IQWiG Reports – Commission No. A21-69

Atezolizumab
(NSCLC – first line) –

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 - Erstlinie) – Nutzenbewertung gemäß § 35a SGB V* (Version 2.0; Status: 10 September 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Atezolizumab, Carcinoma – Non-Small-Cell Lung, Benefit Assessment, NCT02409342, NCT02142738, NCT02220894

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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

The questionnaire on the disease and its treatment was answered by XY and one other person.

IQWiG thanks the respondents for participating in the written exchange about how they experienced the disease and its treatment as well as their treatment goals. The respondents were not involved in the actual preparation of the dossier assessment.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ALK	anaplastic lymphoma kinase
BRAF	rapidly accelerated fibrosarcoma – isoform B
BSC	best supportive care
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IC	immune cell
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
RCT	randomized controlled trial
RCT	randomized controlled trial
ROS1	c-ros oncogene 1
SGB	Sozialgesetzbuch (Social Code Book)
TC	tumour cell

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. 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 21 May 2021.

Research question

The aim of the present report is the assessment of the added benefit of atezolizumab in comparison with the appropriate comparator therapy (ACT) for the first-line treatment of metastatic non-small cell lung cancer (NSCLC) in adult patients whose tumours express programmed cell death ligand 1 (PD-L1) in ≥ 50% of the tumour cells (TC) or in ≥ 10% of the tumour-infiltrating immune cells (IC) without epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK)-positive NSCLC.

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

Table 2: Research questions of the benefit assessment of atezolizumab (multipage table)

Research question	Therapeutic indication	ACT[a]
	First-line treatment of adult patients with metastatic NSCLC whose tumours express programmed cell death ligand 1 (PD-L1) in ≥ 50% of the tumour cells (TC) or in ≥ 10% of the tumour-infiltrating immune cells (IC) without EGFR mutations or ALK-positive NSCLC	
1	Patients with a tumour proportion score (TPS) ≥ 50% (PD-L1 expression)[b]	Pembrolizumab as monotherapy
2	Patients with a TPS of ≥ 1% and < 50% (PD-L1 expression)[b]	▪ Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)[c] or ▪ 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[c] or ▪ carboplatin in combination with nab-paclitaxel or ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with non-squamous histology) or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with squamous histology) or ▪ monotherapy with gemcitabine or vinorelbine (only for patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 2 as an alternative to platinum-based combination treatment)

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. It is assumed that the patients in the present therapeutic indication had no indication for definitive local therapy and that no molecularly stratified therapy (against EGFR, ALK, BRAF or ROS1) could be considered for the patients at the time of treatment with atezolizumab. It is also assumed that the patients were generally eligible for active antineoplastic therapy, which is why BSC was not considered as an ACT in the present case.
c. On cisplatin/carboplatin in combination with a third-generation cytostatic agent: In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the two substances and on the existing comorbidities; see Appendix VI to Section K of the Pharmaceutical Directive.

ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; BSC: best supportive care; 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; ROS1: c-ros oncogene 1; TC: tumour cells; TPS: Tumour Proportion Score

The patients with metastatic NSCLC in the newly approved therapeutic indication of atezolizumab relevant for the present assessment are divided into 2 research questions by the specification of the ACT according to their Tumour Proportion Score (TPS). In the present assessment, the following terms are used for the patient populations of the two research questions:

- Research question 1: patients with a TPS ≥ 50% (PD-L1 expression)
- Research question 2: patients with a TPS ≥ 1% and < 50% (PD-L1 expression)

The company followed the specification on the ACT for research question 1. The company did not consider research question 2 in Module 4 A of its dossier and therefore selected no ACT from the possible alternatives.

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

Research question 1: patients with a TPS ≥ 50% (PD-L1 expression)

Study pool and study design

Concurring with the company, no relevant study on the direct comparison of atezolizumab versus pembrolizumab in the present therapeutic indication was identified from the check of the completeness of the study pool. The company therefore presented an adjusted indirect comparison using the common comparator platinum-based chemotherapy for the assessment of the added benefit of atezolizumab.

For atezolizumab, the study pool comprised the randomized controlled trial (RCT) IMpower110 and for pembrolizumab, it included the RCTs KEYNOTE 024 and KEYNOTE 042 as well as KEYNOTE 042-China. As no information on the patient characteristics of the relevant subpopulation (with PD-L1 TPS ≥ 50%) is available for the KEYNOTE 042-China study, this study is not considered below.

Study with atezolizumab: IMpower110

Impower110 is an ongoing, open-label RCT on the comparison of atezolizumab with a platinum-based combination chemotherapy. The study included adult patients with histologically or cytologically confirmed stage IV NSCLC without EGFR mutation or ALK translocation IV whose tumours had a PD-L1 expression. Prior systemic chemotherapy for the metastatic stage was not allowed.

The study IMpower110 included a total of 572 patients, assigned in a 1:1 ratio either to treatment with atezolizumab (N = 285) or with a platinum-based combination chemotherapy (N = 287). The treatment options for patients with non-squamous NSCLC comprised pemetrexed + cisplatin or pemetrexed + carboplatin; those for patients with squamous NSCLC were gemcitabine + cisplatin or gemcitabine + carboplatin. The platinum component of the chemotherapy was administered for a maximum of 4 to 6 cycles. Thereafter, patients with non-

squamous histology received maintenance treatment with pemetrexed; patients with squamous histology received best supportive care (BSC).

Treatment was performed until disease progression, occurrence of unacceptable side effects or death.

"Overall survival" was the primary outcome of the study.

Studies with the ACT: KEYNOTE 024 and KEYNOTE 042

KEYNOTE 024

As already described in the dossier assessments on the projects A17-06 and A19-30, KEYNOTE 024 is an open-label RCT on the comparison of pembrolizumab with a platinum-based combination chemotherapy. The study included adult patients with histologically or cytologically confirmed metastatic NSCLC without EGFR mutation or ALK translocation, whose tumours had a PD-L1 expression ≥ 50%. Prior systemic antineoplastic treatment for the metastatic stage was not allowed.

The KEYNOTE 024 study included a total of 305 patients, randomized in a 1:1 ratio either to treatment with pembrolizumab monotherapy (N = 154) or to one of 5 possible treatment options as platinum-based combination chemotherapy (N = 151). The treatment options were as follows: pemetrexed + cisplatin, pemetrexed + carboplatin, gemcitabine + cisplatin, gemcitabine + carboplatin, or paclitaxel + carboplatin, whereby the combination with pemetrexed was only an option for patients with non-squamous histology. The platinum component of the chemotherapy was administered for a maximum of 4 to 6 cycles in the KEYNOTE 024 study. Thereafter, patients with non-squamous histology could receive maintenance treatment with pemetrexed, which was also recommended.

Patients were treated until disease progression, occurrence of unacceptable side effects or discontinuation of the study due to decision by the investigator or the patient.

