IQWiG Reports – Commission No. A19-83

# Atezolizumab (NSCLC; combination with bevacizumab, carboplatin and paclitaxel) –

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

## Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment Atezolizumab (NSCLC; Kombination mit Bevacizumab, Carboplatin und Paclitaxel) – Nutzenbewertung gemäß § 35a SGB V (Version 1.0; Status: 20 December 2019). 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 Cares

**Topic**

Atezolizumab (NSCLC; combination with bevacizumab, carboplatin and paclitaxel) – Benefit assessment according to §35a Social Code Book V

**Commissioning agency**

Federal Joint Committee

**Commission awarded on**

26 September 2019

**Internal Commission No.**

A19-83

**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.

**IQWiG employees involved in the dossier assessment**

- Vanessa Voelskow
- Judith Gibbert
- Charlotte Guddat
- Lisa Junge
- Marco Knelangen
- Annette Pusch-Klein
- Dominik Schierbaum
- Volker Vervölgyi

**Keywords:** Atezolizumab, Carboplatin, Paclitaxel, Bevacizumab, Carcinoma – Non-Small-Cell Lung, Benefit Assessment, NCT02366143, NCT00021060

# Table of contents

**List of tables**[2]

**Page**



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

**List of figures**

**Page**

**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| AE | adverse event |
| ALK | anaplastic lymphoma kinase |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DGHO | German Society of Haematology and Medical Oncology |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| EGFR | epidermal growth factor receptor |
| ESMO | European Society for Medical Oncology |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IC | immune cells |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| NOS | not otherwise specified |
| NSCLC | non-small cell lung cancer |
| PD-L1 | programmed cell death ligand 1 |
| PFS | progression-free survival |
| RCT | randomized controlled trial |
| SAE | serious adverse event |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SPC | Summary of product characteristics |
| TC | tumour cells |
| TPS | Tumour Proportion Score |

# 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 atezolizumab in combination with bevacizumab, paclitaxel and carboplatin. 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 26 September 2019.

### Research question

The aim of the present report is the assessment of the added benefit of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in comparison with the appropriate comparator therapy (ACT) as first-line treatment in adults with metastatic non-small cell lung cancer (NSCLC) with non-squamous histology. In patients with epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK)-positive NSCLC, atezolizumab in combination with bevacizumab, paclitaxel and carboplatin is only to be used after failure of the corresponding targeted therapies.

The research questions presented in Table 2 resulted from the appropriate ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin

| Research question | Therapeutic indication | ACT[a] |
|---|---|---|
| 1 | First-line treatment of metastatic non-squamous NSCLC in adults [b] with PD-L1 expression (TPS) < 50%[c] and adults[b] with EGFR- or ALK-positive tumour mutations after targeted pretreatment | Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)<br>or<br>**carboplatin in combination with** a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or **paclitaxel** or pemetrexed) see also Appendix VI to Section K of the pharmaceutical directive [1]<br>or<br>carboplatin in combination with nab-paclitaxel |
| 2 | First-line treatment of the metastatic non-squamous NSCLC in adults[b] with PD-L1 expression (TPS) ≥ 50%[c] without EGFR- or ALK-positive tumour mutations | Pembrolizumab as monotherapy |

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**.
b. For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy.
c. For treatment with atezolizumab, PD-L1 expressions of TC0/1/2 and IC0/1/2 are considered an approximation to a TPS < 50% or PD-L1 expressions of TC3 or IC3 are regarded as approximation to a TPS ≥ 50% (see Section 2.3.3).

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; IC: immune cells; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; TC tumour cells; TPS: Tumour Proportion Score

Research questions 1 and 2 of the present benefit assessment correspond to the company's subquestion 2 or 1. For easier presentation and better readability, the present benefit assessment uses the following terms for the research questions in the running text:

- Research question 1: Programmed-Cell-Death-Ligand-1 (PD-L1) expression (Tumour Proportion Score [TPS]) < 50% or EGFR- or ALK-positive after targeted pretreatment
- Research question 2: PD-L1 expression (TPS) ≥ 50% and no EGFR- or ALK-positive tumour mutations

For research question 1, the company specified the options of the G-BA presented in Table 4 as ACT. However, it deviated from the G-BA's specification insofar as it expanded the ACT of the G-BA by possible additional administration of bevacizumab (in addition to the respective platinum-containing double combination chemotherapy) as an alternative under consideration of the approval status for certain patients. Furthermore, the company considered the possibility of maintenance treatment with bevacizumab to be a necessary supplement to the ACT. The company's additions to the ACT were not followed. The benefit assessment of atezolizumab in

combination with bevacizumab, paclitaxel and carboplatin was conducted in comparison with the ACT.

For research question 2, the company followed the G-BA's specification of the ACT and cited monotherapy with pembrolizumab.

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

**Results**

**Research question 1: PD-L1 expression (TPS) < 50% or EGFR- or ALK-positive after targeted pretreatment**

The company presented no relevant data for the assessment of the added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin versus the ACT.

***Direct comparison***

The company used the IMpower150 study for the assessment of the added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin in patients with PD-L1 expression < 50% or EFGR or ALK-positive tumour mutations after targeted pretreatment. However, this randomized controlled trial (RCT) includes no comparison with the ACT specified by the G-BA, but a comparison with bevacizumab + paclitaxel + carboplatin. The IMpower150 study is thus unsuitable to answer research question 1 of the present benefit assessment according to the specification of the G-BA in direct comparison with the ACT.

***Indirect comparison***

Although in its point of view, bevacizumab should be included in the ACT, the company additionally presented an adjusted indirect comparison with carboplatin + paclitaxel via the common comparator bevacizumab + paclitaxel + carboplatin for the assessment of atezolizumab + bevacizumab + paclitaxel + carboplatin versus the ACT specified by the G-BA. The company's study pool comprised 2 RCTs. On atezolizumab + bevacizumab + paclitaxel + carboplatin, it included the IMpower150 study; on carboplatin + paclitaxel it included the study E4599.

