IQWiG Reports – Commission No. A22-05

Amivantamab (NSCLC) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Amivantamab (NSCLC) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 April 2022). 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.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Amivantamab (NSCLC) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
17 January 2022

Internal Commission No.
A22-05

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

Medical and scientific advice

- Ingo Schmidt-Wolf, University Hospital Bonn, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Marina Woeste
- Philip Kranz
- Sabine Ostlender
- Mattea Patt
- Dominik Schierbaum
- Dorothea Sow
- Volker Vervölgyi
- Kathrin Wohlhöfner

Keywords: Amivantamab, Carcinoma – Non-Small-Cell Lung, Benefit Assessment, NCT02609776, NCT02622581

Table of contents

Page

List of tables ..... **iv**
List of abbreviations ..... **v**
2 Benefit assessment **1**
2.1 Executive summary of the benefit assessment **1**
2.2 Research question **5**
2.3 Research question 1: patients for whom further chemotherapy is indicated **6**
2.3.1 Information retrieval and study pool 6
2.3.1.1 Evidence provided by the company 7
2.3.1.1.1 Comparison of individual arms from different studies 7
2.3.2 Results on added benefit 14
2.3.3 Probability and extent of added benefit 14
2.4 Research question 2: patients for whom no further chemotherapy is indicated **15**
2.4.1 Information retrieval and study pool 15
2.4.2 Results on added benefit 15
2.4.3 Probability and extent of added benefit 15
2.5 Probability and extent of added benefit – summary **16**
References for English extract **17**

List of tables[2]

Page

Table 2: Research questions of the benefit assessment of amivantamab 1
Table 3: Amivantamab – probability and extent of added benefit 4
Table 4: Research questions of the benefit assessment of amivantamab 5
Table 5: Amivantamab – probability and extent of added benefit 16

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BMI	body mass index
CRISP	Clinical Research platform Into molecular testing, treatment and outcome of (non-)Small cell lung carcinoma Patients
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IPTW	inverse probability of treatment weighting
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NGM	Network Genomic Medicine
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SCLC	small cell lung cancer
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

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 amivantamab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 17 January 2022.

Research question

The aim of the present report is to assess the added benefit of amivantamab as monotherapy in comparison with the appropriate comparator therapy (ACT) in adult patients with advanced (according to the G-BA, locally advanced or metastatic) non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based therapy.

The research questions shown in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of amivantamab

Research question	Subindication	ACT[a]
1	Adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations after failure of platinum-based chemotherapy for whom further chemotherapy is indicated[b]	**Docetaxel** or **docetaxel in combination with nintedanib** or **pemetrexed**
2	Adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations after failure of platinum-based chemotherapy for whom no further chemotherapy is indicated[b]	Best supportive care[c]

a. Presented is the respective ACT specified by the GBA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. In accordance with the G-BA, it is assumed that patients have no medical indication for definitive local therapy.
c. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

The company followed the G-BA specifications of the ACT for both research questions, and chose all treatment options specified by the G-BA for research question 1.

If necessary for better readability, the present benefit assessment uses the following terms for the patient populations of the research questions presented in Table 2:

- Research question 1: patients for whom further chemotherapy is indicated
- Research question 2: patients for whom no further chemotherapy is indicated

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Research question 1: patients for whom further chemotherapy is indicated

Results

Concurring with the company, the check of the completeness of the study pool produced no randomized controlled trials (RCTs) for the comparison of amivantamab with the ACT specified by the G-BA.

As the company did not identify any RCTs for a direct comparison or an adjusted indirect comparison using a common comparator between amivantamab and the ACT, it conducted an information retrieval for non-randomized, non-comparative clinical studies with amivantamab. The company identified the CHRYSALIS study. On the ACT side, the company did not identify any relevant evidence in its search for non-randomized, non-comparative clinical studies and non-interventional retrospective observational studies. However, this search by the company is not suitable for the reliable identification of such studies. The company stated that it had therefore entered into a cooperation with the Clinical Research platform Into molecular testing, treatment and outcome of (non-)Small cell lung carcinoma Patients (CRISP) registry as well as with the Network Genomic Medicine (NGM) research platform, in order to enable a comparison between amivantamab and the ACT on the basis of these registry data, taking into account the requirements of rapid report A19-43 (*Development of scientific concepts for the generation of routine practice data and their analysis for the benefit assessment of drugs according to §35a Social Code Book V*).

As the company considered the used CRISP and NGM registry studies to only provide information with limited informative value on safety and tolerability of the ACT, it also conducted an additional search for RCTs in patients with NSCLC and an EGFR wild type, any EGFR mutation and unclear EGFR status. In this search in the extended therapeutic indication, the company identified 16 RCTs with the ACT and used these individual arms of different studies for a descriptive comparison with the CHRYSALIS study for the assessment of adverse events (AEs).

None of the studies or analyses presented by the company is suitable for deriving an added benefit of amivantamab for the patients of research question 1 in the present therapeutic indication. This is explained below.

Comparison of individual arms from different studies

The company presented a comparison of individual arms from different studies, consisting of individual patient data on amivantamab from the uncontrolled CHRYSALIS study and individual patient data form the CRISP and NGM registries for representing the ACT.