The primary outcome of the study was progression-free survival (PFS). Patient-relevant secondary outcomes were "overall survival", outcomes on morbidity, health-related quality of life and AEs.

KEYNOTE 042

KEYNOTE 042 is an ongoing, randomized, open-label RCT. The study compared pembrolizumab with a combination of carboplatin and either paclitaxel or pemetrexed. A total of 1274 patients were randomly allocated to the intervention arm (pembrolizumab: N = 637) or to the comparator arm (N = 637) in a 1:1 ratio. The study included adults with histologically or cytologically confirmed diagnosis of NSCLC with locally advanced or metastatic tumours with PD-L1 expression ≥ 1%. Prior systemic treatment was not allowed in the studies. The treatment options in the study were as follows: pemetrexed + carboplatin or paclitaxel + carboplatin, whereby the combination with pemetrexed was only an option for patients with non-squamous

histology. In the KEYNOTE 042 study, patients with non-squamous histology received carboplatin for a maximum of 4 to 6 cycles. After at least 4 cycles, patients with non-squamous histology could receive maintenance treatment with pemetrexed, which was also recommended.

Patients were treated until disease progression, complete response, occurrence of unacceptable side effects or study discontinuation due to decision by the investigator or the patient.

"Overall survival" was the primary outcome of the study. Patient-relevant secondary outcomes were AEs.

Relevant subpopulations of the studies IMpower110 and KEYNOTE 042 (PD-L1 expression [TPS] ≥ 50%)

In each case, only a subpopulation from the included studies IMpower110 and KEYNOTE 042 is relevant. For both studies, the company presented results from a subpopulation of patients whose tumours had PD-L1 expression (TPS) ≥ 50 % of the TCs and who do not have EGFR mutations or ALK-positive NSCLC.

Similarity of the common comparator platinum-based combination chemotherapy in the studies

For the present indirect comparison, the company chose "platinum-based chemotherapy" as common comparator. In the 3 included studies IMpower110, KEYNOTE 024 and KEYNOTE 042, this includes different platinum-based combination chemotherapies. These differed between the studies: For example, paclitaxel was only used on the pembrolizumab side of the indirect comparison, and in the KEYNOTE 042 study only carboplatin was administered as the platinum component. Moreover, the use of gemcitabine was only planned for patients with squamous histology of the NSCLC in the IMpower110 study.

Platinum component of the common comparator

For the IMpower110 study, the choice of the platinum component of the platinum-based chemotherapy was described as being "in accordance with local practice". There is no information on possible selection criteria of the platinum components in the studies KEYNOTE 024 and KEYNOTE 042; in each case, there is only the information that the choice took place on an individual basis prior to randomization.

Chemotherapy component of the common comparator

In the IMpower110 study, patients with non-squamous histology could only receive pemetrexed in addition to the platinum component. In KEYNOTE 024, gemcitabine or paclitaxel could also be administered; however, it can be seen that the majority of patients (82%) received pemetrexed. There is no information for the relevant subpopulation of the KEYNOTE 042 study.

In the IMpower110 study, patients with squamous histology only received gemcitabine in addition to the platinum component. In KEYNOTE 024, paclitaxel could also be administered,

however, most patients (81%) received gemcitabine. In the KEYNOTE 042 study, patients with squamous histology could only receive paclitaxel.

A total of 11% of the patients (with squamous and non-squamous histology) received paclitaxel in KEYNOTE 024.

Maintenance treatment in the common comparator

In the IMpower110 study, all patients with non-squamous histology received maintenance therapy with pemetrexed, whereas in the KEYNOTE 024 study, only 37% of these patients received maintenance therapy with pemetrexed, although this maintenance therapy was recommended according to the study documents. In the KEYNOTE 042 study, administration of a maintenance treatment was at the investigator's discretion and was recommended. There was no information for the relevant subpopulation.

Summary

The described differences (paclitaxel only on the comparator side of the indirect comparison, maintenance treatment with pemetrexed only mandatory on the intervention side, in the KEYNOTE 042 study only carboplatin as platinum component) between the platinum-based chemotherapies of the 3 studies did not result in a fundamental questioning of the similarity of the common comparators for the indirect comparison. These differences were considered in the interpretation of the results of the outcomes on side effects.

Summary of the similarities of the studies in the adjusted indirect comparison

Similarity is a key requirement for the consideration of studies in the adjusted indirect comparison. The 3 studies IMpower110, KEYNOTE 024 and KEYNOTE 042 have a very similar study design and the patient populations are also sufficiently similar. Differences between the studies IMpower110, KEYNOTE 024 and KEYNOTE 042 are particularly found in the common comparator platinum-based chemotherapy (paclitaxel only on the comparator side of the indirect comparison, maintenance treatment with pemetrexed only mandatory on the intervention side, in KEYNOTE 042 only carboplatin as platinum component). Certain aspects cannot be assessed due to missing data (treatment and observation periods, subsequent therapies). Overall, the similarity assumption for the indirect comparison is not rejected. However, the described differences between the platinum-based chemotherapies of the studies were taken into account when interpreting the results on AEs.

Risk of bias

The risk of bias across outcomes was rated as low for the studies considered. The outcome-specific risk of bias of the results on the outcome "overall survival" was rated as low for each of the studies IMpower110, KEYNOTE 024 and KEYNOTE 042. For the results on the outcomes "serious adverse events (SAEs)", "severe AEs" and "discontinuation due to AEs", the risk of bias was rated as high for both the IMpower110 study and the KEYNOTE 024 study.

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes. Moreover, the risk of bias of the results on the outcomes of the category “side effects” was rated as high in the studies IMpower110 and KEYNOTE 024. The certainty of results of the results from the indirect comparisons is therefore not sufficient. Therefore, no indirect comparison was performed for these outcomes, and no hint of an added benefit was derived.

Results

Mortality

Overall survival

The adjusted indirect comparison showed no statistically significant difference between the treatment groups for the outcome "overall survival". Hence, there was no hint of an added benefit of atezolizumab in comparison with pembrolizumab; an added benefit is therefore not proven.

Morbidity

Module 4 A of the dossier provides no usable data for the outcomes of the morbidity category. Hence, there was no hint of an added benefit of atezolizumab in comparison with pembrolizumab; an added benefit is therefore not proven.

Health-related quality of life

Module 4 A provides no usable data for the outcomes of the category "health-related quality of life". Hence, there was no hint of an added benefit of atezolizumab in comparison with pembrolizumab; an added benefit is therefore not proven.

Side effects

Due to an insufficient certainty of results in the two studies IMpower110 and KEYNOTE 024, no indirect comparison was calculated for the outcomes “SAEs”, “severe AEs” and “discontinuation due to AEs”. The differences regarding the maintenance treatments in the common comparator arms (platinum-based chemotherapies) must be considered. Moreover, there are no usable data for the outcome “immune-related AEs” for the relevant subpopulation of the IMpower110 study. Hence, no usable data on the AE outcomes are available for the indirect comparison. This resulted in no hint of greater or lesser harm from atezolizumab in comparison with pembrolizumab; greater or lesser harm is therefore not proven.