The IMpower150 study is an ongoing 3-arm randomized, controlled, open-label, parallel-group study that started in 2015 on the comparison of atezolizumab + paclitaxel + carboplatin with or without bevacizumab with treatment with bevacizumab + paclitaxel + carboplatin. The study included adults with confirmed stage IV non-squamous NSCLC irrespective of PD-L1 expression and EGFR- or ALK-positive tumour mutation, although PD-L1 expression and EGFR and ALK status had to be known for an inclusion in the study. Patients with EGFR mutation or ALK translocation could only be included after disease progression or intolerance to a prior corresponding targeted therapy. Other pretreatments against stage IV of the NSCLC were not allowed. A total of 1202 patients were included and randomized in a 1:1:1 ratio either to treatment with atezolizumab + paclitaxel + carboplatin (arm A, irrelevant for the indirect comparison) (N = 402), with atezolizumab + bevacizumab + paclitaxel + carboplatin (arm B)

(N = 400) or with bevacizumab + paclitaxel + carboplatin (arm C) (N = 400). The company presented analyses on the total population and on a subpopulation referred to by it as NEM population. The NEM population comprised patients with an approximate PD-L1 expression < 50% (TPS), i.e. with TC0/1/2 and IC0/1/2 according to Ventana PD-L1(SP142) immunohistochemistry assay (hereinafter referred to as PD-L1 expression < 50%) or with EGFR- or ALK-positive tumour mutations. Complete data on the patient characteristics are only available for the total population.

The E4599 study is a randomized, controlled, open-label, parallel-group study conducted from 2001 to 2005 on the comparison of paclitaxel + carboplatin with bevacizumab + paclitaxel + carboplatin. The study included adults with NSCLC classified other than squamous NSCLC, confirmation of a non-squamous NSCLC was no inclusion criterion. Moreover, an advanced (stage IIIB with malignant pleural effusion), metastatic (stage IV) or recurrent disease had to be present upon study inclusion. Prior systemic chemotherapy was not allowed. PD-L1 expression and EGFR or ALK status were not recorded in study E4599. The study E4599 included a total of 878 patients, randomized in a 1:1 ratio either to treatment with paclitaxel + carboplatin (N = 444) or with bevacizumab + paclitaxel + carboplatin (N = 434).

*Differences in the treatment of NSCLC due to different study conduction periods*

The two RCTs IMpower150 and E4599 differ with regard to the period of study. There are about 12 years between the respective last data cut-offs of the two studies. Within this period, there were relevant changes or innovations in the treatment of NSCLC, which is reflected in differences in the pretreatments and subsequent therapies. Since the targeted therapies recommended today, such as tyrosine kinase inhibitors, angiogenesis inhibitors or immunotherapies, were not approved before 2001, such therapies were not available as pre-treatment for patients in study E4599. The IMpower150 study, in contrast, included patients with EGFR mutation or ALK translocation only after failure of a prior targeted therapy. In the total population of the IMpower150 study, approx. 14% (n = 110) of the patients had such mutation or translocation. For study E4599, the proportion of patients with EGFR- or ALK-positive tumour mutations for whom such a targeted therapy would basically have been an option prior to study inclusion was unclear. Moreover, there were further differences in treatment between the studies IMpower150 and E4599; for instance, in the number of patients with prior surgery in connection with their cancer. In IMpower150, for example, about half (382 of 800) of the patients included in the study had undergone surgery before being included in the study; in E4599, the proportion of these patients was about 20% (n = 164).

The main difference with regard to subsequent therapies is that the most commonly administered subsequent therapy in the respective common comparator arm (bevacizumab + paclitaxel + carboplatin) of the IMpower150 study was immunotherapy with a proportion of about 35% (n = 117). Moreover, in the IMpower150 study, a total of 9% (n = 61) of the patients without EGFR- or ALK-positive tumour mutations received targeted subsequent therapy across the intervention and common comparator arm. In late 2005, immunotherapies were not yet available on the market. Thus, these were not available to the patients included in the E4599

study as an option for subsequent therapy. Moreover, no information was available on whether, and if so, how many patients received targeted subsequent therapy approved within the study period from 2001 to 2005.

*Patient characteristics not sufficiently similar or verification of similarity not possible*

In line with the target population of atezolizumab + bevacizumab + paclitaxel + carboplatin, the IMpower150 study only included patients with non-squamous NSCLC. The E4599 study, in contrast, also included 19% of patients with unspecified carcinoma (histological type: "not otherwise specified" [NOS]), as a confirmation of non-squamous histology of the NSCLC was not an inclusion criterion for the E4599 study. Only patients with confirmed squamous cell carcinoma were excluded. It can thus not be ruled out that patients with NOS had squamous NSCLC. In this case, patients would not correspond to the patient population to be assessed according to the approval of atezolizumab + bevacizumab + paclitaxel + carboplatin. Additional specifications on the histology of the carcinoma, such as categorization as adenocarcinoma, are also only comparable to a limited extent due to the large proportion of NOS patients in the E4599 study. Almost all patients in the IMpower150 study had adenocarcinoma; in E4599, it were about 70%.

*Lack of information on other possibly predictive features for the check of similarity*

Apart from the described differences, conclusions on the similarity of the two studies are not possible for the possibly predictive features “smoking status”, “time since diagnosis of the disease” and “tumour size at baseline”. These features were only recorded in one of the two studies respectively. Comparison of the concomitant treatments between the studies was also impossible, since these had not been recorded in E4599.

*Summary*

Overall, the assumption of similarity is not sufficiently fulfilled due to the described differences between the studies IMpower150 and E4599 as well as uncertainties regarding other possibly predictive factors. Therefore, the adjusted indirect comparison of atezolizumab + bevacizumab + paclitaxel + carboplatin in comparison with the ACT is not usable.

There are thus no data for the benefit assessment suitable for a derivation of an added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin in comparison with the ACT.

**Research question 2: PD-L1 expression (TPS) ≥ 50% and no EGFR- or ALK-positive tumour mutations**

No data are available for the assessment of the added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin in comparison with the ACT as first-line treatment in adult patients with metastatic non-squamous NSCLC and PD-L1 expression (TPS) ≥ 50% without EGFR- or ALK-positive tumour mutations. Hence, there was no hint of an added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin in comparison with the ACT; an added benefit is therefore not proven.

