulation of patients with adenocarcinoma histology: nintedanib + docetaxel (n = 322) placebo + docetaxel (n = 336)	Total duration: probably ~72 months Screening: 14 days Treatment phase: up to occurrence of disease progression, of an unacceptable AE, or until the physician or patient refused to continue treatment or until another predefined criterion for discontinuation was fulfilled[c] Observation period: until death or discontinuation of study participation	211 centres in 27 countries in Asia, Europe, South Africa ongoing study, recruitment completed Start: 12/2008 Data cut-offs: 11/2010[d] (PFS) 2/2013[e] (overall survival)	Primary outcome: progression-free survival Secondary outcomes: overall survival, symptoms, health-related quality of life, adverse events

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: In the case of recurrent disease one additional prior regimen was allowed for adjuvant, neoadjuvant, or neoadjuvant plus adjuvant therapy.
c: For example pregnancy, surgery, concomitant medication or concomitant diagnoses because of which no continued treatment with the study medication is possible.
d: Primary analysis for the outcome "PFS" and interim analysis for the outcome "overall survival"; planned after disease progression or death of 713 patients.
e: Final analysis of the outcome "overall survival"; planned after 1151 deaths or in case of fewer deaths within approximately 48 months study duration. The final analysis on overall survival was conducted after approximately 50 months study duration.

AE: adverse event; AJCC: American Joint Committee on Cancer; N: number of randomized patients; n: relevant subpopulation; NSCLC: non-small cell lung cancer; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel, Study LUME-Lung 1

Intervention	**Comparison**
Nintedanib 200 mg orally, twice daily on days 2-21 of each 21-day treatment cycle + docetaxel 75 mg/m^2, IV, on the first day of each 21-day treatment cycle *Dose reduction scheme:* Nintedanib: 2 steps of dose reduction to initially 150 mg twice daily and then 100 mg twice daily on occurrence of prespecified AEs[a] Docetaxel: dose reduction from 75 to 60 mg/m^2 on occurrence of prespecified AEs[a]	▪ Placebo (twice daily on days 2-21 of each 21-day treatment cycle) ▪ + docetaxel 75 mg/m^2, IV, on the first day of each 21-day treatment cycle ▪ *Dose reduction scheme:* ▪ Placebo and docetaxel: dose reduction as in the intervention arm
Concomitant medication ▪ medications or treatments for adequate patient care may be given if clinically necessary ▪ bisphosphonates in bone metastases ▪ non-oncological treatments including alternative and/or complementary medicine (vitamins, dietary supplements, anaesthetics), palliative radiotherapy for symptom control (in bone metastases in the extremities) ▪ oral corticosteroid (e.g. dexamethasone) for 3 days, starting one day before administration of docetaxel ▪ anticoagulants if clinically necessary to treat AEs ▪ additional chemotherapy, immunotherapy, hormonal therapy or radiotherapy were not allowed	
a: Dose reduction of nintedanib or placebo (sham dose reduction) in the combination therapy was conducted in non-haematological AEs of CTCAE grade ≥ 3, elevated liver enzymes AST and/or ALT, vomiting, nausea or diarrhoea. Treatment was discontinued in case of repeated occurrence. In nintedanib (or placebo) monotherapy, the dose could also be reduced if haematological AEs occurred. For docetaxel, the dose could also be reduced if the following AEs occurred: neutropenia of CTCAE grade 4, febrile neutropenia, cumulative skin reactions or peripheral neurotoxicity of CTCAE grade 2. AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTCAE: Common Terminology Criteria for Adverse Events; IV: intravenous; RCT: randomized controlled trial; vs.: versus	

The LUME-Lung 1 study is an ongoing, randomized, multicentre, double-blind approval study. Adult patients with locally advanced and/or metastatic NSCLC of stage IIIB or IV (according to AJCC) or recurrent NSCLC, in each case after first-line chemotherapy, were enrolled. Since nintedanib in combination with docetaxel is only approved for patients with adenocarcinoma histology, only the corresponding subpopulation of these patients was considered for the present benefit assessment.

PFS was the primary outcome of the LUME-Lung 1 study. The outcomes “overall survival”, “morbidity” and “health-related quality of life” were secondary outcomes. The disease severity of the patients at baseline had to correspond to an ECOG PS of 0 or 1. Patients with more than one prior chemotherapy regimen for advanced and/or metastatic or recurrent NSCLC were excluded from the study. Figure 1 shows the study design of the LUME-Lung 1 study.

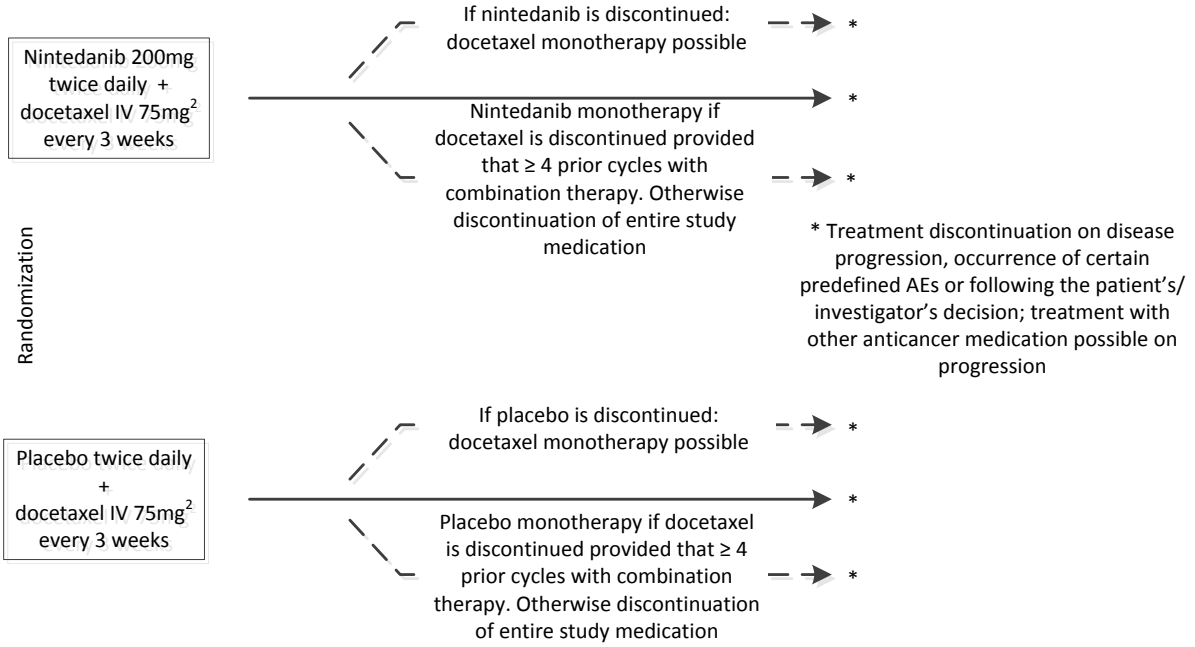

Figure 1: Study design of the LUME-Lung 1 study (nintedanib + docetaxel vs. placebo + docetaxel)

Patients were randomized in a ratio of 1:1 to treatment with nintedanib + docetaxel or to placebo + docetaxel. Randomization was stratified by ECOG PS prior bevacizumab treatment, tumour histology (squamous versus non-squamous cell cancer), and brain metastases at baseline. A total of 1314 patients were randomized (nintedanib + docetaxel: 655 patients; placebo + docetaxel: 659 patients). 658 (approximately 50%) of these patients had adenocarcinoma (nintedanib + docetaxel: 322 patients; placebo + docetaxel: 336 patients). All patients received (non-oncological) concomitant treatment if this was medically indicated to guarantee adequate patient care.