Research question 2: patients with a TPS ≥ 1% and < 50% (PD-L1 expression)

In Module 4 A of its dossier, the company did not consider research question 2, the assessment of the added benefit of atezolizumab in comparison with the ACT as first-line treatment of metastatic NSCLC in adult patients in the newly approved therapeutic indication of atezolizumab whose tumours had a TPS of ≥ 1% and < 50% (PD-L1 expression).

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

On the basis of the results presented, the probability and extent of the added benefit of the drug atezolizumab compared with the ACT are assessed as follows:

Research question 1: patients with a TPS ≥ 50% (PD-L1 expression)

Overall, based on the adjusted indirect comparison using the common comparator platinum-based chemotherapy, there are neither positive nor negative effects of atezolizumab in comparison with pembrolizumab.

However, it should be noted that usable results with sufficient certainty of results for an indirect comparison are only available for the outcome "overall survival". There is no hint of an added benefit of atezolizumab for this outcome, as the indirect comparison showed no statistically significant difference. For the outcomes of the outcome categories of morbidity and health-related quality of life as well as for the outcomes "immune-related AEs" and further specific AEs, sufficient data are not available for at least 1 side of the indirect comparison. Usable data for an indirect comparison are not available for the outcomes "SAEs", "severe AEs" and "discontinuation due to AEs", as the certainty of results was not sufficient for an indirect comparison. Moreover, the differences of the maintenance treatment in the platinum-based chemotherapies of the common comparators must be taken into account when interpreting the results on the outcomes of the side effects category. Balancing of benefit and harm is not possible as the results on the outcome categories "morbidity", "health-related quality of life" and "side effects" are not usable.

In summary, there is no hint of an added benefit of atezolizumab in comparison with the ACT pembrolizumab as first-line treatment of metastatic NSCLC in adult patients in the newly approved therapeutic indication of atezolizumab whose tumours have a TPS ≥ 50% (PD-L1 expression), an added benefit is therefore not proven.

Research question 2: patients with a TPS ≥ 1% and < 50% (PD-L1 expression)

Module 4 A of the dossier provides no data for the assessment of the added benefit of atezolizumab in comparison with the ACT as first-line treatment of metastatic NSCLC in adult patients in the newly approved therapeutic indication of atezolizumab whose tumours have a TPS of ≥ 1% and < 50% (PD-L1 expression). An added benefit for these patients is therefore not proven.

[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].

Table 3 presents a summary of probability and extent of the added benefit of atezolizumab.

Table 3: Atezolizumab – probability and extent of added benefit: (multipage table)

Research question	**Therapeutic indication**	**ACT**[a]	**Probability and extent of added benefit**
	First-line treatment of adult patients with metastatic NSCLC whose tumours express PD-L1 in ≥ 50% of the TCs or in ≥ 10% of the tumour-infiltrating ICs without EGFR mutations or ALK-positive NSCLC		
1	Patients with a TPS ≥ 50% (PD-L1 expression)[b]	Pembrolizumab as monotherapy	Added benefit not proven[c]
2	Patients with a TPS of ≥ 1% and < 50% (PD-L1 expression)[b].	▪ Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)[d] or ▪ 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[d] or ▪ carboplatin in combination with nab-paclitaxel or ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with non-squamous histology) or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with squamous histology) or ▪ monotherapy with gemcitabine or vinorelbine (only for patients with ECOG PS 2 as an alternative to platinum-based combination treatment)	Added benefit not proven

Table 3: Atezolizumab – probability and extent of added benefit: (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. It is assumed that the patients in the present therapeutic indication had no indication for definitive local therapy and that no molecularly stratified therapy (against EGFR, ALK, BRAF or ROS1) could be considered for the patients at the time of treatment with atezolizumab. It is also assumed that the patients were generally eligible for active antineoplastic therapy, which is why BSC was not considered as an ACT in the present case. c. Only patients with an ECOG PS of 0 or 1 were included in the studies for the indirect comparison. It remains unclear whether the observed results can be transferred to patients with an ECOG PS ≥ 2. d. On cisplatin/carboplatin in combination with a third-generation cytostatic agent: In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the two substances and on the existing comorbidities; see Appendix VI to Section K of the Pharmaceutical Directive. ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; 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; ROS1: c-ros oncogene 1; TC: tumour cells; TPS: Tumour Proportion Score			

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

2.2 Research question

The aim of the present report is the assessment of the added benefit of atezolizumab in comparison with the ACT for the first-line treatment of metastatic NSCLC in adult patients whose tumours express PD-L1 in ≥ 50% of the TC or in ≥ 10% of the tumour-infiltrating IC without EGFR mutations or ALK-positive NSCLC.

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

Table 4: Research questions of the benefit assessment of atezolizumab: (multipage table)

Research question	Therapeutic indication	ACT[a]
	First-line treatment of adult patients with metastatic NSCLC whose tumours express PD-L1 in ≥ 50% of the TCs or in ≥ 10% of the tumour-infiltrating ICs without EGFR mutations or ALK-positive NSCLC	
1	Patients with a TPS ≥ 50% (PD-L1 expression)[b]	Pembrolizumab as monotherapy
2	Patients with a TPS of ≥ 1% and < 50% (PD-L1 expression)[b]	▪ Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)[c] or ▪ 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[c] or ▪ carboplatin in combination with nab-paclitaxel or ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with non-squamous histology) or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with squamous histology) or ▪ monotherapy with gemcitabine or vinorelbine (only for patients with ECOG PS 2 as an alternative to platinum-based combination treatment)

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. It is assumed that the patients in the present therapeutic indication had no indication for definitive local therapy and that no molecularly stratified therapy (against EGFR, ALK, BRAF or ROS1) could be considered for the patients at the time of treatment with atezolizumab. It is also assumed that the patients were generally eligible for active antineoplastic therapy, which is why BSC was not considered as an ACT in the present case.
c. On cisplatin/carboplatin in combination with a third-generation cytostatic agent: In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the two substances and on the existing comorbidities; see Appendix VI to Section K of the Pharmaceutical Directive.

ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; BSC: best supportive care; 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; ROS1: c-ros oncogene 1; TC: tumour cells; TPS: Tumour Proportion Score

The patients with metastatic NSCLC in the newly approved therapeutic indication of atezolizumab relevant for the present assessment are divided into 2 research questions by the specification of the ACT according to their TPS. In the present assessment, the following terms are used for the patient populations of the 2 research questions:

- Research question 1: patients with a TPS ≥ 50% (PD-L1 expression)
- Research question 2: patients with a TPS ≥ 1% and < 50% (PD-L1 expression)

The company followed the specification on the ACT for research question 1. The company did not consider research question 2 in Module 4 A of its dossier and therefore selected no ACT from the possible alternatives.