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

Table 3 presents a summary of probability and extent of the added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin.

Table 3: Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin – probability and extent of added benefit

| Research question | Therapeutic indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|---|
| 1 | First-line treatment of metastatic non-squamous NSCLC in adults[b] with PD-L1 expression (TPS) < 50%[c] and adults[b] with EGFR- or ALK-positive tumour mutations after targeted pretreatment | Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)<br>or<br>**carboplatin in combination with** a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or **paclitaxel** or pemetrexed) see also Appendix VI to Section K of the pharmaceutical directive [1]<br>or<br>carboplatin in combination with nab-paclitaxel | Added benefit not proven |
| 2 | First-line treatment of metastatic non-squamous NSCLC in adults[b] with PD-L1 expression (TPS) ≥ 50%[c] without EGFR- or ALK-positive tumour mutations | Pembrolizumab as monotherapy | Added benefit not proven |

a. Presentation of the respective ACT specified by the G-BA.
b. For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy.
c. For treatment with atezolizumab, PD-L1 expressions of TC0/1/2 and IC0/1/2 are considered an approximation to a TPS < 50% or PD-L1 expressions of TC3 or IC3 are regarded as approximation to a TPS ≥ 50% (see Section 2.3.3).

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; IC: immune cells; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; TC tumour cells; TPS: Tumour Proportion Score

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 [2,3].

## 2.2 Research question

The aim of the present report is the assessment of the added benefit of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in comparison with the ACT as first-line treatment in adults with metastatic NSCLC with non-squamous histology. In patients with EGFR mutations or ALK-positive NSCLC, atezolizumab in combination with bevacizumab, paclitaxel and carboplatin is only to be used after failure of the corresponding targeted therapies.

The research questions presented in Table 4 resulted from the appropriate ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin

| **Research question** | **Therapeutic indication** | **ACT[a]** |
|---|---|---|
| 1 | First-line treatment of metastatic non-squamous NSCLC in adults [b] with PD-L1 expression (TPS) < 50%[c] and adults[b] with EGFR- or ALK-positive tumour mutations after targeted pretreatment | Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)<br>or<br>**carboplatin in combination with** a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or **paclitaxel** or pemetrexed) see also Appendix VI to Section K of the pharmaceutical directive [1]<br>or<br>carboplatin in combination with nab-paclitaxel |
| 2 | First-line treatment of metastatic non-squamous NSCLC in adults with PD-L1 expression (TPS) ≥ 50%[c] without EGFR- or ALK-positive tumour mutations | Pembrolizumab as monotherapy |

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**.
b. For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy.
c. For treatment with atezolizumab, PD-L1 expressions of TC0/1/2 and IC0/1/2 are considered an approximation to a TPS < 50% or PD-L1 expressions of TC3 or IC3 are regarded as approximation to a TPS ≥ 50% (see Section 2.3.3).

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; IC: immune cells; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; TC tumour cells; TPS: Tumour Proportion Score

Research questions 1 and 2 of the present benefit assessment correspond to the company's subquestion 2 or 1. For easier presentation and better readability, the present benefit assessment uses the following terms for the research questions in the running text:

- Research question 1: programmed cell death ligand 1 (PD-L1) expression (TPS) < 50% or EGFR- or ALK-positive after targeted pretreatment
- Research question 2: PD-L1 expression (TPS) ≥ 50% and no EGFR- or ALK-positive tumour mutations

For research question 1, the company specified the options of the G-BA presented in Table 4 as ACT. However, it deviated from the G-BA's specification insofar as it expanded the ACT of the G-BA by possible additional administration of bevacizumab (in addition to the respective platinum-containing double combination chemotherapy) as an alternative under consideration of the approval status for certain patients. Furthermore, the company considered the possibility of maintenance treatment with bevacizumab to be a necessary supplement to the ACT. The company's additions to the ACT were not followed (see Section 2.6.1 of the full dossier assessment). The benefit assessment of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin was conducted in comparison with the ACT.

For research question 2, the company followed the G-BA's specification of the ACT and cited monotherapy with pembrolizumab.

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

## 2.3 Research question 1: PD-L1 expression (TPS) < 50% or EGFR- or ALK-positive after targeted pretreatment

### 2.3.1 Information retrieval

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 atezolizumab (status: 9 August 2019)
- bibliographical literature search on atezolizumab (last search on 3 July 2019)
- search in trial registries for studies on atezolizumab (last search on 1 July 2019)
- bibliographical literature search on the ACT (last search on 3 July 2019)
- search in trial registries for studies on the ACT (last search on 1 July 2019)

To check the completeness of the study pool:

- search in trial registries for studies on atezolizumab (last search on 14/10/2019)

Concurring with the company, the check of the completeness of the study pool identified no study relevant for the direct comparison of atezolizumab + bevacizumab + paclitaxel + carboplatin with the ACT specified by the G-BA.

However, the company used the RCT IMpower150 for a direct comparison of atezolizumab + bevacizumab + paclitaxel + carboplatin in comparison with the ACT extended by it (see Section 2.2). Moreover, it presented an adjusted indirect comparison for the assessment of the added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin in comparison with one of the treatment options of the ACT specified by the G-BA (paclitaxel + carboplatin).

Neither the direct comparison nor the indirect comparison are suitable for the derivation of an added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin in comparison with the ACT specified by the G-BA. This is explained below.

### 2.3.2 Direct comparison

The company used the IMpower150 study for the assessment of the added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin in patients with PD-L1 expression < 50% or EFGR or ALK-positive tumour mutations after targeted pretreatment [4-10].