The drugs nintedanib and docetaxel used in the study were administered in treatment regimens that largely comply with the specifications of the respective Summaries of Product Characteristics (SPCs) [4,5]. Deviations from the SPC are commented on in Section 2.7.2.4.1 of the full dossier assessment. However, these deviations had no consequences for the assessment of the relevance of the study.

Nintedanib was administered at a dose of 200 mg twice daily on days 2 to 21 of each 21-day treatment cycle. Placebo administration in the comparator arm was analogous to the intervention arm. In both treatment groups, docetaxel was administered intravenously in a dosage of 75 mg/m^2 on day 1 of each 21-day treatment cycle.

Study medication was to be continued until unacceptable AEs occurred, disease progression was determined, or the physician or patient refused to continue treatment. In these cases, the patients could start other anticancer therapies on disease progression. Approximately 56% of

the patients with adenocarcinoma histology chose this option with approximately 40% of the patients being treated with another chemotherapy (alone or in combination with other anticancer therapies).

Nintedanib treatment regimen

If prespecified nintedanib-associated AEs occurred in the course of the study (see Table 7), the dose was reduced in 2 steps to 150 mg and 100 mg twice daily.

Patients who had to discontinue the combination therapy with nintedanib + docetaxel (or placebo + docetaxel) due to unacceptable AEs under docetaxel, could continue treatment with nintedanib (or placebo) monotherapy. One condition was that the patients had received at least 4 cycles of the combination therapy without disease progression and that none of the predefined reasons for treatment discontinuation was fulfilled (see Section 2.7.2.4.1 of the full dossier assessment). If these conditions were not met, the study medication was discontinued and other anticancer therapies were initiated on disease progression if this was medically reasonable. 32.9% of the randomized patients with adenocarcinoma histology in the nintedanib + docetaxel arm and 25.6% in the placebo + docetaxel arm received nintedanib or placebo monotherapy respectively following the combination therapy (Institute's calculation).

Docetaxel treatment regimen

On occurrence of prespecified docetaxel-related AEs, the docetaxel dose of 75 mg/m^2 was to be reduced to 60 mg/m^2 (see Table 7). Patients who had to discontinue the combination therapy with nintedanib + docetaxel (or placebo + docetaxel) due to unacceptable AEs of nintedanib (or placebo) could continue treatment with docetaxel monotherapy if they were eligible for this treatment. This was the case for 1.6% of the patients in the nintedanib + docetaxel arm and 1.2% of the randomized patients with adenocarcinoma histology in the placebo + docetaxel arm (Institute's calculation).

Table 8 and Table 9 show the planned duration of follow-up of the patients for the individual outcomes and the treatment duration in the LUME-Lung 1 study.

Table 8: Planned duration of follow-up – RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel

Outcome	Planned follow-up
Overall survival	▪ Until death or lost to follow-up
Symptoms	▪ 6–8 weeks after ending the study medication (until first follow-up visit)
Health-related quality of life	▪ 6–8 weeks after ending the study medication (until first follow-up visit)
Adverse events	▪ Up to 28 days after the last treatment with the study medication; then only SAEs associated with the study medication were recorded, and all AEs reported to the sponsor.
AE: adverse event; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus	

Table 9: Information on the course of the study – RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel

Study Characteristics Category	**Nintedanib + docetaxel N = 320**	**Placebo + docetaxel N = 333**
LUME-Lung 1		
Treatment duration		
Median duration of treatment with the study medication: months (min; max)	4.3 (0.13; 41.57)	3.0 (0.03; 31.73)
Observation duration		
For the outcomes considered in the benefit assessment except for the outcome "overall survival"	ND	ND
max: maximum; min: minimum; N: number of randomized patients with at least one dose of the study medication; ND: no data; RCT: randomized controlled trial; vs.: versus		

The median treatment duration in the LUME-Lung 1 study was considerably longer for the patients in the nintedanib + docetaxel arm (4.3 months) than in the docetaxel arm (3.0 months). The data of all patients were included in the analysis of overall survival also after ending the study medication. The recording of other data was conducted outcome-specific beyond the end of treatment. AEs were recorded up to 28 days after the end of treatment. Data on symptoms and quality of life were recorded up to the first follow-up visit at approximately 6 to 8 weeks after ending the study medication. There was no information on the actual observation period for the individual outcomes in the LUME-Lung 1 study, except for the outcome "overall survival".

The LUME-Lung 1 study was not yet completed at the time of the benefit assessment. Analyses on 2 data cut-offs were available. The first data cut-off (2 November 2010) was planned after 713 cases of disease progression and was conducted after the occurrence of 714 events. The final analysis of the primary outcome "PFS" was performed at this time point. For the results on overall survival, the company presented the results of a second data cut-off, which was conducted on 15 February 2013. This analysis was to be conducted when 1151 patients had died or, in case of fewer deaths, after a time period of approximately 48 months had passed since the start of the treatment. The analysis was conducted after approximately 50 months. The data in the dossier were based on the analyses of the second data cut-off and were considered for the present benefit assessment.

Table 10 shows the characteristics of the patients in the study included.

Table 10: Characteristics of the study populations – RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel

Study **Characteristics** **Category**	**Nintedanib + docetaxel** **N = 322**	**Placebo + docetaxel** **N = 336**
LUME-Lung 1		
Age [years]: mean (SD)	58.5 (10.1)	58.6 (9.5)
Sex: [F/M], %	37/63	38/62
Geographical region: n (%)		
Europe	229 (71.1)	234 (69.6)
Asia	86 (26.7)	96 (28.6)
South Africa	7 (2.2)	6 (1.8)
Smoking status: n (%)		
Never-smoker	115 (35.7)	115 (34.2)
Ex-smoker	151 (46.9)	162 (48.2)
Current smoker	56 (17.4)	59 (17.6)
ECOG PS: n (%)		
0	96 (29.8)	99 (29.5)
1	225 (69.9)	237 (70.5)
2	1 (0.3)[a]	0 (0)
Disease stage at first diagnosis: n (%)[b]		
UICC 6th edition	154 (47.8)	158 (47.0)
Stage IV	86 (26.7)	103 (30.7)
Stage IIIB	34 (10.6)	22 (6.5)
Stage < IIIB/IV	34 (10.6)	33 (9.8)
UICC 7th edition	166 (51.6)	178 (53.0)
Stage IV	129 (40.1)	134 (39.9)
Stage IIIB	21 (6.5)	23 (6.8)
Stage < IIIB/IV	16 (5.0)	21 (6.3)
Stage missing	2 (0.6)	0 (0)
Brain metastases at baseline: n (%)	26 (8.1)	23 (6.8)
Pretreatment with bevacizumab: n (%)	24 (7.5)	21 (6.3)

a: Institute's calculation. According to the company, the patient was considered as ECOG PS 1 in the analysis of the study.
b: The TNM classification according to UICC/AJCC was updated during the study. Accordingly, the patients were partly categorized according to the 7th edition, and partly according to the 6th edition.
AJCC: American Joint Committee on Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; N: number of randomized patients; n: number of patients in the category; RCT: randomized controlled trial; SD: standard deviation; TNM: Classification of Malignant Tumours; UICC: Union for International Cancer Control; vs.: versus

The patients in both treatment arms were comparable with regard to the characteristics presented in Table 10. With approximately 60%, more men than women were enrolled in both study arms. Approximately 70% of the patients were enrolled in European study centres. The vast proportion of the patients had tumour stage IV at the time of diagnosis. Approximately 70% of the patients had an ECOG PS of 1. The proportion of patients with brain metastases at baseline or with bevacizumab pretreatment was small in the study (< 10%). The proportion of ex- or current smokers was approximately 65%.