The assessment was 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 with a TPS ≥ 50% (PD-L1 expression)

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 list on atezolizumab (status: 16 March 2021)
- bibliographical literature search on atezolizumab (last search on 17 March 2021)
- search in trial registries/trial results databases for studies on atezolizumab (last search on 16 March 2021)
- search on the G-BA website for atezolizumab (last search on 16 March 2021)
- bibliographical literature search on the ACT (last search on 17 March 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 16 March 2021)
- search on the G-BA website for the ACT (last search on 16 March 2021)

To check the completeness of the study pool:

- search in trial registries for studies on atezolizumab (last search on 9 June 2021); for search strategies, see Appendix A of the full dossier assessment
- search in trial registries for studies on the ACT (last search on 11 June 2021); for search strategies, see Appendix A of the full dossier assessment

Concurring with the company, no relevant study on the direct comparison of atezolizumab versus pembrolizumab in the present therapeutic indication was identified from the check of the completeness of the study pool.

Therefore, the company presented an adjusted indirect comparison according to Bucher [3] for the assessment of atezolizumab in comparison with pembrolizumab using the common comparator platinum-based chemotherapy.

The check of the study pool did not identify any additional relevant study for the adjusted indirect comparison presented by the company. However, as result of its search on the GBA website for the ACT, the company only identified the modules 4 [4,5] and the justification [6,7] of the G-BA for the two studies KEYNOTE 024 and KEYNOTE 042. However, in each case, these procedures are assigned to dossier assessments [8-11] that contain further information on the two studies. For example, the company could have used the results of the KEYNOTE 024 study on frequent AEs at the data cut-off of 9 May 2016 from the Appendix of IQWiG benefit assessment A17-06 [8]. Hence, the information retrieval on the ACT is incomplete.

2.3.1.1 Studies included

The company therefore presented an adjusted indirect comparison using the common comparator platinum-based chemotherapy for the assessment of the added benefit of atezolizumab. The company justified the choice of the common comparator by stating that the identified studies in the relevant therapeutic indication each investigate the efficacy and tolerability of treatment with the drug to be assessed (atezolizumab) or the ACT specified by the G-BA (pembrolizumab) using a comparable common comparator (a platinum-based chemotherapy).

Concurring with the company, a platinum-based chemotherapy was used as common comparator for an adjusted indirect comparison in the benefit assessment.

The studies listed in the following Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, indirect comparison: atezolizumab vs. pembrolizumab:

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Study with atezolizumab						
IMpower110[d] (GO29431)	Yes	Yes	No	Yes [12]	Yes [13,14]	Yes [15,16]
Studies with pembrolizumab						
KEYNOTE 024	No	No	Yes	Yes [17]	Yes [18,19]	Yes [4,6,8-11,20-24]
KEYNOTE 042	No	No	Yes	No	Yes [25,26]	Yes [5,7,10,11,27-29]
KEYNOTE 042-China	No	No	Yes	No	Yes [30]	Yes [31]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to with this designation.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool concurs with that of the company.

For atezolizumab, the study pool comprised the RCT IMpower110 and for pembrolizumab, it included the RCTs KEYNOTE 024 and KEYNOTE 042 as well as KEYNOTE 042-China. The extension study KEYNOTE 042-China was conducted in accordance with the same study protocol as the KEYNOTE 042 study. As no information on the patient characteristics of the relevant subpopulation (with PD-L1 TPS ≥ 50%) is available for the KEYNOTE 042-China study, the company did not consider the KEYNOTE 042-China study further in the indirect comparison.

This approach is comprehensible, because a sufficient similarity of the patient populations in the studies in the indirect comparison is one of the prerequisites for a consideration of KEYNOTE 042-China in the indirect comparison. The similarity cannot be tested without the information on the relevant subpopulation. The KEYNOTE 042-China study is not considered below.

Figure 1 shows a schematic representation of the indirect comparison.

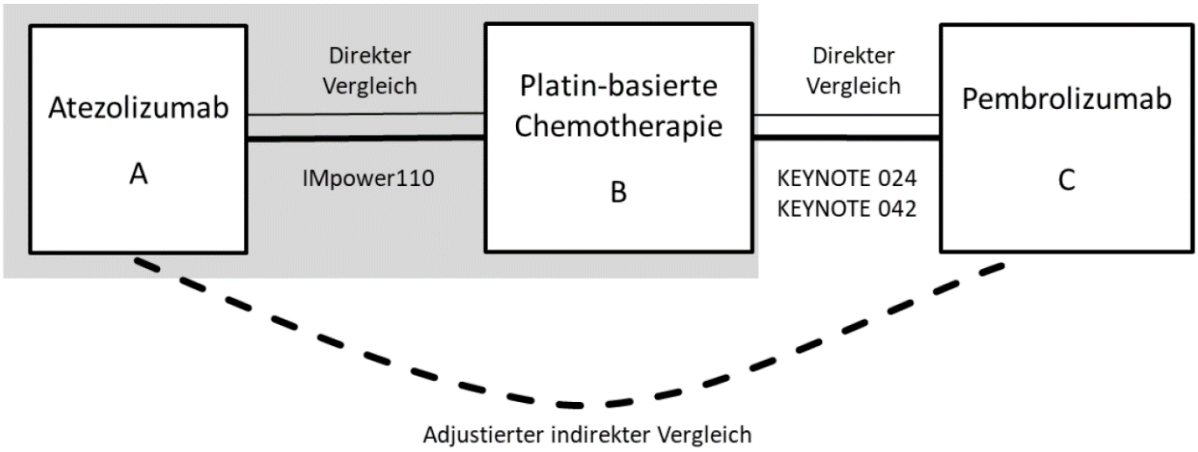

Figure 1: Study pool for the indirect comparison between atezolizumab and the ACT pembrolizumab