This RCT includes no comparison with the ACT specified by the G-BA, but a comparison with bevacizumab + paclitaxel + carboplatin. Section 2.3.3 provides a detailed description of the IMpower150 study. As justification for adding bevacizumab to the ACT specified by the G-BA, the company referred to the approval study E4599 on bevacizumab, which showed the efficacy of the treatment regimen bevacizumab + paclitaxel + carboplatin including maintenance treatment with bevacizumab [11]. The study BEYOND on patients of Chinese family origin also showed the superior efficacy of an administration of bevacizumab in addition to a platinum-containing combination chemotherapy [12]. Moreover, the efficacy of bevacizumab had been confirmed in 2 meta-analyses [13,14]. Furthermore, the company referred to 2 guidelines [15,16].

The company's additions to the ACT were not followed. According to the G-BA's consultation documents, additional administration of bevacizumab is no component of the standard therapy (platinum-containing chemotherapy) in the present therapeutic indication. Rather, the G-BA explicitly excluded bevacizumab from the ACT and justified this in particular with the fact that the guidelines describe bevacizumab (in addition to platinum-containing chemotherapy) merely as a possible treatment option for selected patients. The increased risk of side effects was offset by an unclear prolongation of overall survival. In addition, the G-BA pointed out that bevacizumab (in combination with platinum-containing chemotherapy) was not included in the ACT also in the decision on the benefit assessment of pembrolizumab, which was not criticized by the expert associations [17].

The company presented no references that called into question the assessment of the G-BA. The German S3 guideline describes that bevacizumab in combination with carboplatin and paclitaxel with subsequent maintenance treatment with bevacizumab may be considered an alternative for suitable patients under exclusion of relevant comorbidities associated with increased toxicity of bevacizumab [15]. Recommendations of other professional associations such as the German Society of Haematology and Medical Oncology (DGHO) or the European

Society for Medical Oncology (ESMO) [18,19] also go in this direction for the application of bevacizumab in the treatment setting.

The IMpower150 study is thus unsuitable to answer research question 1 of the present benefit assessment according to the specification of the G-BA in direct comparison with the ACT.

### 2.3.3 Indirect comparison

In its dossier, the company stated that there was presently no directly comparative evidence of atezolizumab + bevacizumab + paclitaxel + carboplatin versus the ACT specified by the G-BA. Although in its point of view, bevacizumab should be included in the ACT (see Section 2.3.2), the company additionally presented an adjusted indirect comparison versus carboplatin + paclitaxel for the assessment of atezolizumab + bevacizumab + paclitaxel + carboplatin versus the ACT specified by the G-BA. The company conducted the comparison via the common comparator bevacizumab + paclitaxel + carboplatin and included 1 RCT for atezolizumab + bevacizumab + paclitaxel + carboplatin and carboplatin + paclitaxel respectively (see Figure 1).

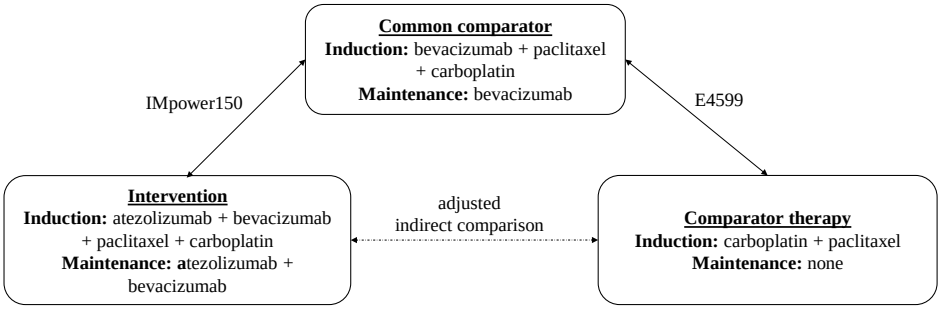


Figure 1: Study pool of the company for the indirect comparison of atezolizumab + bevacizumab + paclitaxel + carboplatin with carboplatin + paclitaxel

Overall, the studies IMpower150 and E4599 presented by the company for the indirect comparison were unsuitable for the derivation of an added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin versus the ACT, because the studies included were not similar enough.

The studies and their lacking suitability for the indirect comparison are described below. Further information on study, intervention and patient characteristics of the studies IMpower150 and E4599 [11,20-26] is presented in Appendix A of the full dossier assessment.

**Study IMpower150**

The IMpower150 study is an ongoing 3-arm randomized, open-label, parallel-group study on the comparison of atezolizumab + paclitaxel + carboplatin with or without bevacizumab including treatment with bevacizumab + paclitaxel + carboplatin. The study included adults with histologically or cytologically confirmed stage IV non-squamous NSCLC irrespective of PD-L1 expression and EGFR- or ALK-positive tumour mutation, although PD-L1 expression and EGFR and ALK status had to be known for an inclusion in the study. Another inclusion criterion was a good to at most slightly impaired general condition (Eastern Cooperative Oncology Group Performance Status [ECOG PS] ≤ 1) of the patients. Patients with EGFR mutation or ALK translocation could only be included after disease progression or intolerance to a prior corresponding targeted therapy. Other pretreatments against stage IV of the NSCLC were not allowed.

In the IMpower150 study, PD-L1 expression in the tumour tissue was determined centrally using a Ventana PD-L1(SP142) immunohistochemistry assay. Both the proportion of PD-L1-positive tumour cells (TC) and the proportion of PD-L1-positive immune cells (IC) are determined and placed in relation to the tumour area. The result of these calculations on the percentage of PD-L1-positive cells is divided into 4 categories each for TC and IC, ranging from category 0 for a missing or very low (< 1%) PD-L1 expression to category 3 for a high PD-L1 expression [27]. In the present benefit assessment, PD-L1 expression according to Ventana-SP142 of TC0/1/2 and IC0/1/2 is considered an approximation to the population according to the G-BA's research question with a Tumour Proportion Score (TPS) < 50%. Complementary to this, a PD-L1 expression of TC3 or IC3 according to Ventana-SP142 is assessed as an approximation to a PD-L1 expression ≥ 50% according to TPS [27-29].

In the IMpower150 study, the EGFR and ALK statuses were determined either centrally or locally in all patients during screening. The central tests were carried out using, for instance, the following kits: Ventana anti-ALK test (D5F3) (immunohistochemistry kit for the determination of the ALK status), Cobas V1 or V2 (both of them being Cobas EGFR mutation tests) and next generation sequencing (NGS).