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
LUME-Lung 1	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for the LUME-Lung 1 study. This concurs with the company's assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the present assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the symptom scales of the questionnaires EORTC QLQ-C30 and the EORTC QLQ-LC13
  - health status measured with the EQ-5D VAS
- Health-related quality of life measured with the functional scales of the EORTC QLQ-C30 questionnaire
- Adverse events

- SAEs
- severe AEs (CTCAE grade ≥ 3)
- discontinuation due to AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4A) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 12 shows for which outcomes data were available in the LUME-Lung 1 study included.

Table 12: Matrix of outcomes – RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel

Study	Outcomes						
	Overall survival	Symptoms[a]	Health status (EQ-5D VAS)	Health-related quality of life (disease-specific instrument)[b]	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs
LUME-Lung 1	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: Measured with the symptom scales of disease-specific instruments (EORTC QLQ-C30 and QLQ-LC13).
b: Measured using the EORTC QLQ-C30.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; QLQ-LC13: Quality of Life Questionnaire-LC13; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

2.4.2 Risk of bias

Table 13 shows the risk of bias for these outcomes.

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel

Study		Outcomes						
	Study level	Overall survival	Symptoms[a]	Health status (EQ-5D VAS)	Health-related quality of life (disease-specific instrument)[b]	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs
LUME-Lung 1	L	L	H[c]	H[d]	H[c]	H[c]	H[c]	H[c]

a: Recorded with the symptom scales of disease-specific instruments (EORTC QLQ-C30 and QLQ-LC13).
b: Recorded using the disease-specific instrument EORTC QLQ-C30.
c: Informative censoring due to different observational periods.
d: High proportion of missing values at the end of the range of analysis; no justification for the choice of the range of analysis.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; H: high; L: low; QLQ-C30: Quality of Life Questionnaire-C30 QLQ-LC13: Quality of Life Questionnaire-LC13; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

For all outcomes considered to be relevant for the assessment, data were available in the dossier.

Only one study was available for the assessment of nintedanib. The LUME-Lung 1 study did not meet the particular requirements placed on the derivation of proof of an added benefit from a single study [1]. Hence, at most indications, e.g. of an added benefit, can be derived from the data.

Due to the different observation periods resulting from the different treatment durations between the nintedanib + docetaxel arm and the placebo + docetaxel arm (median treatment durations: 4.3 months in the nintedanib + docetaxel arm, and 3.0 months in the placebo + docetaxel arm) and the respective follow-up, the study results for all outcomes – except for overall survival – were assessed to have a high risk of bias.

This assessment deviates from that of the company, which assessed the risk of bias for all outcomes as low.

2.4.3 Results

Table 14 to Table 18 summarize the results on the comparison of nintedanib + docetaxel and placebo + docetaxel in adult patients with locally advanced, metastatic or locally recurrent

NSCLC of adenocarcinoma histology after first-line chemotherapy. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Table 14: Results (overall survival) – RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel

Study Outcome	Nintedanib + docetaxel		Placebo + docetaxel		Nintedanib + docetaxel vs. placebo + docetaxel	
	N	Median survival time in months [95% CI]	N	Median survival time in months [95% CI]	HR [95% CI]	p-value
LUME-Lung 1						
Mortality						
Overall survival	322	12.6 [10.6; 15.1]	336	10.3 [8.6; 12.2]	0.83 [0.70; 0.99]	0.036
CI: confidence interval; HR: hazard ratio; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus						

Table 15: Results (morbidity: symptoms) – RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel

Study Outcome	Nintedanib + docetaxel		Docetaxel + placebo		Nintedanib + docetaxel vs. docetaxel + placebo
	N	Median (months) [95% CI] Patients with events n (%)	N	Median (months) [95% CI] Patients with events n (%)	HR [95% CI][a]; p-value
LUME-Lung 1					
Morbidity					
EORTC QLQ-C30 symptom scales – time to worsening of symptoms					
Appetite loss	322	2.1 [1.9; 2.8] 194 (60.2)	336	3.0 [2.3; 3.8] 180 (53.6)	1.15 [0.94; 1.40]; 0.178
Diarrhoea	322	2.1 [1.5; 2.3] 219 (68.0)	336	4.2 [3.5; 5.6] 154 (45.8)	1.90 [1.54; 2.34]; < 0.001
Dyspnoea	322	3.6 [2.8; 4.9] 177 (55.0)	336	3.6 [3.1; 4.9] 166 (49.4)	1.05 [0.85; 1.30]; 0.633
Fatigue	322	1.4 [1.4; 1.9] 230 (71.4)	336	2.1 [1.4; 2.4] 211 (62.8)	1.15 [0.95; 1.38]; 0.141
Insomnia	322	3.6 [2.8; 4.5] 176 (54.7)	336	3.5 [2.9; 4.2] 171 (50.9)	0.98 [0.80; 1.21]; 0.866
Pain	322	2.8 [2.3; 3.7] 206 (64.0)	336	2.8 [2.1; 3.5] 196 (58.3)	0.94 [0.77; 1.14]; 0.527
Nausea and vomiting	322	2.8 [2.2; 3.5] 197 (61.2)	336	3.8 [3.0; 4.4] 173 (51.5)	1.23 [1.00; 1.50]; 0.047
Constipation	322	5.1 [4.1; 7.6] 145 (45.0)	336	4.9 [3.6; 6.4] 140 (41.7)	0.91 [0.72; 1.14]; 0.401
EORTC QLQ-LC13 symptom scales – time to worsening of symptoms					
Haemoptysis	322	14.0 [7.8; NC] 98 (30.4)	336	9.0 [7.2; 11.8] 100 (29.8)	0.90 [0.68; 1.19]; 0.455
Dyspnoea	322	1.8 [1.4; 2.2] 222 (68.9)	336	2.1 [1.5; 2.2] 220 (65.5)	1.03 [0.86; 1.25]; 0.714
Alopecia	322	1.4 [1.2; 1.6] 218 (67.7)	336	1.0 [0.8; 1.4] 230 (68.5)	0.87 [0.72; 1.04]; 0.109
Cough	322	4.2 [3.3; 5.7] 168 (52.2)	336	4.2 [3.4; 5.1] 166 (49.4)	0.97 [0.78; 1.20]; 0.764
Sore mouth	322	4.3 [2.9; 6.0] 156 (48.4)	336	4.2 [3.5; 5.6] 145 (43.2)	1.02 [0.81; 1.28]; 0.847
Peripheral neuropathy	322	3.5 [2.8; 4.3] 176 (54.7)	336	3.7 [2.9; 4.5] 161 (47.9)	1.02 [0.83; 1.27]; 0.831
Dysphagia	322	7.9 [4.9; 10.9] 132 (41.0)	336	5.6 [4.2; 7.1] 136 (40.5)	0.92 [0.72; 1.17]; 0.480
Pain (arm/shoulder)	322	5.8 [4.3; 8.7] 143 (44.4)	336	4.2 [3.6; 4.9] 160 (47.6)	0.80 [0.63; 1.00]; 0.046