2.3.1.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, indirect comparison: atezolizumab vs. pembrolizumab: (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Study with atezolizumab						
IMpower110	RCT, open-label, parallel	Adult patients with histologically or cytologically confirmed stage IV NSCLC, PD-L1 expressing tumours, without EGFR mutation or ALK translocation, ECOG PS ≤ 1, without previous systemic therapy[b]	Atezolizumab (N = 285) platinum-based chemotherapy (N = 287) relevant subpopulation thereof[c]: atezolizumab (n = 134) platinum-based chemotherapy (n = 126)	Screening: 28 days treatment: until progression (or beyond, as long as the patient benefits for atezolizumab), unacceptable side effects or death observation: outcome-specific[d], at most until death (for the outcome "overall survival")	144 centres in: Brazil, China, France, Germany, Greece, Great Britain, Italy, Japan, Poland, Romania, Russia, Serbia, South Korea, Spain, Thailand, Turkey, Ukraine, Hungary, United States of America 07/2015–ongoing data cut-offs: 10 September 2018 4 February 2020	Primary: overall survival secondary: morbidity, health-related quality of life, AEs
Studies with pembrolizumab						
KEYNOTE 024	RCT, open-label, parallel	Adult patients with histologically or cytologically confirmed stage IV NSCLC, PD-L1 expressing tumours (TPS ≥ 50%)[c] without EGFR mutation or ALK translocation, ECOG PS ≤ 1, without previous systemic therapy[b]	Pembrolizumab (N = 154) platinum-based chemotherapy (N = 151)	Screening: 30 days prior to the start of treatment treatment: until progression (or beyond, as long as the patient benefits), unacceptable side effects, study discontinuation due to decision by the investigator or the patient, complete response or a maximum of 35 cycles of pembrolizumab[e] observation: outcome-specific[d], at most until death (for the outcome "overall survival")	142 centres in: Australia, Austria, Belgium, Canada, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Netherlands, New Zealand, Spain, United Kingdom, USA 09/2014–05/2016[f] data cut-offs: 9 May 2016 10 July 2017 (final analysis on overall survival) 1 June 2020: (analysis on 5-year overall survival)	Primary: PFS secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, indirect comparison: atezolizumab vs. pembrolizumab: (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE 042	RCT, open-label, parallel	Adult patients with histologically or cytologically confirmed locally advanced or metastatic NSCLC, PD-L1 expressing tumours (TPS ≥ 1%) without EGFR mutation or ALK translocation, ECOG PS ≤ 1, without previous systemic therapy[b]	Pembrolizumab (N = 637) platinum-based chemotherapy (N = 637) relevant subpopulation thereof[c]: pembrolizumab (n = 299) platinum-based chemotherapy (n = 300)	Screening: 30 days prior to the start of treatment treatment: until progression, unacceptable side effects, study discontinuation due to decision by the investigator or the patient, complete response or a maximum of 35 cycles of pembrolizumab[e] observation: outcome-specific[d], at most until death (for the outcome "overall survival")	196 centres: Argentina, Brazil, Bulgaria, Canada, Columbia, Czech Republic, Chile, China, Estonia, Guatemala, Hong Kong, Hungary, Japan, Latvia, Lithuania, Malaysia, Mexico, Peru, Philippines, Poland, Portugal, Romania, Russia, South Africa, South Korea, Sweden, Switzerland, Taiwan, Thailand, Turkey, Ukraine, Vietnam 11/2014–ongoing data cut-offs: 26 February 2018 4 September 2018 (final PFS analysis)	Primary: overall survival secondary: AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant outcomes for this benefit assessment.
b. Without prior systemic therapy for the metastatic NSCLC stage (IMpower110, KEYNOTE 024) or the advanced or metastatic NSCLC stage (KEYNOTE 042).
c. Patients with NSCLC with high PD-L1 expression, without EGFR mutation or ALK translocation (WT; TPS ≥ 50 %, PD-L1 IHC 22C3-Test).
d. Outcome-specific information is provided in Table 9.
e. Patients in the pembrolizumab arm (KEYNOTE 024 and KEYNOTE 042) could temporarily discontinue treatment after confirmed complete response or after achievement of the maximum number of treatment cycles for pembrolizumab, and restart treatment with pembrolizumab at the investigator's discretion ("second course phase") after subsequent confirmed progression (if certain conditions regarding previous treatment duration and disease status were met). It is to be assumed that only < 5% of the patients in the total study population (KEYNOTE 024 and KEYNOTE 042) reached the "second course phase".
f. Since pembrolizumab was superior to platinum-based chemotherapy with respect to overall survival, the study was stopped at the time point of the data cut-off of the second interim analysis (9 May 2016). This second data cut-off was prospectively planned to be performed after 175 events for the outcome "PFS" had been reached. All patients in the treatment arm with solely platinum-based chemotherapy were offered to switch to the pembrolizumab arm.

Table 6: Characteristics of the studies included – RCT, indirect comparison: atezolizumab vs. pembrolizumab: (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ACT: appropriate comparator therapy; AE: adverse event; ALK: anaplastic lymphoma kinase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; n: relevant subpopulation; N: number of randomized patients; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; PFS: progression-free survival; RCT: randomized controlled trial; TPS: Tumour Proportion Score; WT: wild type						

Table 7: Characteristics of the intervention – RCT, indirect comparison: atezolizumab vs. pembrolizumab (multipage table)

Study	Intervention	Common comparator
Study with atezolizumab		
IMpower110	Atezolizumab 1200 mg on day 1 of a 21-day cycle, IV	<u>Platinum-based combination chemotherapy</u> <u>induction phase (4 or 6 cycles)</u> non-squamous: Pemetrexed 500 mg/m$^{2\ BSA}$, IV + cisplatin 75 mg/m^2, IV or carboplatin: AUC of 6 mg/mL/min, IV on day 1 of each 21-day cycle squamous: gemcitabine 1000 or 1250 mg/m^2 BSA, IV, on day 1 and 8 of a 21-week cycle) + cisplatin 75 mg/m^2 BSA, IV or carboplatin AUC of 5 mg/mL/min, IV on day 1 of each 21-day cycle <u>maintenance period</u> non-squamous: pemetrexed 500 mg/m^2 BSA, IV, on day 1 of a 21-week cycle squamous: BSC
	dose adjustments: ▪ atezolizumab: no dose adjustment allowed; interruption allowed for up to 105 days in case of side effects ▪ chemotherapy: dose adjustments allowed according to the SPC	
	pretreatment ▪ chemotherapy and/or radiotherapy as part of neoadjuvant or adjuvant treatment in the non-metastatic stage; the last treatment had to be administered at least 6 months prior to the diagnosis of the metastatic disease ▪ stable pain therapy; complete recovery from palliative radiotherapy for bone metastases or metastases causing nerve entrapment **non-permitted pretreatment** ▪ CD137 agonists or immune checkpoint inhibitors, anti-PD-1 and anti-PD-L1 therapeutic antibodies ▪ systemic corticosteroids or other systemic immunosuppressants ≤ 2 weeks before randomization **premedication** ▪ for atezolizumab: antihistamines (from cycle 2 onwards) ▪ for pemetrexed + platinum therapy folic acid, vitamin B12 and dexamethasone	

Table 7: Characteristics of the intervention – RCT, indirect comparison: atezolizumab vs. pembrolizumab (multipage table)