Overall, however, the comparison presented by the company is not suitable for the derivation of an added benefit of amivantamab in comparison with the ACT specified by the G-BA. This is mainly due to the following aspects:

- The study pool on the ACT side is potentially incomplete.
- The inclusion criteria for identifying confounders are not appropriate with regard to the outcomes and the year of publication and may lead to an incompleteness of the relevant confounders.
- The registries lack data on patient characteristics that were used by the company for the selection of the patient population in the registry studies and were also partly identified as relevant confounders. The company's handling of missing data in the registry studies, which among other things affected the formation of the analysed patient populations and the adjustment for confounders, is not appropriate. In addition, due to the lack of information, it is not possible to assess the extent to which the drugs specified by the G-BA as ACT were administered in compliance with the Summaries of Product Characteristics (SPCs) and the guideline.
- Comparative data in the therapeutic indication under investigation are only available for the patient-relevant outcome of overall survival. A weighing of benefit and harm within the framework of the benefit assessment is therefore not possible on the basis of the data presented. Furthermore, the effects found for the outcome of overall survival are not large enough that they cannot be explained exclusively by systematic bias in the present data situation.

Overall, the comparison of individual arms from the CHRYSALIS study and the CRISP and NGM registries presented by the company does not allow an adequate comparison of amivantamab with the ACT.

Thus, there are no suitable data for the assessment of the added benefit of amivantamab for research question 1. This results in no hint of an added benefit of amivantamab compared with the ACT in adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations after failure of platinum-based chemotherapy for whom further chemotherapy is indicated. An added benefit for this research question is therefore not proven.

Research question 2: patients for whom no further chemotherapy is indicated

No data are available for the assessment of the added benefit of amivantamab in comparison with the ACT in adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations after failure of platinum-based chemotherapy for whom no

further chemotherapy is indicated. This results in no hint of an added benefit of amivantamab in comparison with the ACT; an added benefit is therefore not proven for this research question.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of the probability and extent of added benefit of amivantamab.

Table 3: Amivantamab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations after failure of platinum-based chemotherapy for whom further chemotherapy is indicated[b]	**Docetaxel** or **docetaxel in combination with nintedanib** or **pemetrexed**	Added benefit not proven
2	Adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations after failure of platinum-based chemotherapy for whom no further chemotherapy is indicated[b]	Best supportive care[c]	Added benefit not proven

a. Presented is the respective ACT specified by the GBA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. In accordance with the G-BA, it is assumed that patients have no medical indication for definitive local therapy.
c. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

The G-BA decides on the added benefit.

[3] 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). 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, added benefit not proven, or less benefit). For further details see [1,2].

2.2 Research question

The aim of the present report is to assess the added benefit of amivantamab as monotherapy in comparison with the ACT in adult patients with advanced (according to the G-BA, locally advanced or metastatic) NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy.

The research questions shown in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of amivantamab

Research question	Subindication	ACT[a]
1	Adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations after failure of platinum-based chemotherapy for whom further chemotherapy is indicated[b]	**Docetaxel** or **docetaxel in combination with nintedanib** or **pemetrexed**
2	Adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations after failure of platinum-based chemotherapy for whom no further chemotherapy is indicated[b]	Best supportive care[c]

a. Presented is the respective ACT specified by the GBA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. In accordance with the G-BA, it is assumed that patients have no medical indication for definitive local therapy.
c. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

The company followed the G-BA specifications of the ACT for both research questions, and chose all treatment options specified by the G-BA for research question 1.

If necessary for better readability, the present benefit assessment uses the following terms for the patient populations of the research questions presented in Table 4:

- Research question 1: patients for whom further chemotherapy is indicated
- Research question 2: patients for whom no further chemotherapy is indicated

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Research question 1: patients for whom further chemotherapy is indicated

2.3.1 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 lists on amivantamab (status: 16 December 2021)
- bibliographical literature search on amivantamab (last search on 16 November 2021)
- search in trial registries/trial results databases for studies on amivantamab (last search on 16 November 2021)
- search on the G-BA website for amivantamab (last search on 16 November 2021)
- study list on the ACT (status: 16 December 2021)
- bibliographical literature search on the ACT (last search on 16 November 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 1 December 2021)
- search on the G-BA website for the ACT (last search on 6 December 2021)

To check the completeness of the study pool:

- search in trial registries for studies on amivantamab (last search on 1 February 2022); for search strategies, see Appendix A of the full dossier assessment
- exploratory search to find out whether other disease registries exist in the therapeutic indication

Concurring with the company, the check of the completeness of the study pool produced no RCTs for the comparison of amivantamab with the ACT specified by the G-BA.

As the company did not identify any RCTs for a direct comparison or an adjusted indirect comparison using a common comparator between amivantamab and the ACT, it conducted an information retrieval for non-randomized, non-comparative clinical studies with amivantamab. The company identified the CHRYSALIS study. On the ACT side, the company did not identify any relevant evidence in its search for non-randomized, non-comparative clinical studies and non-interventional retrospective observational studies. However, this search by the company is not suitable for the reliable identification of such studies (see below). The company stated that it had therefore entered into a cooperation with the CRISP registry as well as with the NGM research platform, in order to enable a comparison between amivantamab and the ACT on the basis of these registry data, taking into account the requirements of rapid report A19-43 (*Development of scientific concepts for the generation of routine practice data and their analysis for the benefit assessment of drugs according to §35a Social Code Book V*) [3].