In the IMpower150 study, a total of 1202 patients were included and randomized in a 1:1:1 ratio either to treatment with atezolizumab + paclitaxel + carboplatin (arm A) (N = 402), with atezolizumab + bevacizumab + paclitaxel + carboplatin (arm B) (N = 400) or with bevacizumab + paclitaxel + carboplatin (arm C) (N = 400). Arm A of IMpower150 was irrelevant for the presented adjusted indirect comparison and is thus not considered further. Randomization was stratified by sex (male vs female), liver metastases at the start of the study (yes vs. no) and PD-L1 expression (TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1).

Treatment was carried out according to the specifications of the SPC [30-32] both in the intervention arm (atezolizumab + bevacizumab + carboplatin + paclitaxel) and in the control arm (bevacizumab + paclitaxel + carboplatin); in the control arm, administration of carboplatin took place in compliance with the pharmaceutical directive for off-label use (Appendix VI to

Section K) [1]. In the intervention arm, the 4 or 6-cycle induction phase was followed by a maintenance phase with atezolizumab + bevacizumab. In the control arm, the patients received monotherapy with bevacizumab as maintenance treatment after termination of 4 or 6 cycles (see Table 10 of the full dossier assessment). There is no information on the number of patients who received such maintenance treatment.

Patients were treated until disease progression, occurrence of unacceptable toxicity, withdrawal of consent or death. However, further treatment with atezolizumab beyond disease progression was possible if, at the investigator's discretion, clinical benefit continued to exist. There were no recommendations regarding subsequent therapies.

Primary outcomes of the IMpower150 study were "overall survival" and "progression-free survival (PFS)" according to RECIST (version 1.1) recorded by the investigator. Patient-relevant outcomes of the categories "morbidity", "health-related quality of life" and "AEs" were also recorded. In the IMpower150 study, the severity of the AEs was rated based on version 4.0 of the Common Terminology Criteria for Adverse Events (CTCAE) criteria.

*(Sub-)populations analyzed by the company*

The company presented analyses on the total population and on a subpopulation referred to by it as NEM population. The NEM population comprised patients with an approximate PD-L1 expression < 50% (TPS), i.e. with TC0/1/2 and IC0/1/2 according to Ventana PD-L1(SP142) immunohistochemistry assay (hereinafter referred to as PD-L1 expression < 50%) or those with EGFR- or ALK-positive tumour mutations. The NEM population is the best possible approximation to the population in accordance with the research question of the G-BA. However, for the results on AEs, the company only presented results on the total population of the IMpower150 study.

The company used the results of the total population of the IMpower150 study for the derivation of the added benefit, arguing that there was a survival benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin irrespective of the PD-L1 status and that the proportion of patients with PD-L1 expressions < 50% in the total population was less than 20%.

*Data cut-offs*

Results on 2 data cut-offs were available for the IMpower150 study:

- 15 September 2017 (first data cut-off): final PFS analysis and first interim analysis for overall survival
- 22 January 2018 (second data cut-off): 2nd interim analysis for overall survival

On the first data cut-off, all outcomes presented by the company in the dossier were analyzed. Moreover, there are results on the 2nd data cut-off for the outcome "overall survival" as well as for the outcomes on AEs. Both data cut-offs were prespecified. The company used the last data cut-off for all outcomes presented in the dossier.

**Study E4599**

The E4599 study is a randomized, controlled, open-label, parallel-group study conducted from 2001 to 2005 on the comparison of paclitaxel + carboplatin with bevacizumab + paclitaxel + carboplatin. The study included adults with NSCLC classified other than squamous NSCLC, confirmation of a non-squamous NSCLC was no inclusion criterion. Moreover, an advanced (stage IIIB with malignant pleural effusion), metastatic (stage IV) or recurrent disease had to be present upon study inclusion. Another inclusion criterion was a good to slightly impaired general condition (ECOG-PS ≤ 1). Prior systemic chemotherapy was not allowed.

PD-L1 expression was not recorded in study E4599. The EGFR and ALK statuses are also unknown for the patients included in the E4599 study, as these were not determined.

The study E4599 included a total of 878 patients, randomized in a 1:1 ratio either to treatment with paclitaxel + carboplatin (N = 444) or with bevacizumab + paclitaxel + carboplatin (N = 434). Randomization was stratified by disease stage (stage IIIB with pleural effusion vs. stage IV or relapse), previous radiotherapy (yes vs. no), weight loss within the last 6 months (< 5% vs. ≥ 5%), and the presence of a measurable disease (yes vs. no) according to RECIST in the version according to [33].

Treatment with bevacizumab and paclitaxel was carried out according to the specifications of the SPCs on bevacizumab [32], and carboplatin was administered in compliance with the requirements of the Pharmaceutical Directive for off-label use (Appendix VI to Section K) [1]. Maximum treatment duration in the paclitaxel + carboplatin arm was 6 cycles without subsequent maintenance treatment. In the bevacizumab + paclitaxel + carboplatin arm, the induction phase comprising 6 cycles of the triple combination without progression of the disease was followed by a maintenance phase with bevacizumab. In the common comparator arm (bevacizumab + paclitaxel + carboplatin) 276 (63.6%) patients in the total population received > 5 cycles of bevacizumab during the induction and maintenance phase.

Within the framework of the described maximum treatment duration, patients were treated until disease progression or occurrence of unacceptable toxicity. There were no recommendations regarding subsequent therapies.

Overall survival was the primary outcome of study E4599. Other patient-relevant outcomes according to the protocol were the systematic recording of non-haematological AEs CTCAE grade 3-5 and haematological AEs CTCAE grade 4-5. The protocol required no regular reporting of other AEs by the investigators. In the E4599 study, the severity of the AEs was rated based on version 2.0 of the CTCAE criteria.

Since no information on PD-L1 expression, EGFR or ALK status was available for study E4599, the company used data from the entire population.