Study	Intervention	Common comparator
	Concomitant treatment ▪ palliative radiotherapy for bone metastases or pain ▪ systemic corticosteroids for the treatment of atezolizumab-related side effects **non-permitted concomitant treatment** ▪ any anticancer therapy (including hormonal therapy) from 3 weeks before the first dose of the study medication until treatment discontinuation ▪ denosumab (switch to bisphosphonates, with consent at the start of the study) ▪ live vaccines, from 4 weeks before randomization to 5 months after administration of the last atezolizumab dose	
Studies with pembrolizumab		
KEYNOTE 024	Pembrolizumab 200 mg IV (as 30-minute infusion) on day 1 of a 21-day cycle	Platinum-based combination chemotherapy[b] for 4 to 6 cycles: <u>induction phase (4 to 6 cycles)</u> <u>only non-squamous:</u> pemetrexed 500 mg/m^2 BSA, IV, on day 1 of a 21-week cycle + cisplatin 75 mg/m^2 BSA, IV or carboplatin: AUC of 5 or 6 mg/mL/min, IV on day 1 of each 21-day cycle non-squamous and squamous: gemcitabine 1250 mg/m^2 BSA, IV, on day 1 and 8 of a 21-week cycle + cisplatin 75 mg/m^2 BSA, IV, day 1 of a 21-day cycle or carboplatin AUC of 5 or 6 mg/mL/min IV, day 1 of a 21-day cycle or paclitaxel 200 mg/m^2 BSA, IV, on day 1 of a 21-week cycle + carboplatin AUC of 5 or 6 mg/mL/min IV, day 1 of a 21-day cycle <u>maintenance period</u> only non-squamous: after at least 4 cycles carboplatin + pemetrexed, cisplatin + pemetrexed or paclitaxel + carboplatin, further treatment with pemetrexed 500 mg/m² BSA, IV, on day 1 of a 21-day cycle, was at the investigator's discretion

Table 7: Characteristics of the intervention – RCT, indirect comparison: atezolizumab vs. pembrolizumab (multipage table)

Study	Intervention	Common comparator
	Dose adjustments: ▪ pembrolizumab: no dose adjustment allowed (according to the SPC), interruption allowed in case of side effects ▪ chemotherapy: dose adjustments allowed according to the SPC	
	pretreatment ▪ chemotherapy and/or radiotherapy as part of neoadjuvant or adjuvant treatment; the last treatment had to be administered at least 6 months prior to the diagnosis of the metastatic disease **non-permitted pretreatment** ▪ systemic therapy for stage IV NSCLC ▪ CD137 agonists, anti-PD-1, anti-PD-L1, anti PD-L2 and CTLA-4 therapeutic antibodies or immune checkpoint inhibitors **non-permitted concomitant treatment** ▪ immunotherapies other than pembrolizumab ▪ other chemotherapies ▪ surgery for symptom and tumour control ▪ live vaccines ▪ corticosteroids except for the treatment of AEs or used as premedication of a platinum-based combination chemotherapy used in the study ▪ bisphosphonate or anti-RANK-L inhibitors[b]	
KEYNOTE 042	Pembrolizumab 200 mg, IV, on day 1 of a 21-day cycle	Carboplatin-based combination chemotherapy[a] for 4 to at most 6 cycles: <u>induction phase (4 to 6 cycles)</u> only non-squamous: pemetrexed 500 mg/m² BSA, IV, on day 1 of a 21-day cycle + carboplatin AUC of 5 or 6 mg/mL/min IV, day 1 of a 21-day cycle non-squamous and squamous: paclitaxel 200 mg/m² BSA, IV, on day 1 of a 21-day cycle + carboplatin AUC of 5 or 6 mg/mL/min IV, day 1 of a 21-day cycle <u>maintenance period</u> <u>only non-squamous:</u> after at least 4 cycles of the platinum-based combination chemotherapy, further treatment with pemetrexed 500 mg/m² BSA, IV, on day 1 of a 21-day cycle, was at the investigator's discretion

Table 7: Characteristics of the intervention – RCT, indirect comparison: atezolizumab vs. pembrolizumab (multipage table)

Study	Intervention	Common comparator
	Dose adjustments: ▪ pembrolizumab: no dose adjustment allowed (treatment could be interrupted or discontinued) ▪ chemotherapy: dose adjustments allowed according to the SPC	
	pretreatment ▪ adjuvant or neoadjuvant therapy; the last treatment had to be administered at least 6 months prior to the development of the metastatic disease **non-permitted pretreatment** ▪ systemic therapy for the advanced or metastatic NSCLC stage ▪ CD137 agonists, anti-PD-1, anti-PD-L1, anti PD-L2 and CTLA-4 therapeutic antibodies or immune checkpoint inhibitors **non-permitted concomitant treatment** ▪ other chemotherapies or immunotherapies ▪ surgery for symptom and tumour control ▪ radiotherapy ▪ live vaccines ▪ corticosteroids except for the treatment of AEs or used as premedication of a chemotherapy used in the study	

a. Within the framework of the chemotherapy, the investigator chose an individual combination therapy prior to randomization.
b. In the study, continuation of these therapies was only allowed for patients whose treatment had started prior to study inclusion.

AE: adverse event; AUC: area under the curve; BSA: body surface area; CD137: cluster of differentiation 137; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; IV: intravenous; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein1; PD-L1/PD-L2: programmed cell death ligand 1/2; RCT: randomized controlled trial; RANKL: receptor activator of nuclear factor kappa-B ligand

Study design

Study with atezolizumab: IMpower110

Impower110 is an ongoing, open-label RCT on the comparison of atezolizumab with a platinum-based combination chemotherapy. The study included adult patients with histologically or cytologically confirmed stage IV NSCLC without EGFR mutation or ALK translocation IV whose tumours had a PD-L1 expression. Initially, only patients with non-squamous NSCLC were included the IMpower110 study. With amendment 4 (June 2016) to the study protocol, patients with squamous NSCLC could also be included. Moreover, patients with non-squamous NSCLC with known EGFR mutation or ALK translocation could be included at the start of the study if they had already received targeted therapy and had experienced disease progression under the therapy or had not tolerated the therapy. With amendment 5 (March 2017) to the study protocol, these patients were excluded from the study. At this time, 18 patients with known EGFR mutation or ALK translocation had already been included in the study. Patients had to be in good general condition (according to Eastern Cooperative Oncology Group Performance Status [ECOG PS] ≤ 1). Prior systemic chemotherapy for the metastatic stage was not allowed.

The study IMpower110 included a total of 572 patients, assigned in a 1:1 ratio either to treatment with atezolizumab (N = 285) or with a platinum-based combination chemotherapy (N = 287). The treatment options for patients with non-squamous NSCLC comprised pemetrexed + cisplatin or pemetrexed + carboplatin; those for patients with squamous NSCLC were gemcitabine + cisplatin or gemcitabine + carboplatin. The planned number of chemotherapy cycles (4 or 6 cycles) were specified by the investigator prior to randomization. The choice of the platinum component (cisplatin or carboplatin) was made according to local practice, depending on the study centre. Randomization was stratified by sex (male, female), histology (squamous, non-squamous), ECOG PS (0, 1) and PD-L1 expression in the tumour tissue as determined by IHC on TC and IC (TC1/2/3 and any IC, TC0 and IC1/2/3).

Tumour tissue PD-L1 expression on TCsls and tumour-infiltrating IC was determined in the study using the Ventana PD-L1 assay (SP142; hereafter SP142 assay). Moreover, the PD-L1 expression of the tumour tissue was determined by means of further assays, e.g. the Dako Commercial Ready Assay (monoclonal, PD-L1-targeted antibody of the 22C3 clone) using immunohistochemistry.