As the company considered the used CRISP and NGM registry studies to only provide information with limited informative value on safety and tolerability of the ACT, it also conducted an additional search for RCTs in patients with NSCLC and an EGFR wild type, any EGFR mutation and unclear EGFR status. In this search in the extended therapeutic indication, the company identified 16 RCTs with the ACT and used these individual arms of different studies for a descriptive comparison with the CHRYSALIS study for the assessment of AEs.

None of the studies or analyses presented by the company is suitable for deriving an added benefit of amivantamab for the patients of research question 1 in the present therapeutic indication. This is explained in the following sections.

2.3.1.1 Evidence provided by the company

2.3.1.1.1 Comparison of individual arms from different studies

The company presented a comparison of individual arms from different studies, consisting of individual patient data on amivantamab from the uncontrolled CHRYSALIS study and individual patient data form the CRISP and NGM registries for representing the ACT.

Overall, however, the comparison presented by the company is not suitable for the derivation of an added benefit of amivantamab in comparison with the ACT specified by the G-BA. This is mainly due to the following aspects:

- The study pool on the ACT side is potentially incomplete.
- The inclusion criteria for identifying confounders are not appropriate with regard to the outcomes and the year of publication and may lead to an incompleteness of the relevant confounders.
- The registries lack data on patient characteristics that were used by the company for the selection of the patient population in the registry studies and were also partly identified as relevant confounders. The company's handling of missing data in the registry studies, which among other things affected the formation of the analysed patient populations and the adjustment for confounders, is not appropriate. In addition, due to the lack of information, it is not possible to assess the extent to which the drugs specified by the G-BA as ACT were administered in compliance with the SPCs [4-6] and the guideline [7].
- Comparative data in the therapeutic indication under investigation are only available for the patient-relevant outcome of overall survival. A weighing of benefit and harm within the framework of the benefit assessment is therefore not possible on the basis of the data presented. Furthermore, the effects found for the outcome of overall survival are not large enough that they cannot be explained exclusively by systematic bias in the present data situation.

The evidence presented by the company is described below, providing reasons as to why the analyses are unsuitable for the assessment of the added benefit of amivantamab in comparison with the ACT. Further information on the study characteristics is presented in Appendix B of the full dossier assessment.

Data sources

Data source for the intervention amivantamab

Study CHRYSALIS

The CHRYSALIS study is an ongoing, uncontrolled, open-label, multicentre study [8-16]. It included adult patients with histologically or cytologically confirmed metastatic or unresectable NSCLC. Patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

The CHRYSALIS study had 2 parts. The aim of the first part (dose escalation) of the study was to determine the recommended phase 2 dose of amivantamab as monotherapy and of the combination therapies amivantamab + lazertinib or amivantamab + carboplatin + pemetrexed. The aim of the second part (dose expansion) of the study was to determine the safety, tolerability and antitumour activity of amivantamab as monotherapy or amivantamab + lazertinib.

For part 2 of the study, patients had to have measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Patients in part 2 of the study were enrolled in one of 7 cohorts (cohort A–D, MET-1, MET-2 or cohort E) depending on their mutation status and their prior therapy. Patients received either amivantamab as monotherapy (cohort A–D, MET-1 and MET-2) or amivantamab + lazertinib (cohort E). The combination therapies of amivantamab + lazertinib and amivantamab + carboplatin + pemetrexed investigated in the CHRYSALIS study are not relevant for the benefit assessment of amivantamab in the present therapeutic indication and, concurring with the company, are not considered further.

For the assessment of the added benefit of amivantamab in the present therapeutic indication, the company considered all patients from part 1 and 2 of the CHRYSALIS study with EGFR Exon 20 insertion mutations after failure of platinum-based chemotherapy who received amivantamab as monotherapy at the approved dose (analogous to the company, hereinafter referred to as “cohort D+”).

The patients in cohort D+ used by the company received intravenous amivantamab in compliance with the recommendations in the SPC [17]. Patients were treated until disease progression, unacceptable toxicity, or treatment discontinuation following the physician’s or patient’s decision.

The primary outcome of the study was the objective response rate. Secondary outcomes included overall survival as well as outcomes on symptoms, health-related quality of life and side effects.

Data cut-offs and analysis populations

In Module 4 A, the company presented 2 analysis populations of the D+ cohort separately for efficacy and side effect outcomes at the data cut-off from 30 March 2021 for the CHRYSALIS study. Analogous to the approval procedure [16], the analysis population for the main analysis on efficacy outcomes (n = 114) comprised patients who were included in the study until 4 June 2020 and either had ≥ 3 follow-up visits after the start of the study or discontinued therapy for any reason (including progression or death). The analysis population for side effect outcomes (n = 153) included all patients who had received at least one dose of the study medication (regardless of the date of study entry). For the data cut-off of 30 March 2021, the company considered an additional analysis population that comprised 10 additional patients who had been included after 4 June 2020 for the outcome of all-cause mortality. Moreover, the company presented analyses for efficacy outcomes for the data cut-off on 8 October 2020. The approach of the company to restrict the analysis of efficacy outcomes (including overall survival) to patients who fulfil the above-mentioned criteria (including a defined number of follow-up visits after the start of the study) is not appropriate. Rather, an analysis taking into account all patients would be adequate, analogous to the analysis population for outcomes on side effects.

Data sources for the appropriate comparator therapy

On the ACT side, the company used the registries CRISP [9,15,18-22] and NGM [9,15,21,23,24] as well as 16 RCTs in the extended therapeutic indication of NSCLC for analyses on side effect outcomes (see Section 2.3.1).