*Data cut-offs*

Three data cut-offs were performed for study E4599. The first two data cut-offs were interim analyses on overall survival (data cuts on 7 September 2004 and 9 February 2005), the third data cut-off was the final analysis. The final data cut-off took place on 30 December 2005.

The company used the respective final analysis for all outcomes presented in the dossier.

**Insufficient similarity of the studies IMpower150 and E4599 included by the company**

The studies IMpower150 and E4599 investigated atezolizumab + bevacizumab + paclitaxel + carboplatin or one of the options specified as ACT by the G-BA (paclitaxel + carboplatin). However, a prerequisite for an indirect comparison via an adequate common comparator is a sufficient similarity of the included studies. This similarity is missing for several characteristics. Data important for the assessment of the similarity are also missing.

***Differences in the treatment of NSCLC due to different study conduction periods***

The two studies IMpower150 and E4599 differ with regard to the period of study. There are about 12 years between the respective last data cut-offs of the two studies (see Table 9 of the full dossier assessment). Within this period, there were relevant changes or innovations in the treatment of NSCLC, which is reflected in differences in the pretreatments and subsequent therapies.

*Prior therapies*

Whereas in the IMpower150 study, patients with EGFR mutation or ALK translocation could only be included after failure of prior corresponding targeted therapy, targeted pretreatment of patients with EGFR mutation or ALK translocation was not possible in the E4599 study with the therapies recommended today, such as tyrosine kinase inhibitors, angiogenesis inhibitors or immunotherapies [15,34], as these were only approved after the start of the E4599 study in 2001. Moreover, for study E4599, the proportion of patients with EGFR- or ALK-positive tumour mutations for whom such a targeted therapy would basically have been an option was unclear. In the NEM population and the total population of the IMpower150 study, 17% (n = 110) or approx. 14% (n = 110) of the patients had such mutation or translocation. Moreover, there was another difference in treatment between the studies IMpower150 and E4599; for instance, in the number of patients with prior surgery in connection with their cancer. In IMpower150, for example, about half (382 of 800) of the patients included in the study had undergone surgery in connection with the cancer before being included in the study; in E4599, the proportion of these patients was about 20% (n = 164).

*Subsequent therapies*

There were also relevant differences between IMpower150 and E4599 regarding the subsequent therapies. The main difference is that the most commonly administered subsequent therapy in the common comparator arm (bevacizumab + paclitaxel + carboplatin) of the IMpower150 study was immunotherapy with a share of about 35% (n = 117). In the IMpower150 study, for

instance, about 30% (n = 98) of the patients in the common comparator arm received nivolumab as subsequent therapy. In addition, a total of 9% (n = 61) of the patients in the IMpower150 study received targeted subsequent therapy across the intervention and the common comparator arm. These figures refer to patients without EGFR- or ALK-positive tumour mutations and to the earlier data cut-off of 15 September 2017, since no data were available for the NEM population, the total population or the last data cut-off. The proportion of patients of the actually relevant NEM population (comprised patients independent of EGFR- or ALK-positive tumour mutations) with a targeted subsequent therapy in the IMpower150 study is therefore underestimated by this information. In the E4599 study, no immunotherapies were available on the market at the time of the data cut-off of 30 December 2005 and were therefore not available as an option for subsequent therapy to the patients included in the E4599 study. Moreover, no information was available on whether, and if so, how many patients received targeted subsequent therapy approved within the study period from 2001 to 2005. The proportion of patients receiving chemotherapy as subsequent therapy differed between the studies insofar as in the IMpower150 study a total of 27% (n = 190) patients received such subsequent therapy, while the proportion in the E4599 study was 49% (n = 425) and thus almost twice as high.

***Patient characteristics not sufficiently similar or verification of similarity not possible***

In line with the target population of atezolizumab + bevacizumab + paclitaxel + carboplatin, the IMpower150 study only included patients with non-squamous NSCLC. The E4599 study, in contrast, also included a high proportion (18.8%) of patients with unspecified carcinoma (histological type: "NOS", see Table 11 of the full dossier assessment), as a confirmation of non-squamous histology of the NSCLC was not an inclusion criterion for the E4599 study. Only patients with confirmed squamous cell carcinoma were excluded (see Table 9 of the full dossier assessment). It can thus not be ruled out that patients with NOS had squamous NSCLC. In this case, patients would not correspond to the patient population to be assessed according to the approval of atezolizumab + bevacizumab + paclitaxel + carboplatin. Additional specifications on the histology of the carcinoma, such as categorization as adenocarcinoma, are also only comparable to a limited extent due to the large proportion of NOS patients in the E4599 study. Almost all patients (94.3%) in the IMpower150 study had adenocarcinoma; in E4599, it were 68.6%. The maximum proportion of patients with adenocarcinoma in the E4599 study is therefore in any case lower than in the IMpower150 study, because even under the assumption that all patients with unspecified carcinoma had had adenocarcinoma, the proportion of patients with adenocarcinoma in the E4599 study would have been 87.4%. Moreover, as already described, the size of the proportion of patients with EGFR- or ALK-positive tumour mutation in the E4599 study was unclear. For these patients, targeted pretreatment was a prerequisite for a therapy with atezolizumab + bevacizumab + paclitaxel + carboplatin. However, such pretreatment was not available to the affected patients in the E4599 study.

***Lack of information on other possibly predictive features for the check of similarity***

Apart from the described differences, conclusions on the similarity of the two studies are not possible for the possibly predictive features “smoking status”, “time since diagnosis of the

disease" and "tumour size at baseline". These features were only recorded in one of the two studies (see Table 11 of the full dossier assessment). Comparison of the concomitant treatments between the studies was also impossible, since these had not been recorded in E4599.

***Summary***

Overall, the assumption of similarity is not sufficiently fulfilled due to the described differences between the studies IMpower150 and E4599 as well as uncertainties regarding other possibly predictive factors. Therefore, the adjusted indirect comparison of atezolizumab + bevacizumab + paclitaxel + carboplatin in comparison with the ACT is not usable.

There are thus no data for the benefit assessment suitable for a derivation of an added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin in comparison with the ACT.