Administration of atezolizumab was in compliance with the requirements of the SPC [32]. The platinum-based chemotherapies (pemetrexed + cisplatin or carboplatin, gemcitabine + cisplatin or carboplatin) were administered in accordance with the requirements of the respective SPCs [33-36] or the AM-RL for the off-label use (Appendix VI to Section K [37]). The platinum component of the chemotherapy was administered for a maximum of 4 to 6 cycles in the IMpower110 study. Thereafter, patients with non-squamous histology received maintenance treatment with pemetrexed; patients with squamous histology received BSC. Treatment was performed until disease progression, occurrence of unacceptable side effects or death. A switch of the patients from the study arm with the platinum-based chemotherapy to treatment with atezolizumab was not allowed in the IMpower110 study. There was no further limitation regarding subsequent therapies.

"Overall survival" was the primary outcome of the study. Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life and adverse events (AEs).

Studies with the ACT: KEYNOTE 024 and KEYNOTE 042

KEYNOTE 024

As already described in the dossier assessments on the projects A17-06 and A19-30 [8,10], KEYNOTE 024 is an open-label RCT on the comparison of pembrolizumab with a platinum-based combination chemotherapy. The study included adult patients with histologically or cytologically confirmed metastatic NSCLC without EGFR mutation or ALK translocation, whose tumours had a PD-L1 expression ≥ 50%. The patients had to be in good general condition (according to an ECOG PS ≤ 1). Prior systemic antineoplastic treatment for the metastatic stage was not allowed.

The KEYNOTE 024 study included a total of 305 patients, randomized in a 1:1 ratio either to treatment with pembrolizumab monotherapy (N = 154) or to one of 5 possible treatment options as platinum-based combination chemotherapy (N = 151). The treatment options were as follows: pemetrexed + cisplatin, pemetrexed + carboplatin, gemcitabine + cisplatin, gemcitabine + carboplatin, or paclitaxel + carboplatin, whereby the combination with pemetrexed was only an option for patients with non-squamous histology. The treatment suitable for each patient was specified by an investigator on an individual basis prior to randomization. Randomization was stratified by histology (squamous, non-squamous), geographical region (East Asia, not East Asia) and ECOG PS (0, 1).

In the study, the PD-L1 expression of the tumour tissue was determined by means of immunohistochemistry using the 22C3 assay.

The administration of pembrolizumab concurred with the requirements of the SPC [38]. The maximum treatment duration for pembrolizumab was 35 cycles. In the KEYNOTE 024 study, no patient in the total study population reached this maximum treatment duration. The platinum-based chemotherapies (pemetrexed + cisplatin, pemetrexed + carboplatin, gemcitabine + cisplatin, gemcitabine + carboplatin, paclitaxel + carboplatin) were administered in accordance with the requirements of the respective SPCs [33-36,39] or the AM-RL for the off-label use (Appendix VI to Section K [37]). The platinum component of the chemotherapy was administered for a maximum of 4 to 6 cycles in the KEYNOTE 024 study. Thereafter, patients with non-squamous histology could receive maintenance treatment with pemetrexed, which was also recommended. Overall, 46 (37%) of the patients with non-squamous histology in the comparator arm received such maintenance treatment.

Patients were treated until disease progression, occurrence of unacceptable side effects, or discontinuation of the study due to decision by the investigator or the patient. After disease progression, suitable patients in the comparator arm could switch to monotherapy with pembrolizumab. The approval of pembrolizumab specifies this treatment option after prior chemotherapy. There was no further limitation regarding subsequent therapies.

The primary outcome of the study was PFS. Patient-relevant secondary outcomes were “overall survival”, outcomes on morbidity, health-related quality of life and AEs.

KEYNOTE 042

KEYNOTE 042 is an ongoing, randomized, open-label RCT. The study compared pembrolizumab with a combination of carboplatin and either paclitaxel or pemetrexed. A total of 1274 patients were randomly allocated to the intervention arm (pembrolizumab: N = 637) or to the comparator arm (N = 637) in a 1:1 ratio. Randomization was stratified by ECOG PS (0, 1), histology (squamous, non-squamous), PD-L1 expression (≥ 50%, 1 to 49%) and geographical region (East Asia/not East Asia). The study included adults with histologically or cytologically confirmed diagnosis of NSCLC with locally advanced or metastatic tumours with PD-L1 expression ≥ 1%. Prior systemic treatment was not allowed in the studies. For patients

who had received adjuvant or neoadjuvant therapy, treatment had to be terminated at least 6 months prior to the development of metastases. The ECOG-PS had to be 0 or 1 in the included patients. Prior to randomization, an investigator decided which treatment option (pemetrexed + carboplatin or paclitaxel + carboplatin) would be suitable for each individual patient in the event of randomization to the comparator arm; however, the combination with pemetrexed was only considered for patients with non-squamous histology.

In the study, the PD-L1 expression of the tumour tissue was determined by means of immunohistochemistry using the 22C3 assay.

Patients in the intervention arm received pembrolizumab in accordance with the requirements of the SPC [38]. The maximum treatment duration was 35 cycles. In the KEYNOTE 042 study, this maximum treatment duration was only reached by approx. < 7% of the patients in the total study population. The platinum-based chemotherapies (pemetrexed + carboplatin or paclitaxel + carboplatin) were also administered in accordance with the requirements of the SPC [35,36,39] or the AM-RL for the off-label use (Appendix VI to Section K [37]). In the KEYNOTE 042 study, patients with non-squamous histology received carboplatin for a maximum of 4 to 6 cycles. After at least 4 cycles, patients with non-squamous histology could receive maintenance treatment with pemetrexed, which was also recommended. 196 (52.3%) patients with non-squamous histology in the total population of the KEYNOTE 042 study received such maintenance treatment.

Patients were treated until disease progression, complete response, occurrence of unacceptable side effects or study discontinuation due to decision by the investigator or the patient.

After discontinuation of the study medication (e.g. due to disease progression), the patients in both treatment arms could receive subsequent therapies. There were no limitations regarding the type of subsequent therapy. The study design did not explicitly intend a switch of treatment from the ACT to pembrolizumab monotherapy after disease progression.

“Overall survival” was the primary outcome of the study. Patient-relevant secondary outcomes were AEs.

Relevant subpopulations of the studies IMpower110 and KEYNOTE 042 (PD-L1 expression [TPS] ≥ 50%)

In each case, only a subpopulation from the included studies IMpower110 and KEYNOTE 042 is relevant. For both studies, the company presented results from a subpopulation of patients whose tumours had PD-L1 expression (TPS) ≥ 50 % of the TCs and who do not have EGFR mutations or ALK-positive NSCLC.