Registry study CRISP

CRISP is an ongoing, open-label, non-interventional, prospective, clinical registry involving about 150 centres in Germany. Patient inclusion started in 2015. The registry records data on molecular testing, treatment and course of disease of patients with NSCLC and small cell lung cancer (SCLC).

According to information provided by the company in Module 4 A, primary and secondary outcomes include overall survival, response, progression, time to subsequent therapy and AEs. According to the company, in the course of the cooperation with the registry operator, a prospective survey on safety and tolerability data was started from 29 April 2021 for the subpopulation analysed by the company in the present benefit assessment.

Data cut-offs and analysis populations

For the present benefit assessment, the company used a cohort from the CRISP registry that comprises patients with NSCLC EGFR Exon 20 insertion mutation after failure of platinum-based therapy. These patients had to fulfil the inclusion criteria of the CHRYSALIS study and have been treated with the ACT (docetaxel, docetaxel + nintedanib or pemetrexed). Patients could have received several therapy regimens with docetaxel, docetaxel + nintedanib or pemetrexed during the observation period. A patient was included in the main analysis of the company for each of these treatment lines – and thus possibly several times. The analysis

population of the company (main analysis) from the CRISP registry comprised 7 patients, each of whom was included in the analysis with only one treatment line. In Module 4 A, the company presented the data cut-off from 30 June 2021 for the CRISP registry study.

Registry study NGM

NGM is an ongoing, open-label, prospective registry with retrospective data collection. It was established in 2010 by the University Hospital of Cologne in a cooperation with over 300 regional hospitals and medical practices. The registry specializes in molecular pathological diagnostics of patients with lung cancer and collects both molecular and clinical data.

According to information provided by the company in Module 4 A, primary and secondary outcomes include overall survival, response, progression, time to subsequent therapy and AEs.

Data cut-offs and analysis populations

For the present benefit assessment, the company used a cohort from the NGM registry that comprises patients with NSCLC EGFR Exon 20 insertion mutation after failure of platinum-based therapy. These patients had to fulfil the inclusion criteria of the CHRYSALIS study and have been treated with the ACT (docetaxel, docetaxel + nintedanib or pemetrexed). Patients could have received several therapy regimens with docetaxel, docetaxel + nintedanib or pemetrexed during the observation period. A patient was included in the main analysis of the company for each of these treatment lines – and thus possibly several times. The analysis population of the company (main analysis) from the NGM registry therefore comprised 24 patients with 27 lines of treatment. In Module 4 A, the company presented the data cut-off from 8 July 2021 for the NGM registry study.

RCTs in the extended therapeutic indication of NSCLC for side effect outcomes

According to the company, prospective data on AEs from the CRISP registry study are only available for a limited documentation time (approximately 2 months). For the NGM registry study, the company stated that the documentation of AEs from patient records in the NGM registry cannot be compared to a regularly conducted systematic collection of safety and tolerability data in clinical studies. For these reasons, the company – as stated in Module 4 A – provided only a descriptive presentation of the results on the side effect outcomes from the registry studies (overall rates). Since only information with limited informative value on safety and tolerability was available within the scope of the registry studies used, the company conducted a supplementary information retrieval for RCTs and non-randomized controlled trials with the ACT in the therapeutic indication of NSCLC, irrespective of the presence of an EGFR mutation (NSCLC with EGFR wild type, any EGFR mutation or unclear EGFR status). In its supplementary information retrieval, the company identified the 16 RCTs CheckMate 078 [25], CTONG0806 [26], EMD 72000-031 [27], GALAXY-2 [28], H3E-MC-S103 [29], I4E-MC-JXBC [30], IND211 [31], INTEREST [32], NCI-2013-01128 [33], PARAMOUNT [34], PROLUNG [35], REVEL [36], TAILOR [37], TARGET [38], TARSEQ (GFPC 10.02) [39] and ZODIAC [40], and used individual arms of these studies for a descriptive comparison

with the CHRYSALIS study. For this purpose, the company assumed that AEs occur independently of the mutation status during treatment with a specific medication and that, in the absence of data on the specific mutation, the side effects in similar therapeutic indications can therefore be used.

The company's approach is not appropriate. Data on side effects from other therapeutic indications of NSCLC cannot be transferred per se to the present therapeutic indication. As the company did not adequately prepare the comparison, it is unclear, for example, to what extent the patient populations of the 16 RCTs used for the comparison are sufficiently similar to the patients with Exon 20 insertion mutation in the CHRYSALIS study with regard to prognostic factors (e.g. tumour status, prior therapies). Irrespective of this, the purely descriptive comparison of results on AEs from different studies is not suitable for the benefit assessment, as it does not allow valid comparative conclusions on side effects. These 16 studies and the analyses presented by the company for these studies are therefore not considered further.

Assessment of the evidence presented by the company

Study pool of the company is potentially incomplete

The information retrieval of the company does not guarantee the completeness of the study pool on the ACT side with regard to the registries (registry studies) or non-comparative clinical studies and non-interventional retrospective observational studies.