(continued)

Table 15: Results (morbidity: symptoms) – RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel (continued)

Study Outcome	Nintedanib + docetaxel		Docetaxel + placebo		Nintedanib + docetaxel vs. docetaxel + placebo
	N	Median (months) [95% CI] Patients with events n (%)	N	Median (months) [95% CI] Patients with events n (%)	HR [95% CI][a]; p-value
Pain (chest)	322	4.2 [2.8; 5.7] 170 (52.8)	336	4.2 [3.4; 5.0] 157 (46.7)	1.03 [0.83; 1.28]; 0.775
Pain (other parts)	322	5.1 [3.8; 6.2] 150 (46.6)	336	4.1 [3.4; 5.5] 153 (45.5)	0.86 [0.69; 1.08]; 0.184

a: Time to worsening of the score by at least 10 points versus the baseline value.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio from Cox regression; N: number of analysed patients; n: number of patients with worsening of the score by at least 10 points; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-C30; QLQ-LC13: Quality of Life Questionnaire-LC13; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 16: Results (morbidity: EQ-5D VAS) – RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel

Study Outcome category Outcome	Nintedanib + docetaxel		Placebo + docetaxel		Treatment effect nintedanib + docetaxel vs. placebo + docetaxel
	N[a]	mean[b] (SD)	N[a]	mean[b] (SD)	Mean difference of the AUC [95% CI]; p-value
LUME-Lung 1					
Morbidity					
Health status using the EQ-5D VAS	300	66.7 (ND)	319	66.7 (ND)	−0.0 [−1.6; 1.5][c]; 0.963

a: The EQ-5D VAS was assessed up to week 18. The number of patients who still participated in the assessment in week 18 was 169 under nintedanib + docetaxel, and 147 under placebo + docetaxel.
b: Mean value up to median follow-up time.
c: Estimator from longitudinal model adjusted for the stratification variables “ECOG status”, “bevacizumab pretreatment” and “brain metastases”; mean value up to median follow-up time, which was estimated with the AUC of the individual treatment profiles using the adjusted longitudinal model.

AUC: area under the curve; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; EQ-5D: European Quality of Life-5 Dimensions; N: number of patients who received a questionnaire at the start of the study and hence were included in the analysis; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

Table 17: Results (health-related quality of life) – RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel

Study Outcome	Nintedanib + docetaxel		Docetaxel + placebo		Nintedanib + docetaxel vs. docetaxel + placebo
	N	Median (months) [95% CI] Patients with events n (%)	N	Median (months) [95% CI] Patients with events n (%)	HR [95% CI]; p-value
LUME-Lung 1					
EORTC QLQ-C30 functional scales – time to worsening of health-related quality of life[a]					
Global health status	322	2.9 [2.4; 3.7] 195 (60.6)	336	2.8 [2.1; 3.0] 198 (58.9)	0.88 [0.72; 1.07]; 0.191
Emotional functioning	322	3.5 [2.8; 4.5] 175 (54.3)	336	3.8 [3.5; 4.9] 164 (48.8)	1.07 [0.86; 1.32]; 0.535
Cognitive functioning	322	2.8 [2.1; 3.5] 187 (58.1)	336	3.0 [2.6; 3.6] 177 (52.7)	1.03 [0.84; 1.27]; 0.770
Physical functioning	322	2.8 [2.4; 3.5] 191 (59.3)	336	2.8 [2.1; 3.6] 196 (58.3)	0.92 [0.75; 1.12]; 0.393
Role functioning	322	2.1 [1.5; 2.5] 217 (67.4)	336	2.1 [1.6; 2.8] 202 (60.1)	1.04 [0.86; 1.26]; 0.708
Social functioning	322	2.8 [2.3; 3.4] 195 (60.6)	336	2.8 [2.1; 3.4] 189 (56.3)	0.97 [0.80; 1.19]; 0.797

a: Time to worsening of the score by at least 10 points versus the baseline value.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio from Cox regression; N: number of analysed patients; n: number of patients with worsening of the score by at least 10 points; QLQ-C30: Quality of Life Questionnaire-C30; RCT: randomized controlled trial; vs.: versus

Table 18: Results (AEs) – RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel

Study Outcome	Nintedanib + docetaxel		Docetaxel + placebo		Nintedanib + docetaxel vs. docetaxel + placebo
	N	Median [days] [95% CI] Patients with events n (%)	N	Median [days] [95% CI] Patients with events n (%)	HR [95% CI]; p-value
LUME-Lung 1					
Adverse events[a]					
AEs	320	7.0 [5.0; 8.0] 308 (96.3)	333	8.0 [7.0; 8.0] 314 (94.3)	
SAEs	320	NC 111 (34.7)	333	NC 107 (32.1)	1.01 [0.78; 1.32]; 0.932
Severe AEs (CTCAE grade ≥ 3)	320	27.0 [21.0; 29.0] 243 (75.9)	333	29.0 [15.0; 40.0] 228 (68.5)	1.10 [0.92; 1.32]; 0.266
Discontinuation due to AEs	320	NC 67 (20.9)	333	NC 59 (17.7)	1.08 [0.76; 1.54]; 0.656

a: AEs are considered that occurred up to 28 days after the last study medication; then only SAEs associated with the study medication were recorded, and all AEs reported to the sponsor.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio from Cox regression; N: number of analysed patients; n: number of patients with event; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Mortality

Overall survival

A statistically significant difference in overall survival between nintedanib + docetaxel and placebo + docetaxel was shown in the LUME-Lung 1 study. The sensitivity analyses conducted by the company (see Section 2.7.2.2 of the full dossier assessment) did not contradict the results of the primary analysis on overall survival. In addition, there was an indication of an effect modification by the characteristic “presence of brain metastases”. For patients without brain metastases, this results in an indication of an added benefit of nintedanib + docetaxel in comparison with the ACT. For patients with brain metastases, there is no hint of an added benefit, an added benefit is therefore not proven for these patients (see Section 2.4.4).

This deviates from the company’s assessment, which overall derived an indication of an added benefit of nintedanib + docetaxel for the outcome “overall survival” for the approval population.

Morbidity

Symptoms (time to worsening)

The morbidity of the patients was recorded with the symptom scales of the disease-specific questionnaires EORTC QLQ-C30 and EORTC QLQ-LC13.

For each of the outcomes **"diarrhoea"** and **"nausea and vomiting"**, there was a statistically significant difference to the disadvantage of nintedanib + docetaxel for the time to worsening of the symptom. For both symptoms, this results in a hint of lesser benefit of nintedanib + docetaxel in comparison with the ACT; however, due to effect modifications in nausea and vomiting, this hint only applies to the subgroup of patients with brain metastases at baseline (see Section 2.4.4). This deviates from the company's assessment, which derived an indication of a disadvantage of nintedanib + docetaxel for the total target population (patients with adenocarcinoma histology) for each of the outcomes on diarrhoea and nausea and vomiting.