### 2.3.4 Results on added benefit

No suitable data are available for the assessment of the added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin in comparison with the ACT as first-line treatment in adult patients with metastatic non-squamous NSCLC and PD-L1 expression (TPS) < 50% with EGFR- or ALK-positive tumour mutations after targeted pretreatment. Hence, there was no hint of an added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin in comparison with the ACT; an added benefit is therefore not proven.

### 2.3.5 Probability and extent of added benefit

Since the company presented no suitable data for the assessment of the added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin in comparison with the ACT as first-line treatment in adult patients with metastatic non-squamous NSCLC and PD-L1 expression (TPS) < 50% or with EGFR- or ALK-positive tumour mutations after targeted pretreatment, an added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin is not proven for these patients.

This deviates from the company's assessment, which derived proof of considerable added benefit on the basis of the direct and indirect comparisons presented by it.

### 2.3.6 List of included studies

Not applicable as the company did not present any relevant data for the benefit assessment.

## 2.4 Research question 2: PD-L1 expression (TPS) ≥ 50% and no EGFR- or ALK-positive tumour mutations

### 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 list on atezolizumab (status: 9 August 2019)
- bibliographical literature search on atezolizumab (last search on 3 July 2019)
- search in trial registries for studies on atezolizumab (last search on 1 July 2019)
- bibliographical literature search on the ACT (last search on 3 July 2019)
- search in trial registries for studies on the ACT (last search on 1 July 2019)

To check the completeness of the study pool:

- search in trial registries for studies on atezolizumab (last search on 14 October 2019)

In its dossier, the company presented no study on research question 2. Nor was a relevant study identified from the check of the completeness.

### 2.4.2 Results on added benefit

No data are available for the assessment of the added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin in comparison with the ACT as first-line treatment in adult patients with metastatic non-squamous NSCLC and PD-L1 expression (TPS) ≥ 50% without EGFR- or ALK-positive tumour mutations. Hence, there was no hint of an added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin in comparison with the ACT; an added benefit is therefore not proven.

### 2.4.3 Probability and extent of added benefit

Since the company presented no data for the assessment of the added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin in comparison with the ACT as first-line treatment in adult patients with metastatic non-squamous NSCLC and PD-L1 expression (TPS) ≥ 50% or with EGFR- or ALK-positive tumour mutations, an added benefit of atezolizumab + bevacizumab + paclitaxel + carboplatin is not proven for these patients.

This concurs with the company’s assessment.

### 2.4.4 List of included studies

Not applicable as the company presented no data for research question 2 for the benefit assessment.

## 2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of atezolizumab + nab-paclitaxel + carboplatin in comparison with the ACT is summarized in Table 5.

Table 5: Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin – probability and extent of added benefit

| **Research question** | **Therapeutic indication** | **ACT[a]** | **Probability and extent of added benefit** |
|---|---|---|---|
| 1 | First-line treatment of metastatic non-squamous NSCLC in adults[b] with PD-L1 expression (TPS) < 50%[c] and adults[b] with EGFR- or ALK-positive tumour mutations after targeted pretreatment | Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)<br>or<br>**carboplatin in combination with** a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or **paclitaxel** or pemetrexed) see also Appendix VI to Section K of the pharmaceutical directive [1]<br>or<br>carboplatin in combination with nab-paclitaxel | Added benefit not proven |
| 2 | First-line treatment of metastatic non-squamous NSCLC in adults[b] with PD-L1 expression (TPS) ≥ 50%[c] without EGFR- or ALK-positive tumour mutations | Pembrolizumab as monotherapy | Added benefit not proven |

a. Presentation of the respective ACT specified by the G-BA.
b. For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy.
c. For treatment with atezolizumab, PD-L1 expressions of TC0/1/2 and IC0/1/2 are considered an approximation to a TPS < 50% or PD-L1 expressions of TC3 or IC3 are regarded as approximation to a TPS ≥ 50% (see Section 2.3.3).

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; IC: immune cells; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; TC tumour cells; TPS: Tumour Proportion Score

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. Gemeinsamer Bundesausschuss. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie: Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (sog. Off-Label-Use) [online]. 17.10.2019 [Accessed: 10.12.2019]. URL: https://www.g-ba.de/downloads/83-691-569/AM-RL-VI-Off-label-2019-10-17.pdf.

2. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

3. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58.

4. F. Hoffmann-La Roche. A phase III, open-label, randomized study of MPDL3280A (anti-PDL-1 antibody) in combination with carboplatin + paclitaxel with or without bevacizumab compared with carboplatin + paclitaxel + bevacizumab in chemotherapy-naive patients with stage IV non-squamous non-small cell lung cancer: study GO29436 (IMpower 150); clinical study report [unpublished]. 2018.

5. F. Hoffmann-La Roche. Zusatzanalysen: study GO29436, (IMpower 150): a phase III, open-label, randomized study of MPDL3280A (anti-PDL-1 antibody) in combination with carboplatin + paclitaxel with or without bevacizumab compared with carboplatin + paclitaxel + bevacizumab in chemotherapy-naive patients with stage IV non-squamous non-small cell lung cancer [unpublished]. 2019.

6. Hoffmann-La Roche. A study of atezolizumab in combination with carboplatin plus (+) paclitaxel with or without bevacizumab compared with carboplatin+paclitaxel+bevacizumab in participants with stage IV non-squamous non-small cell lung cancer (NSCLC) (IMpower150): study details [online]. In: ClinicalTrials.gov. 20.08.2019 [Accessed: 28.10.2019]. URL: https://ClinicalTrials.gov/show/NCT02366143.

7. F. Hoffmann-La Roche. A phase III, open-label, randomized study of atezolizumab (mpdl3280a, anti−pd-l1 antibody) in combination with carboplatin+paclitaxel with or without bevacizumab compared with carboplatin+paclitaxe+bevacizumab in chemotherapy-naive patients with stage iv non-squamous non−small cell lung cancer [online]. In: EU Clinical Trials Register. [Accessed: 28.10.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-003207-30.