On the one hand, this is due to the fact that the company used a search filter in bibliographical databases that is only suitable for identifying studies with non-randomized comparator groups. Thus, by using this filter, neither non-comparative studies nor registry studies can be reliably identified. On the other hand, the search for non-comparative clinical studies and non-interventional retrospective observational studies described by the company would not be sufficient to ensure the completeness of the study pool on the ACT side. In order to ensure a complete identification of further investigations on the ACT in the present therapeutic indication, it would have been necessary overall not to make any restriction with regard to study types, or to additionally search specifically for registries and registry studies. The fact that the company's information retrieval did not guarantee the completeness of the study pool on the ACT side is also shown by the fact that the company did not identify the CRISP and NGM registries it used. Rather, the company selectively entered into a cooperation with the CRISP and NGM registry operators.

An exploratory search and a review of the approval documents show that further potentially relevant studies or registries exist for the present therapeutic indication. For example, for the European approval of amivantamab, the company submitted data on a retrospective cohort in the relevant therapeutic indication from the Flatiron registry in addition to the CHRYSALIS study to the European Medicines Agency (EMA) [16]. The company did not explain in the dossier why it did not consider this registry study for the present benefit assessment. In addition, other registries (e.g. Fred Hutch Cancer Surveillance System [41], Thoracic Tumours Register

[RTT] [42]) exist in the therapeutic indication of NSCLC, which included patients possibly relevant to the present research question.

Overall, the study pool on the ACT side is therefore potentially incomplete. The company did not address this in the dossier and did not draw any consequences for the benefit assessment.

Confounders: identification and completeness

Since the necessary structural equality between the treatment groups is not guaranteed in non-randomized studies, group differences in possible confounders, i.e. factors that are related to both the treatment and outcomes and can thus alter the estimation of the treatment effect, must be taken into account in the estimation. The first prerequisite for this is that relevant confounders are systematically identified. Then it must be ensured that the data set used contains the necessary information on the identified confounders. Based on this, a possible biasing effect of confounders must then be taken into account adequately using suitable adjustment methods (e.g. propensity score weighting).

Confounder identification

In Module 4 A Section 4.3.2.3.2.3.1, the company stated that it had conducted a confounder analysis for the identification of relevant confounders that considered the overall survival of patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations. In accordance with the requirements of rapid report A19-43 [3], a systematic literature search had been conducted to identify potential confounding variables, according to the company. The identified confounding variables were supplemented and validated by expert interviews. In addition, according to the company, the causal relationships between the individual confounding variables were investigated and presented in a causal directed acyclic graph. Through the graphical representation, the company stated to have identified relevant confounding variables, which it used for adjustment in propensity score matching and multivariable regression.

The company's approach for the information retrieval of confounders is not appropriate. The search of the company may not be sensitive enough, especially with an additional search block on outcomes (search terms on survival and quality of life). This also applies to the restriction to the publication period from 2015 to 2020 for observational studies, and 2019 to 2020 for clinical practice guidelines and systematic reviews for the inclusion criterion of publication year [43], which was not justified by the company. In addition, the information retrieval was already conducted on 31 August 2020 [43] and therefore did not take into account the most recent period before submission of the dossier. This possibly leads to an incompleteness of the relevant confounders.

Completeness of the identified confounders in the data set used

The company identified the following relevant confounders in its information retrieval (listed from most to least relevant according to the company): ECOG PS, number of treatment lines, total number of metastases regardless of location, brain metastases in particular, age, Asian

family origin, body mass index (BMI), EGFR TP53 co-mutation, baseline anaemia, smoking, disease stage, sex, re-biopsy, programmed cell death ligand 1 (PD-L1) status, prognostic score, hepatic and renal insufficiency.

Data on the confounders ECOG status and BMI are lacking in the registries to a relevant extent. The company did not provide any information in its dossier on other confounders such as baseline anaemia, EGFR TP53 co-mutation, re-biopsy, prognostic score or hepatic and renal insufficiency, so that the proportion of patients with missing values remains unclear. The confounders identified as relevant by the company are therefore not complete in the present data set. The company did not draw sufficient conclusions from this for the benefit assessment (see following section).

Selection of patient populations, adjustment for confounders and handling of missing data by the company

In order to achieve homogeneity between the patient populations, the company first applied the inclusion and exclusion criteria of the CHRYSALIS study to the CRISP and NGM registry studies (restriction approach). The company excluded patients included in the registries from the analysis if laboratory values, certain comorbidities, other cancer diagnoses or the status of brain metastases violated the criteria defined in the CHRYSALIS study. The company then carried out a further adjustment for relevant confounders using the inverse probability of treatment weighting (IPTW) method based on the propensity score. However, according to the company, data on the expression of all inclusion and exclusion criteria were not available for all patients in the registries. If information on these criteria was missing in the registries, the company assumed values in the normal range and included these patients in its analyses.

The company's approach is not appropriate. A selection of patient populations based on an assumption of normal values is not adequate. On the one hand, it remains unclear how the company defined values in the normal range. On the other hand, the company did not specify in detail for which criteria and to what extent data were missing in the registries. Overall, it is therefore largely unclear how many patients in the registry studies fulfilled the applied inclusion or exclusion criteria purely on the basis of the assumption of normal values and were then included in the analyses presented by the company. At least for the inclusion criterion of ECOG PS, the company stated that data were missing for about 30% (CRISP registry) and 75% (NGM registry) of the patients considered and that an ECOG PS of 0 or 1 was assumed for these patients. The company presented sensitivity analyses that included only patients with documented ECOG PS of 0 or 1. However, on the one hand, it also remained unclear in these sensitivity analyses to what extent patients were included in the analyses purely on the basis of the assumption of normal values in further inclusion or exclusion criteria. On the other hand, reporting of these sensitivity analyses was incomplete (including missing information on the overlap of the propensity scores of the compared patient populations).