For the outcome **"pain (arm/shoulder)"**, there was a statistically significant difference in favour of nintedanib + docetaxel for the time to worsening of symptoms. The extent of the effect in this non-serious/non-severe outcome was no more than marginal. There was no statistically significant difference between the treatment groups for each of the outcomes "**pain (chest)", "pain"**, and "**pain (other parts)"**. In addition, there was proof of an effect modification by the characteristic "bevacizumab pretreatment" for the outcome **"pain (chest)"** (see Section 2.4.4). The extent of the effect in this non-serious/non-severe outcome was no more than marginal. Overall, no added benefit could be derived for any outcome from the category "pain" for nintedanib + docetaxel in comparison with the ACT. This deviates from the company's assessment, which derived an indication of added benefit of nintedanib + docetaxel for each of the outcomes "improvement of pain" and "worsening of pain in arm/shoulder".

There was no statistically significant difference between the treatment groups for the outcome **"appetite loss"**. However, there was proof of an effect modification by the characteristic "presence of brain metastases" for this outcome (see Section 2.4.4). For the group of patients with brain metastases at baseline, this results in a hint of lesser benefit of nintedanib + docetaxel in comparison with the ACT. For patients without brain metastases, there is no hint of an added benefit, an added benefit is therefore not proven for these patients. This deviates from the company's assessment, which overall derived no added benefit for this outcome.

There was no statistically significant difference between the treatment groups for the outcome **"constipation"**. However, there was proof of an effect modification by the characteristic "bevacizumab pretreatment" for this outcome (see Section 2.4.4). For patients with bevacizumab pretreatment, this results in a hint of an added benefit of nintedanib + docetaxel in comparison with the ACT. For patients without bevacizumab pretreatment, there is no hint of an added benefit, an added benefit is therefore not proven for these patients. This deviates from the company's assessment, which overall derived no added benefit for this outcome.

There was no statistically significant difference between the treatment options for any of the following outcomes: **dyspnoea, fatigue, insomnia, haemoptysis, alopecia, cough, sore mouth, peripheral neuropathy** and **dysphagia**. This results in no hint of an added benefit of nintedanib + docetaxel in comparison with the ACT, an added benefit for these outcomes is therefore not proven. This concurs with the company's assessment.

Health status

Health status was determined with the VAS for self-assessment of the current health status from the EQ-5D. There was no statistically significant difference between the treatment groups. This results in no hint of an added benefit of nintedanib + docetaxel in comparison with the ACT, an added benefit is therefore not proven. This assessment concurs with that of the company, which allocated the results based on the VAS to health-related quality of life, however.

Health-related quality of life (time to worsening)

There was no statistically significant difference between the treatment groups for any of the following outcomes: **global health status, emotional functioning, cognitive functioning, physical functioning, role functioning** and **social functioning**. This results in no hint of an added benefit of nintedanib + docetaxel in comparison with the ACT, an added benefit for these outcomes is therefore not proven. This concurs with the company's assessment.

Adverse events

An overview of the most common AEs, SAEs, severe AEs, and discontinuations due to AEs can be found in Appendix B of the full dossier assessment.

Serious adverse events, severe adverse events (CTCAE grade ≥ 3) and discontinuation due to adverse events

There was no statistically significant difference between the treatment groups regarding the outcomes **"SAEs"** and **"discontinuation due to AEs"**. This results in no hint of greater or lesser harm of nintedanib + docetaxel in comparison with the ACT for these outcomes, an added benefit is therefore not proven. This concurs with the company's assessment.

There was no statistically significant difference between the treatment groups for the outcome **"severe AEs"** (CTCAE grade ≥ 3). However, there was proof of an effect modification by the characteristic "sex" for this outcome (see Section 2.4.4). For female patients, this results in a hint of greater harm from treatment with nintedanib + docetaxel in comparison with the ACT. For male patients, this results in no hint of greater or lesser harm of nintedanib + docetaxel in comparison with the ACT, an added benefit is therefore not proven for this patient group. This deviates from the company's assessment, which derived no added benefit for the outcome "severe AEs (CTCAE grade ≥ 3).

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered to be relevant for the present benefit assessment:

- age (< 65 years/≥ 65 years)
- sex (male/female)
- geographical region (Asia/South Africa/Europe)
- ECOG PS at baseline (0/1)
- brain metastases at baseline (yes/no)
- bevacizumab pretreatment (yes/no)
- smoking status (never-smoker/current smoker or ex-smoker)

Except for the subgroup characteristic "geographical region", all characteristics as well as their dimensions and cut-off values were predefined in the LUME-Lung 1 study.

Hereinafter, for the outcome "overall survival", only the results for subgroups are presented for which at least an indication of an effect modification was shown. There was a high risk of bias for the further outcomes used in the benefit assessment. Only subgroup analyses with proof of an interaction ($p < 0.05$) were included in the present benefit assessment to account for the uncertainty of the results (see Section 2.7.2.2 of the full dossier assessment).

Mortality

Overall survival

There was an indication of an effect modification by the characteristic "brain metastases at baseline" for the outcome "overall survival" (Table 19) (interaction test $p = 0.125$).

Table 19: Subgroups: outcome overall survival, RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel

Study Outcome	Nintedanib + docetaxel		Placebo + docetaxel		Nintedanib + docetaxel vs. placebo + docetaxel
Characteristic Subgroup	N	Median survival time in months [Q1; Q3] Patients with events n (%)	N	Median survival time in months [Q1; Q3] Patients with events n (%)	HR [95% CI]; p-value
LUME-Lung 1					
Overall survival					
Brain metastases					
Yes	26	6.8 [5.1; 17.9] 24 (92.3)	23	11.6 [5.7; 19.9] 18 (78.3)	1.27 [0.67; 2.38]; 0.460[a]
No	296	13.5 [5.6; 24.6] 235 (79.4)	313	10.3 [5.5; 19.9] 258 (82.4)	0.80 [0.67; 0.96]; 0.015[a]
				Interaction:	0.125

a: Institute's calculation, asymptotic.
CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; Q1: 25% quartile; Q3: 75% quartile; RCT: randomized controlled trial; vs.: versus

There was a statistically significant result in favour of nintedanib + docetaxel in comparison with placebo + docetaxel for patients without brain metastases. Since there is an indication of an effect modification and the subgroup result corresponds to the result of the total population (see Table 14), there is an indication of an added benefit of nintedanib + docetaxel in comparison with the ACT for the outcome "overall survival" in patients without brain metastases.

There was no statistically significant difference between the treatment groups for patients with brain metastases. Since regarding the effect estimation a reversed direction of effect in comparison with the total population was shown, there is no hint of an added benefit of nintedanib + docetaxel in comparison with docetaxel for these patients regarding overall survival, an added benefit is therefore not proven.

This deviates from the company's assessment, which overall derived an indication of an added benefit of nintedanib + docetaxel for the outcome "overall survival" for the approval population.

Morbidity

Time to worsening of symptoms

Table 20 and Table 21 show the results for the outcome category "morbidity (time to worsening of symptoms)" for which there is proof of an effect modification. Due to the high

risk of bias (see Section 2.7.2.2 of the full dossier assessment), at most a hint of an added benefit or of lesser benefit can be derived for all outcomes in this category.