8. F. Hoffmann-La Roche. A phase III, open-label, randomized study of MPDL3280A (anti-PD-L1 antibody) in combination with carboplatin + paclitaxel with or without bevacizumab compared with carboplatin + paclitaxel + bevacizumab in chemotherapy-naive patients with stage IV non-squamous non-small cell lung cancer: study GO29436 (IMpower 150); update clinical study report [unpublished]. 2018.

9. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med 2018; 378(24): 2288-2301.

10. Reck M, Mok TSK, Nishio M, Jotte RM, Cappuzzo F, Orlandi F et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150). Lancet Respir Med 2019; 7(5): 387-401.

11. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006; 355(24): 2542-2550.

12. Zhou C, Wu YL, Chen G, Liu X, Zhu Y, Lu S et al. BEYOND: a randomized, double-blind, placebo-controlled, multicenter, phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non-small-cell lung cancer. J Clin Oncol 2015; 33(19): 2197-2204.

13. Soria JC, Mauguen A, Reck M, Sandler AB, Saijo N, Johnson DH et al. Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. Ann Oncol 2013; 24(1): 20-30.

14. Cui J, Cai X, Zhu M, Liu T, Zhao N. The efficacy of bevacizumab compared with other targeted drugs for patients with advanced NSCLC. PLoS One 2013; 8(4): e62038.

15. Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF. Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms: Langversion 1.0 [online]. 2018. URL: https://www.awmf.org/uploads/tx_szleitlinien/020-007OL_l_S3_Lungenkarzinom_2018-03.pdf.

16. Goeckenjan G, Sitter H, Thomas M, Branscheid D, Flentje M, Griesinger F et al. Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms. Pneumologie 2010; 64(Suppl 2): e1-e164.

17. Gemeinsamer Bundesausschuss. Niederschrift (finale Fassung) zum Beratungsgespräch gemäß § 8 AM-NutzenV: Beratungsanforderung 2018-B-110; Wirkstoff: Atezolizumab [unpublished]. 2018.

18. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C et al. Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29(Suppl 4): iv192-iv237.

19. Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie. DGHO Leitlinie Lungenkarzinom, nicht-kleinzellig (NSCLC), ICD10: C34 [online]. 11.2018. URL: https://www.onkopedia.com/de/onkopedia/guidelines/lungenkarzinom-nicht-kleinzellig-nsclc/@@view/html/index.html.

20. Genentech. A randomized phase II/III trial of paclitaxel plus carboplatin with or without bevacizumab (NSC 704865) in patients with advanced nonsquamous NSCLC E4599: clinical study report [unpublished]. 2006.

21. Brahmer JR, Dahlberg SE, Gray RJ, Schiller JH, Perry MC, Sandler A et al. Sex differences in outcome with bevacizumab therapy: analysis of patients with advanced-stage non-small cell lung cancer treated with or without bevacizumab in combination with paclitaxel and carboplatin in the Eastern Cooperative Oncology Group Trial 4599. J Thorac Oncol 2011; 6(1): 103-108.

22. Dahlberg SE, Sandler AB, Brahmer JR, Schiller JH, Johnson DH. Clinical course of advanced non-small-cell lung cancer patients experiencing hypertension during treatment with bevacizumab in combination with carboplatin and paclitaxel on ECOG 4599. J Clin Oncol 2010; 28(6): 949-954.

23. Lopez-Chavez A, Young T, Fages S, Leon L, Schiller JH, Dowlati A et al. Bevacizumab maintenance in patients with advanced non-small-cell lung cancer, clinical patterns, and outcomes in the Eastern Cooperative Oncology Group 4599 study: results of an exploratory analysis. J Thorac Oncol 2012; 7(11): 1707-1712.

24. Ramalingam SS, Dahlberg SE, Langer CJ, Gray R, Belani CP, Brahmer JR et al. Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599. J Clin Oncol 2008; 26(1): 60-65.

25. Sandler A, Yi J, Dahlberg S, Kolb MM, Wang L, Hambleton J et al. Treatment outcomes by tumor histology in Eastern Cooperative Group Study E4599 of bevacizumab with paclitaxel/carboplatin for advanced non-small cell lung cancer. J Thorac Oncol 2010; 5(9): 1416-1423.

26. Tyagi P. Bevacizumab, when added to paclitaxel/carboplatin, prolongs survival in previously untreated patients with advanced non-small-cell lung cancer. Clin Lung Cancer 2005; 6(5): 276-278.

27. Qualitätssicherungs-Initiative Pathologie. PD-L1-Portal: Definitionen von PD-L1 [online]. [Accessed: 26.11.2019]. URL: https://www.pdl1portal.eu/#definitionen.

28. Scheel AH, Dietel M, Heukamp LC, Jöhrens K, Kirchner T, Reu S et al. Harmonized PD-L1 immunohistochemistry for pulmonary squamous-cell and adenocarcinomas. Mod Pathol 2016; 29(10): 1165-1172.

29. Vennapusa B, Baker B, Kowanetz M, Boone J, Menzl I, Bruey JM et al. Development of a PD-L1 complementary diagnostic immunohistochemistry assay (SP142) for atezolizumab. Appl Immunohistochem Mol Morphol 2019; 27(2): 92-100.

30. Roche Registration. Fachinformation Tecentriq 1.200 mg Konzentrat zur Herstellung einer Infusionslösung [online]. URL: https://www.fachinfo.de.

31. Roche. Avastatin [online]. 04.2019 [Accessed: 24.10.2019]. URL: http://www.fachinfo.de.

32. Fresenius Kabi Deutschland. Fachinformation Paclitaxel Kabi 6 mg/ml [online]. URL: https://www.fachinfo.de.

33. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000; 92(3): 205-216.

34. American Cancer Society. Targeted therapy for non-small cell lung cancer [online]. 01.10.2019 [Accessed: 07.12.2019]. URL: https://www.cancer.org/cancer/lung-cancer/treating-non-small-cell/targeted-therapies.html.

*The full report (German version) is published under* https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-83-atezolizumab-nsclc-combination-chemotherapy-with-paclitaxel-benefit-assessment-according-to-35a-social-code-book-v.12692.html.