Since the selection of the patient population was already based on the inadequate assumption of normal values in the absence of data, a detailed description of the methods for further confounder adjustment based on this assumption by the company is not provided.

Missing data on the appropriate comparator therapy

The registries contain no information on the dosages or the numbers of cycles patients received of the drugs docetaxel, docetaxel + nintedanib or pemetrexed, which the G-BA had specified as ACT. In the dossier, the company only stated that the prescribed therapy documented in the registry was at the discretion of the physician, taking into account the respective approval status. Therefore, it cannot be assessed to what extent these drugs were administered in compliance with the SPCs [4-6] and the guideline [7] and this corresponded to an adequate implementation of the ACT.

Comparative data only for patient-relevant outcome of overall survival

Irrespective of the deficiencies described above, in the present therapeutic indication, there are only comparative data for the patient-relevant outcome of overall survival. A weighing of benefit and harm within the framework of the benefit assessment is therefore not possible on the basis of the data presented. Furthermore, the effects found for the outcome of overall survival are not large enough that they cannot be explained exclusively by systematic bias in the present data situation.

Summary

Overall, the data presented by the company are not suitable for the benefit assessment and do not allow an adequate comparison of amivantamab with the ACT.

2.3.2 Results on added benefit

No suitable data are available for the assessment of the added benefit of amivantamab in comparison with the ACT in adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations after failure of platinum-based chemotherapy for whom further chemotherapy is indicated. This results in no hint of an added benefit of amivantamab in comparison with the ACT; an added benefit is therefore not proven for this research question.

2.3.3 Probability and extent of added benefit

As no suitable data are available for the assessment of the added benefit of amivantamab in comparison with the ACT in adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations after failure of platinum-based chemotherapy for whom further chemotherapy is indicated, an added benefit of amivantamab for research question 1 is not proven.

This deviates from the assessment of the company, which derived a hint of a non-quantifiable added benefit of amivantamab in comparison with the ACT for research question 1.

2.4 Research question 2: patients for whom no further chemotherapy is indicated

2.4.1 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 lists on amivantamab (status: 16 December 2021)
- bibliographical literature search on amivantamab (last search on 16 November 2021)
- search in trial registries/trial results databases for studies on amivantamab (last search on 16 November 2021)
- search on the G-BA website for amivantamab (last search on 16 November 2021)
- study list on the ACT (status: 16 December 2021)
- bibliographical literature search on the ACT (last search on 16 November 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 1 December 2021)
- search on the G-BA website for the ACT (last search on 6 December 2021)

To check the completeness of the study pool:

- search in trial registries for studies on amivantamab (last search on 1 February 2022); for search strategies, see Appendix A of the full dossier assessment

No relevant study was identified from the check. The company also identified no suitable studies.

2.4.2 Results on added benefit

No data are available for the assessment of the added benefit of amivantamab in comparison with the ACT in adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations after failure of platinum-based chemotherapy for whom no further chemotherapy is indicated. This results in no hint of an added benefit of amivantamab in comparison with the ACT; an added benefit is therefore not proven for this research question.

2.4.3 Probability and extent of added benefit

As no data are available for the assessment of the added benefit of amivantamab in comparison with the ACT in adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations after failure of platinum-based chemotherapy for whom no further chemotherapy is indicated, an added benefit of amivantamab for research question 2 is not proven.

This concurs with the company’s assessment.

2.5 Probability and extent of added benefit – summary

Table 5 summarizes the result of the assessment of added benefit of amivantamab in comparison with the ACT.

Table 5: Amivantamab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations after failure of platinum-based chemotherapy for whom further chemotherapy is indicated[b]	**Docetaxel** or **docetaxel in combination with nintedanib** or **pemetrexed**	Added benefit not proven
2	Adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations after failure of platinum-based chemotherapy for whom no further chemotherapy is indicated[b]	Best supportive care[c]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. In accordance with the G-BA, it is assumed that patients have no medical indication for definitive local therapy.
c. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Konzepte zur Generierung versorgungsnaher Daten und deren Auswertung zum Zwecke der Nutzenbewertung von Arzneimitteln nach § 35a SGB V; Rapid Report [online]. 2020 [Accessed: 02.06.2020]. URL: https://www.iqwig.de/download/A19-43_Versorgungsnahe-Daten-zum-Zwecke-der-Nutzenbewertung_Rapid-Report_V1-1.pdf.

4. AxioNovo. Fachinformation Docetaxel Axios 20 mg/ml. Stand: September 2020. URL: https://www.fachinfo.de.

5. Boehringer Ingelheim International. Fachinformation Vargatef Weichkapseln. Stand: April 2021 [online]. URL: https://www.fachinfo.de.

6. Seacross Pharma. Zusammenfassung der Merkmale des Arzneimittels. Pemetrexed Seacross 100mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung. Stand: Februar 2021.

7. Leitlinienprogramm Onkologie. Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms; Langversion 1.0; AWMF-Registernummer: 020/007OL [online]. 2018 [Accessed: 03.03.2022]. URL: https://www.awmf.org/uploads/tx_szleitlinien/020-007OL_1_S3_Lungenkarzinom_2018-03.pdf.