Table 20: Subgroups: time to worsening of symptoms (EORTC QLQ-C30) by characteristic "brain metastases and bevacizumab pretreatment" – RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel

Study Outcome Characteristic Subgroup	Nintedanib + docetaxel N	Nintedanib + docetaxel Median in months [95% CI] Patients with events n (%)	Placebo + docetaxel N	Placebo + docetaxel Median in months [95% CI] Patients with events n (%)	Nintedanib + docetaxel vs. placebo + docetaxel HR [95% CI]; p-value
LUME-Lung 1					
Appetite loss					
Brain metastases					
Yes	26	1.6 [0.8; 3.4] 21 (80.8)	23	2.8 [1.4; NC] 11 (47.8)	2.35 [1.12; 4.94] 0.024[a]
No	296	2.2 [1.9; 2.9] 173 (58.4)	313	3.0 [2.3; 4.1] 169 (54.0)	1.08 [0.87; 1.33] 0.477[a]
				Interaction:	0.043
Nausea and vomiting					
Brain metastases					
Yes	26	1.6 [0.9; 3.7] 20 (76.9)	23	4.1 [2.5; 24.0] 11 (47.8)	2.72 [1.26; 5.86] 0.011[a]
No	296	2.9 [2.2; 3.6] 177 (59.8)	313	3.7 [2.9; 4.4] 162 (51.8)	1.15 [0.93; 1.42] 0.196[a]
				Interaction:	0.031
Constipation					
Bevacizumab pretreatment					
Yes	24	NC [2.1; NC] 8 (33.3)	21	3.0 [0.8; 6.4] 11 (52.4)	0.33 [0.13; 0.82] 0.018[a]
No	298	5.0 [3.8; 7.3] 137 (46.0)	315	5.2 [3.8; 7.2] 129 (41.0)	0.97 [0.76; 1.24] 0.807[a]
				Interaction:	0.013

a: Institute's calculation, asymptotic.

CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NC: not calculable; RCT: randomized controlled trial; vs.: versus

Table 21: Subgroups: time to worsening of symptoms (EORTC QLQ-LC13) by characteristic "bevacizumab pretreatment" – RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel

Study Outcome Characteristic	Nintedanib + docetaxel		Placebo + docetaxel		Nintedanib + docetaxel vs. placebo + docetaxel
Subgroup	N	Median in months [95% CI] Patients with events n (%)	N	Median in months [95% CI] Patients with events n (%)	HR [95% CI]; p-value
LUME-Lung 1					
Pain (chest)					
Bevacizumab pretreatment					
Yes	24	NC [2.1; NC] 8 (33.3)	21	3.6 [0.8; 8.7] 10 (47.6)	0.38 [0.15; 0.98] 0.043[a]
No	298	3.7 [2.7; 5.2] 162 (54.4)	315	4.2 [3.4; 5.2] 147 (46.7)	1.11 [0.88; 1.38] 0.363[a]
				Interaction:	0.017

a: Institute's calculation, asymptotic.

CI: confidence interval; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-LC13; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NC: not calculable; RCT: randomized controlled trial; vs.: versus

Appetite loss

There was proof of an effect modification by the characteristic "presence of brain metastases at baseline" for the outcome "appetite loss" (interaction test $p = 0.043$). There was a statistically significant difference to the disadvantage of treatment with nintedanib + docetaxel for patients with brain metastases. There was no statistically significant difference between the 2 treatment groups in the group of patients without brain metastases. For patients with brain metastases, this results in a hint of a lesser benefit of nintedanib + docetaxel in comparison with the ACT. For patients without brain metastases, there is no hint of added benefit or lesser benefit of nintedanib + docetaxel in comparison with the ACT, an added benefit is therefore not proven for these patients.

The company derived no added benefit of nintedanib + docetaxel in comparison with the ACT for the outcome "appetite loss".

Nausea and vomiting

There was proof of an effect modification by the characteristic "brain metastases at baseline" for the outcome "nausea and vomiting" (interaction test $p = 0.031$). There was a statistically significant difference to the disadvantage of treatment with nintedanib + docetaxel for patients with brain metastases. There was no statistically significant difference between the 2 treatment groups in the group of patients without brain metastases.

For patients with brain metastases, this results in a hint of a lesser benefit for treatment with nintedanib + docetaxel in comparison with the ACT for the outcome "nausea and vomiting". For patients without brain metastases, there is no hint of added benefit or lesser benefit of nintedanib + docetaxel in comparison with the ACT, an added benefit is therefore not proven.

The company derived an indication of a disadvantage of treatment with nintedanib + docetaxel in comparison with treatment with docetaxel for the outcome "nausea and vomiting (time to worsening)" for the target population (patients with adenocarcinoma histology).

Constipation

There was proof of an effect modification by the characteristic "bevacizumab pretreatment" for the outcome "constipation" ($p = 0.013$). There was a statistically significant difference in favour of treatment with nintedanib + docetaxel for patients with bevacizumab pretreatment. There was no statistically significant difference between the 2 treatment groups in the group of patients without bevacizumab pretreatment.

For patients with bevacizumab pretreatment, this results in a hint of an added benefit of treatment with nintedanib + docetaxel in comparison with the ACT. For patients without bevacizumab pretreatment, there is no hint of added benefit or lesser benefit of nintedanib + docetaxel in comparison with the ACT, an added benefit is therefore not proven.

The company derived no added benefit of treatment with nintedanib + docetaxel in comparison with the ACT for the outcome "constipation".

Pain (chest)

There was proof of an effect modification by the characteristic "bevacizumab pretreatment" for the outcome "pain (chest)" ($p = 0.017$). There was a statistically significant difference in favour of treatment with nintedanib + docetaxel for patients with bevacizumab pretreatment. The effect estimation in this non-serious/non-severe outcome was no more than marginal, however. There was no statistically significant difference between the 2 treatment groups in the group of patients without bevacizumab pretreatment.

This results in no hint of an added benefit of nintedanib + docetaxel in comparison with the ACT, an added benefit for this outcome is therefore not proven. This concurs with the company's assessment.

Adverse events

Severe AEs (CTCAE grade ≥ 3)

There was proof of an effect modification by the characteristic "sex" for the outcome "severe AEs (CTCAE grade ≥ 3)" (interaction test $p = 0.024$; Table 22).

Table 22: Subgroups: AEs CTCAE grade ≥ 3 by characteristic "sex" – RCT, direct comparison: nintedanib + docetaxel vs. placebo + docetaxel

Study Outcome Characteristic Subgroup	Nintedanib + docetaxel N	Nintedanib + docetaxel Median [95% CI] Patients with events n (%)	Placebo + docetaxel N	Placebo + docetaxel Median [95% CI] Patients with events n (%)	Nintedanib + docetaxel vs. placebo + docetaxel HR [95% CI]; p-value
LUME-Lung 1					
Severe AEs (CTCAE grade ≥ 3)					
Sex					
Female	119	15.0 [8.0; 26.0] 103 (86.6)	126	22.5 [9.0; 43.0] 89 (70.6)	1.44 [1.08; 1.91] 0.012[a]
Male	201	30.0 [23.0; 45.0] 140 (69.7)	207	29.0 [15.0; 50.0] 139 (67.1)	0.95 [0.75; 1.20] 0.669[a]
				Interaction:	0.024

a: Institute's calculation, asymptotic.
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; vs.: versus

There was a statistically significant difference to the disadvantage of treatment with nintedanib + docetaxel for female patients. There was no statistically significant difference between the 2 treatment groups in the group of male patients.