8. Janssen Cilag. CHRYSALIS - MARCH 2021 Datacut; study CHRYSALIS (EDI1001); Zusatzanalysen Teil 1 [unpublished].

9. Janssen Cilag. CHRYSALIS vs NGM; CHRYSALIS vs CRISP; CHRYSALIS vs Pooled NGM and CRISP; Datacut Chrysalis March 2021; Amivantamab vs G-BA Comparator; Zusatzanalysen Teil 2 [unpublished].

10. Park K, Haura EB, Leighl NB et al. Amivantamab in EGFR Exon 20 Insertion-Mutated Non-Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study. J Clin Oncol 2021; 39(30): 3391-3402. https://dx.doi.org/10.1200/jco.21.00662.

11. Janssen Research & Development. Study of Amivantamab, a Human Bispecific EGFR and cMet Antibody, in Participants With Advanced Non-Small Cell Lung Cancer [online]. 2022 [Accessed: 11.02.2022]. URL: https://ClinicalTrials.gov/show/NCT02609776.

12. Janssen Pharmaceutical. A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Subjects with Advanced Non-Small Cell Lung Cancer [online]. 2021 [Accessed: 11.02.2022]. URL: https://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-184169.

13. Janssen Research & Development. A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Subjects with Advanced Non-Small Cell Lung Cancer; study 61186372EDI1001; Interim Clinical Study Report [unpublished]. 2020.

14. Janssen Research & Development. A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Subjects with Advanced Non-Small Cell Lung Cancer; study 61186372EDI1001; Addendum to Interim Clinical Study Report dated 27 October 2020; Efficacy Analyses [08 October 2020 Cutoff] [unpublished]. 2020.

15. Janssen-Cilag. Amivantamab (Rybrevant); Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4 A; Erwachsene Patienten mit fortgeschrittenem nicht-kleinzelligem Lungenkarzinom (non-small cell lung cancer, NSCLC) und aktivierenden Exon-20-Insertionsmutationen des epidermalen Wachstumsfaktor-Rezeptors (EGFR) nach Versagen einer platinbasierten Therapie [online]. 2022. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/783/#dossier.

16. European Medicines Agency. Rybrevant; CHMP assessment report [online]. 2021 [Accessed: 04.02.2022]. URL: https://www.ema.europa.eu/documents/assessment-report/rybrevant-epar-public-assessment-report_en.pdf.

17. Janssen. Rybrevant 350 mg [online]. 2021 [Accessed: 21.01.2022]. URL: https://www.fachinfo.de.

18. AIO-Studien-gGmbH. Clinical Research Platform Into Molecular Testing, Treatment and Outcome of (Non-)Small Cell Lung Carcinoma Patients (CRISP) [online]. 2021 [Accessed: 08.03.2022]. URL: https://www.clinicaltrials.gov/ct2/show/NCT02622581.

19. AIO-Studien-gGmbH. Clinical Research platform Into melecular testing, treatment and outcome of non-Small cell lung carcinoma Patients; Project Plan; Version 5 [online]. 2020 [Accessed: 10.03.2022]. URL: https://www.pei.de/SharedDocs/Downloads/DE/awb/nis-0301-0400/0356-beoplan.pdf?__blob=publicationFile&v=2.

20. Griesinger F, Eberhardt W, Nusch A et al. Biomarker testing in non-small cell lung cancer in routine care: Analysis of the first 3,717 patients in the German prospective, observational, nation-wide CRISP Registry (AIO-TRK-0315). Lung Cancer 2021; 152: 174-184. https://dx.doi.org/10.1016/j.lungcan.2020.10.012.

21. Adjusted comparison of outcomes for Amivantamab in CHRYSALIS (EDI1001) versus standard of care in RWE sources in platinum-pretreated EGFR+ Exon20ins advanced NSCLC patients; Health Technology Assessment Statistical Analysis Plan - Germany [unpublished].

22. Janssen, AIO, iOMEDICO. Real world evidence study of treatment and prognostic patterns for patients with locally advanced or metastatic EGFR and EGFR Ex20ins mutated NSCLC with reference to the German CRISP registry"; (Study Protocol for prognostic and predictive values in non-small cell lung cancer (NCSLC) using Real-World-Evidence within German CRISP registry); Sub-study synopsis [unpublished].

23. Büttner R, Wolf J, Kron A. [The national Network Genomic Medicine (nNGM) : Model for innovative diagnostics and therapy of lung cancer within a public healthcare system]. Pathologe 2019; 40(3): 276-280. https://dx.doi.org/10.1007/s00292-019-0605-4.

24. Janssen, NGM. Retrospective cohort study of treatment and real-world outcomes for patients with advanced or metastatic EGFR Exon 20 insertion (EGFR Exon20ins) mutated Non-Small Lung Cancer NSCLC with reference to the German network for genomic medicine (NGM) [unpublished].

25. Wu YL, Lu S, Cheng Y et al. Nivolumab Versus Docetaxel in a Predominantly Chinese Patient Population With Previously Treated Advanced NSCLC: CheckMate 078 Randomized Phase III Clinical Trial. J Thorac Oncol 2019; 14(5): 867-875. https://dx.doi.org/10.1016/j.jtho.2019.01.006.

26. Zhou Q, Cheng Y, Yang JJ et al. Pemetrexed versus gefitinib as a second-line treatment in advanced nonsquamous nonsmall-cell lung cancer patients harboring wild-type EGFR (CTONG0806): a multicenter randomized trial. Ann Oncol 2014; 25(12): 2385-2391. https://dx.doi.org/10.1093/annonc/mdu463.