For female patients, this results in a hint of greater harm from treatment with nintedanib + docetaxel in comparison with the ACT for the outcome "severe AEs". For male patients, this results in no hint of greater or lesser harm of nintedanib + docetaxel in comparison with the ACT, an added benefit is therefore not proven.

The company derived no added benefit of treatment with nintedanib + docetaxel in comparison with the ACT for the outcome "severe AEs (CTCAE grade ≥ 3)".

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 resulted in indications or hints of an added benefit of nintedanib + docetaxel in comparison with docetaxel for the outcomes “overall survival” and “constipation”. Hints of lesser benefit were shown for the following outcomes: diarrhoea, appetite loss, nausea/vomiting and severe AEs.

Effect modifications were shown for the characteristics “brain metastases at baseline” “bevacizumab pretreatment” and “sex”. The extent of the respective added benefit at outcome level was estimated from these results (see Table 23).

Table 23: Extent of added benefit at outcome level: nintedanib + docetaxel vs. docetaxel

Outcome category **Outcome**	**Nintedanib + docetaxel vs. placebo + docetaxel** **Proportion of events**[a] **effect estimate [95% CI]** **p-value** **probability**[b]	**Derivation of extent**[c]
Mortality		
Overall survival		
Brain metastases - Yes	HR: 1.27 [0.67; 2.38] p = 0.460[d]	Lesser benefit/added benefit not proven
Brain metastases - No	Median survival [months]: 13.5 vs. 10.3 HR: 0.80 [0.67; 0.96] p = 0.015[d] probability: "indication"	Outcome category "mortality" $0.95 < CI_u < 1.00$ added benefit, extent "minor"
Morbidity		
EORTC QLQ-C30 and QLQ-LC13: time to worsening of symptoms		
Appetite loss		
Brain metastases - Yes	80.8% vs. 47.8% HR: 2.35 [1.12; 4.94] HR: 0.43 [0.20; 0.89][e] p = 0.024[d] probability: "hint"	Outcome category: non-serious/non-severe symptoms $0.80 < CI_u < 0.90$ lesser benefit, extent: "minor"
Brain metastases - No	HR: 1.08 [0.87; 1.33] p = 0.477[d]	Lesser benefit/added benefit not proven
Diarrhoea	68.0% vs. 45.8% HR: 1.90 [1.54; 2.34] HR: 0.53 [0.43; 0.65][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms $CI_u < 0.80$ lesser benefit, extent: "considerable"
Dyspnoea	QLQ-C30: HR: 1.05 [0.85; 1.30] p = 0.633	Lesser benefit/added benefit not proven
	QLQ-LC13: HR: 1.03 [0.86; 1.25] p = 0.714	Lesser benefit/added benefit not proven
Fatigue	HR: 1.15 [0.95; 1.38] p = 0.141	Lesser benefit/added benefit not proven
Insomnia	HR: 0.98 [0.80; 1.21] p = 0.866	Lesser benefit/added benefit not proven
Pain	HR: 0.94 [0.77; 1.14] p = 0.527	Lesser benefit/added benefit not proven

(continued)

Table 23: Extent of added benefit at outcome level: nintedanib + docetaxel vs. docetaxel (continued)

Outcome category **Outcome**	**Nintedanib + docetaxel vs. placebo + docetaxel** **Proportion of events[a]** **effect estimate [95% CI]** **p-value** **probability[b]**	**Derivation of extent[c]**
Nausea and vomiting		
Brain metastases - Yes	76.9% vs. 47.8% HR: 2.72 [1.26; 5.86] HR: 0.37 [0.17; 0.79][e] p = 0.011[d] probability: "hint"	Outcome category: non-serious/non-severe symptoms $CI_u < 0.80$ lesser benefit, extent: "considerable"
Brain metastases - No	HR: 1.15 [0.93; 1.42] p = 0.196[d]	Lesser benefit/added benefit not proven
Constipation		
Bevacizumab pretreatment - Yes	33.3% vs. 52.4% HR: 0.33 [0.13; 0.82] p = 0.018[d] probability: "hint"	Outcome category: non-serious/non-severe symptoms $0.80 < CI_u < 0.90$ added benefit, extent: "minor"
Bevacizumab pretreatment - No	HR: 0.97 [0.76; 1.24] p = 0.807[d]	Lesser benefit/added benefit not proven
Haemoptysis	HR: 0.90 [0.68; 1.19] p = 0.455	Lesser benefit/added benefit not proven
Alopecia	HR: 0.87 [0.72; 1.04] p = 0.109	Lesser benefit/added benefit not proven
Cough	HR: 0.97 [0.78; 1.20] p = 0.764	Lesser benefit/added benefit not proven
Sore mouth	HR: 1.02 [0.81; 1.28] p = 0.847	Lesser benefit/added benefit not proven
Peripheral neuropathy	HR: 1.02 [0.83; 1.27] p = 0.831	Lesser benefit/added benefit not proven
Dysphagia	HR: 0.92 [0.72; 1.17] p = 0.480	Lesser benefit/added benefit not proven
Pain (arm/shoulder)	HR: 0.80 [0.63; 1.00] p = 0.046	Outcome category: non-serious/non-severe symptoms $0.90 < CI_u < 1.00$ added benefit not proven

(continued)

Table 23: Extent of added benefit at outcome level: nintedanib + docetaxel vs. docetaxel (continued)

Outcome category **Outcome**	**Nintedanib + docetaxel vs. placebo + docetaxel** **Proportion of events[a]** **effect estimate [95% CI]** **p-value** **probability[b]**	**Derivation of extent[c]**
Pain (chest)		
Bevacizumab pretreatment - Yes	HR: 0.38 [0.15; 0.98] p = 0.043[d]	Outcome category: non-serious/non-severe symptoms $0.90 < CI_u < 1.00$ added benefit not proven
Bevacizumab pretreatment - No	HR: 1.11 [0.88; 1.38] p = 0.363[d]	Lesser benefit/added benefit not proven
Pain (other parts)	HR: 0.86 [0.69; 1.08] p = 0.184	Lesser benefit/added benefit not proven
EQ VAS: health status	Mean difference of the AUC: –0.0 [–1.6; 1.5] p = 0.963	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 functional scales – time to worsening		
Global health status	HR: 0.88 [0.72; 1.07] p = 0.191	Lesser benefit/added benefit not proven
Emotional functioning	HR: 1.07 [0.86; 1.32] p = 0.535	Lesser benefit/added benefit not proven
Cognitive functioning	HR: 1.03 [0.84; 1.27] p = 0.770	Lesser benefit/added benefit not proven
Physical functioning	HR: 0.92 [0.75; 1.12] p = 0.393	Lesser benefit/added benefit not proven
Role functioning	HR: 1.04 [0.86; 1.26] p = 0.708	Lesser benefit/added benefit not proven
Social functioning	HR: 0.97 [0.80; 1.19] p = 0.797	Lesser benefit/added benefit not proven
Adverse events		
SAEs	HR: 1.01 [0.78; 1.32] p = 0.932	Greater/lesser harm not proven

(continued)

Table 23: Extent of added benefit at outcome level: nintedanib + docetaxel vs. docetaxel (continued)

Outcome category **Outcome**	**Nintedanib + docetaxel vs. placebo + docetaxel** **Proportion of events**[a] **effect estimate [95% CI]** **p-value** **probability**[b]	**Derivation of extent**[c]
Severe AEs (CTCAE grade ≥ 3)		
Female	HR: 1.44 [1.08; 1.91] HR: 0.69 [0.52; 0.93][e] 86.6% vs. 70.6% p = 0.012[d] probability: "hint"	Outcome category: serious/severe AEs $0.90 < CI_u < 1.00$ greater harm, extent: "minor"
Male	HR: 0.95 [0.75; 1.20] p = 0.669[d]	Greater/lesser harm not proven
Treatment discontinuation due to AEs	HR: 1.08 [0.76; 1.54] p = 0.656	Greater/lesser harm not proven

a: Proportion of events provided if statistically significant differences were present.
b: Probability provided if statistically significant differences were present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: Institute's calculation, asymptotic.
e: Proportion of events nintedanib + docetaxel vs. placebo + docetaxel (reversed direction of effect to enable direct use of limits to derive the extent of added benefit).