27. Schiller JH, von Pawel J, Schütt P et al. Pemetrexed with or without matuzumab as second-line treatment for patients with stage IIIB/IV non-small cell lung cancer. J Thorac Oncol 2010; 5(12): 1977-1985. https://dx.doi.org/10.1097/JTO.0b013e3181f4a5c9.

28. Pillai RN, Fennell DA, Kovcin V et al. Randomized Phase III Study of Ganetespib, a Heat Shock Protein 90 Inhibitor, With Docetaxel Versus Docetaxel in Advanced Non-Small-Cell Lung Cancer (GALAXY-2). J Clin Oncol 2020; 38(6): 613-622. https://dx.doi.org/10.1200/jco.19.00816.

29. Lee DH, Lee JS, Kim SW et al. Three-arm randomised controlled phase 2 study comparing pemetrexed and erlotinib to either pemetrexed or erlotinib alone as second-line treatment for never-smokers with non-squamous non-small cell lung cancer. Eur J Cancer 2013; 49(15): 3111-3121. https://dx.doi.org/10.1016/j.ejca.2013.06.035.

30. Kim ES, Neubauer M, Cohn A et al. Docetaxel or pemetrexed with or without cetuximab in recurrent or progressive non-small-cell lung cancer after platinum-based therapy: a phase 3, open-label, randomised trial. Lancet Oncol 2013; 14(13): 1326-1336. https://dx.doi.org/10.1016/s1470-2045(13)70473-x.

31. Bradbury PA, Morris DG, Nicholas G et al. Canadian Cancer Trials Group (CCTG) IND211: A randomized trial of pelareorep (Reolysin) in patients with previously treated advanced or metastatic non-small cell lung cancer receiving standard salvage therapy. Lung Cancer 2018; 120: 142-148. https://dx.doi.org/10.1016/j.lungcan.2018.03.005.

32. Kim ES, Hirsh V, Mok T et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008; 372(9652): 1809-1818. https://dx.doi.org/10.1016/s0140-6736(08)61758-4.

33. Li T, Piperdi B, Walsh WV et al. Randomized Phase 2 Trial of Pharmacodynamic Separation of Pemetrexed and Intercalated Erlotinib Versus Pemetrexed Alone for Advanced Nonsquamous, Non-small-cell Lung Cancer. Clin Lung Cancer 2017; 18(1): 60-67. https://dx.doi.org/10.1016/j.cllc.2016.10.003.

34. Gridelli C, Maione P, Rossi A. The PARAMOUNT trial: a phase III randomized study of maintenance pemetrexed versus placebo immediately following induction first-line treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small cell lung cancer. Rev Recent Clin Trials 2013; 8(1): 23-28. https://dx.doi.org/10.2174/1574887112079990040.

35. Arrieta O, Barrón F, Ramírez-Tirado LA et al. Efficacy and Safety of Pembrolizumab Plus Docetaxel vs Docetaxel Alone in Patients With Previously Treated Advanced Non-Small Cell Lung Cancer: The PROLUNG Phase 2 Randomized Clinical Trial. JAMA Oncol 2020; 6(6): 856-864. https://dx.doi.org/10.1001/jamaoncol.2020.0409.

36. Garon EB, Ciuleanu TE, Arrieta O et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 2014; 384(9944): 665-673. https://dx.doi.org/10.1016/s0140-6736(14)60845-x.

37. Garassino MC, Martelli O, Broggini M et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. Lancet Oncol 2013; 14(10): 981-988. https://dx.doi.org/10.1016/s1470-2045(13)70310-3.

38. Endocyte. Phase 2 Study of EC145 Alone Versus EC145+Docetaxel Versus Docetaxel Alone in Participants With FR(++) 2nd Line Non Small Cell Lung Cancer (TARGET) [online]. 2021 [Accessed: 08.03.2022]. URL: https://clinicaltrials.gov/ct2/show/NCT01577654.

39. Auliac JB, Chouaid C, Greillier L et al. Randomized open-label non-comparative multicenter phase II trial of sequential erlotinib and docetaxel versus docetaxel alone in patients with non-small-cell lung cancer after failure of first-line chemotherapy: GFPC 10.02 study. Lung Cancer 2014; 85(3): 415-419. https://dx.doi.org/10.1016/j.lungcan.2014.07.006.

40. Herbst RS, Sun Y, Eberhardt WE et al. Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): a double-blind, randomised, phase 3 trial. Lancet Oncol 2010; 11(7): 619-626. https://dx.doi.org/10.1016/s1470-2045(10)70132-7.

41. Fred Hutchinson Cancer Research Center. Cancer Surveillance System (CSS) [online]. [Accessed: 10.03.2022]. URL: https://www.fredhutch.org/en/research/divisions/public-health-sciences-division/research/epidemiology/cancer-surveillance-system.html.

42. Spanish Lung Cancer Group. Thoracic Tumours Register (RTT) [online]. 2021 [Accessed: 10.03.2022]. URL: https://clinicaltrials.gov/ct2/show/NCT02941458.

43. Xcenda, Amerisource Bergen. Systematic Literature Review for Confounders in Non-Small Cell Lung Cancer and Expert Validation; Final Report [unpublished]. 2021.

The full report (German version) is published under https://www.iqwig.de/en/projects/a22-05.html.