AE: adverse event; AUC: area under the curve; CI: confidence interval; CI_u: upper limit of the CI; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ VAS: visual analogue scale of the European Quality of Life; HR: hazard ratio; QLQ-C30: Quality of Life Questionnaire-C30; QLQ-LC13: Quality of Life Questionnaire-LC13; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 24 summarizes the results that were considered in the overall conclusion on the extent of added benefit of nintedanib + docetaxel.

Table 24: Positive and negative effects from the assessment of nintedanib + docetaxel in comparison with docetaxel

Positive effects	Negative effects
Brain metastases - No ▪ indication of added benefit – extent: "minor" (mortality: overall survival)	Hint of lesser benefit – extent: "considerable" (non-serious/non-severe symptoms: diarrhoea)
Bevacizumab pretreatment - Yes ▪ hint of added benefit – extent: "minor" (non-serious/non-severe symptoms: constipation)	Brain metastases - Yes ▪ hint of lesser benefit – extent: "minor" (non-serious/non-severe symptoms: appetite loss) ▪ hint of lesser benefit – extent: "considerable" (non-serious/non-severe symptoms: nausea and vomiting)
	Sex – Women ▪ hint of greater harm – extent "minor" (serious/severe adverse events: serious adverse events)

In the overall assessment, there are positive and negative effects of different certainty of results and extent, partly for different subgroups. There are positive effects for patients without brain metastases in the outcome category "mortality" and – for patients with bevacizumab pretreatment – in the outcome category "non-serious/non-severe symptoms". Negative effects were shown for different subgroups in the outcome categories "non-serious/non-severe symptoms" and "serious/severe AEs".

Below, balancing of the positive and negative effects is conducted separately for patients with and without brain metastases at baseline.

Patients without brain metastases

There is an indication of minor added benefit for the outcome "overall survival" for patients without brain metastases. This is decisive because of the outcome category "mortality" and the greater certainty of results for this patient group on the side of positive results. On the negative side, this is offset to an important degree by a hint of lesser benefit with the extent "considerable" for the outcome "diarrhoea" (outcome category "non-serious/non-severe symptoms"). Due to the certainty of results, the negative effects cannot raise doubts about the positive effects so that overall there is an indication of minor added benefit of nintedanib + docetaxel in comparison with the ACT for patients without brain metastases.

Patients with brain metastases

There are several negative effects of the same certainty of results (hint) for patients with brain metastases. Due to the extent, the hint of lesser benefit with the extent "considerable" is decisive. On the positive side, this is offset by a hint of a minor added benefit (outcome category "non-severe/non-serious symptoms"), which only applies to the subgroup of patients with bevacizumab pretreatment, however. For this reason, the positive effect is unsuitable to

outweigh the negative effects so that there is a hint of lesser benefit of nintedanib + docetaxel in comparison with the ACT for patients with brain metastases.

The result of the assessment of the added benefit of nintedanib + docetaxel in comparison with the ACT is summarized in Table 25.

Table 25: Nintedanib + docetaxel – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Subgroup**	**Extent and probability of added benefit**
Nintedanib is used in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy	**Chemotherapy with docetaxel** or pemetrexed or gefitinib or erlotinib (only for patients with activating EGFR) or crizotinib (only for patients with activating ALK)	Patients without brain metastases	Indication of a minor added benefit
		Patients with brain metastases	Hint of lesser benefit
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer			

In summary, there is an indication of minor added benefit of nintedanib + docetaxel versus the ACT docetaxel for adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy who have not been diagnosed with brain metastases. In contrast, there is a hint of a lesser benefit in patients with brain metastases.

This deviates from the company's approach, which derived an indication of added benefit with the extent "considerable" for the total target population of nintedanib + docetaxel.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.6 List of included studies

LUME-Lung 1

Boehringer Ingelheim. LUME-Lung 1: BIBF 1120 plus docetaxel as compared to placebo plus docetaxel in 2nd line non small cell lung cancer; full text view [online]. In: ClinicalTrials.gov. 27 November 2014 [accessed: 5 March 2015]. URL: https://clinicaltrials.gov/ct2/show/NCT00805194.

Boehringer Ingelheim. LUME-Lung 1: BIBF 1120 plus docetaxel as compared to placebo plus docetaxel in 2nd line non small cell lung cancer; study results [online]. In: ClinicalTrials.gov. 27 November 2014 [accessed: 5 March 2015]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00805194.

Boehringer Ingelheim International. Multicentre, randomised, double-blind, Phase III trial to investigate the efficacy and safety of oral BIBF 1120 plus standard docetaxel therapy compared to placebo plus standard docetaxel therapy in patients withstage IIIB/IV or recurrent non small cell lung cancer after failure of first line chemotherapy [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 5 March 2015]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

Boehringer Ingelheim International. Multicentre, randomised, double-blind, Phase III trial to investigate the efficacy and safety of oral BIBF 1120 plus standard docetaxel therapy compared to placebo plus standard docetaxel therapy in patients with stage IIIB/IV or recurrent non small cell lung cancer after failure of first line chemotherapy [online]. In: EU Clinical Trials Register. [Accessed: 5 March 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-004803-36/DE.

Boehringer Ingelheim Pharma. Multicentre, randomised, double-blind, phase III trial to investigate the efficacy and safety of oral BIBF 1120 plus standard docetaxel therapy compared to placebo plus standard docetaxel therapy in patients with stage IIIB/IV or recurrent non small cell lung cancer after failure of first line chemotherapy (LUME-Lung 1): study 1199.13; clinical trial report (primary PFS analysis) [unpublished]. 2012.

Boehringer Ingelheim Pharma. Multicentre, randomised, double-blind, phase III trial to investigate the efficacy and safety of oral BIBF 1120 plus standard docetaxel therapy compared to placebo plus standard docetaxel therapy in patients with stage IIIB/IV or recurrent non small cell lung cancer after failure of first line chemotherapy (LUME-Lung 1): study 1199.13; clinical trial report (final OS analysis) [unpublished]. 2013.

Boehringer Ingelheim Pharma. Multicentre, randomised, double-blind, phase III trial to investigate the efficacy and safety of oral BIBF 1120 plus standard docetaxel therapy compared with placebo plus standard docetaxel therapy in patients with stage IIIB/IV or recurrent non-small cell lung cancer after failure of first-line chemotherapy (LUME-Lung 1): study 1199.13; final health economic report [unpublished]. 2014.

Reck M, Kaiser R, Mellemgaard A, Douillard JY, Orlov S, Krzakowski M et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. The Lancet Oncology 2014; 15(2): 143-155.

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Please see full dossier assessment for full reference list.

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