Patients were included in the IMpower110 study based on a positive PD-L1 detection in the tumour tissue using the SP142 assay. Among other things, the PD-L1 expression was also investigated using the 22C3 assay (in 534 of 554 patients [approx. 96%]). Since the PD-L1

expression was determined using the 22C3 assay both in the KEYNOTE 042 and in the KEYNOTE 024 study, the company used the results of the 22C3 assay as the basis for the formation of the subpopulation of the IMpower110 study in order to improve the comparability of the studies in the indirect comparison. This approach is comprehensible. However, the approval of atezolizumab in the therapeutic indication is based on data from a subpopulation of the study with high PD-L1 expression as determined using the SP142 assay (TC3, IC3). It must be ensured that the two assays consistently identify the same patients. Therefore, the concordance of the PD-L1 assays used is checked.

Concordance of the PD-L1 assays used

The publication on the IMpower110 study [15] shows that the results of the two PD-L1 assays SP142 and 22C3 are only partially consistent. The publication shows that the patient populations with high PD-L1 expression according to the 22C3 assay (TPS ≥ 50%) and those with high PD-L1 expression according to the SP142 assay (TC3, IC3) only overlap by about 50%. The systematic review on the comparability of PD-L1 assays in NSCLC by Koomen et al. 2020 [40] supports this assessment. Studies investigating the concordance between different assays identified a lower concordance between the assays 22C3 and SP142.

The moderate concordance between the SP142 and the 22C3 assay thus presents an uncertainty for the IMpower110 study. This is because the subpopulation of patients in the IMpower110 study included in the indirect comparison only corresponds to approx. 58% of the patients for whom atezolizumab was approved in the indication. However, in Module 4 A (Section 4.3.1.3.1.1 of the full benefit assessment), the company shows that the effects for the outcome "overall survival" in the IMpower110 study are almost identical between the populations with high PD-L1 expression according to the SP142 assay and according to the 22C3 assay. The subpopulation of the IMpower110 study presented by the company is therefore used for the indirect comparison.

Summary

The subpopulations of the IMpower110 study and the KEYNOTE 042 study relevant for the present research question are the populations with PD-L1 ≥ 50% on the TCs according to the 22C3 assay. KEYNOTE 024 included patients with PD-L1 ≥ 50% according to the 22C3 assay, therefore, the entire subpopulation is relevant.

Molecular testing of the patients

It can be inferred from the G-BA's specifications on the ACT that no molecularly stratified therapy (directed against EGFR, ALK, rapidly accelerated fibrosarcoma – isoform B [BRAF] or c-ros oncogene 1 [ROS1]) can be considered for the patients at the time of treatment with atezolizumab. The S3 guideline [41] stipulates that molecular pathological examinations regarding all therapeutically relevant molecular changes (according to the current status before first-line treatment, EGFR mutations in exons 18-21, ALK fusions and ROS1 fusions, BRAF V600 mutations as a minimum requirement) are to be initiated on the basis of the available

tumour tissue/TCs of all non-curatively treatable non-squamous NSCLC. This also applies to squamous cell carcinoma of never smokers/light smokers. According to the S3 guideline, targeted therapies are available for patients with the cited mutations or translocations [41].

In the 3 studies IMpower110, KEYNOTE 024 and KEYNOTE 042, patients with non-squamous NSCLC and unknown EGFR and/or ALK status had to be tested for this mutation or translocation before randomization into the 3 RCTs. However, in patients with squamous NSCLC and unknown EGFR and/or ALK status, testing was not required according to study protocols. Moreover, the respective study protocols do not indicate any planned screening or testing of the tumour tissue for ROS1 translocations or BRAF V600 mutations. It is therefore possible that the studies included patients with non-squamous NSCLC who had a ROS1 translocation or BRAF V600 mutation. It is also possible that never smokers or light smokers with squamous NSCLC who had an (unknown) EGFR mutation, ALK translocation, ROS1 translocation or BRAF V600 mutation were included. Patients with EGFR mutation or ALK translocation were excluded from the IMpower110 study only after a protocol amendment. At this time, 18 patients (3%) with known EGFR mutations or ALK translocations had already been included in the study.

Due to the rather rare occurrence of the individual mutations in the respective populations (non-squamous NSCLC/squamous NSCLC) and the proportionally smaller share of patients with squamous NSCLC in the individual studies, it is assumed that the number of included patients with the described mutations or translocations was too small to call the similarity or relevance of the study populations into question.

Similarity of the common comparator platinum-based combination chemotherapy in the studies

For the present indirect comparison, the company chose “platinum-based chemotherapy” as common comparator. In the 3 included studies IMpower110, KEYNOTE 024 and KEYNOTE 042, this includes different platinum-based combination chemotherapies. These differed between the studies: For example, paclitaxel was only used on the pembrolizumab side of the indirect comparison (see also Table 7), and in the KEYNOTE 042 study, only carboplatin was administered as the platinum component. Moreover, the use of gemcitabine was only planned for patients with squamous histology of the NSCLC in the IMpower110 study (see also Table 7).

Table 8 shows which options of platinum-based chemotherapy were administered to the patients in the 3 studies.

Table 8: Distribution of the platinum-based combination chemotherapy regimens of the studies IMpower110, KEYNOTE 024 and KEYNOTE 042

Study with atezolizumab	**Studies with pembrolizumab**	
IMpower110 (N = 126)	**KEYNOTE 024 (N = 151)**	**KEYNOTE 042 (N = 300)**
Non-squamous histology		
n = 88 (70%)	**n = 124 (82%)**	**n = 186 (62%)**
Received at least 1 dose: 79 (62.7%[a]) pemetrexed + ▪ cisplatin ▪ carboplatin maintenance treatment with pemetrexed; for all patients	Pemetrexed + ▪ cisplatin: 36 (29.2%)[b] ▪ carboplatin: 66 (53,7%) maintenance treatment with pemetrexed: 46 (30.5%)[b] gemcitabine + ▪ cisplatin: 4 (3.2%) ▪ carboplatin: 5 (4.1%) paclitaxel + carboplatin: 12 (9.8%)	Pemetrexed + carboplatin: ND for the relevant subpopulation paclitaxel + carboplatin: ND for the relevant subpopulation maintenance treatment with pemetrexed: ND for the relevant subpopulation
Squamous histology		
n = 38 (30%)	**n = 27 (18%)**	**n = 114 (38%)**
Received at least 1 dose: 36 (28.6 %[a]) gemcitabine + ▪ cisplatin ▪ carboplatin	Gemcitabine + ▪ cisplatin: 7 (25.9 %) ▪ carboplatin: 15 (55.5 %) paclitaxel + carboplatin: 5 (18.5%)	Paclitaxel + carboplatin: 114 (38%)
Total		
Cisplatin: 42 (33.3%) carboplatin: 76 (60.3%)	▪ Cisplatin: 47 (31.1%) ▪ carboplatin: 103 (68.2%)	Carboplatin: 300 (100%)
a. Institute's calculation, related to the entire control group N = 126 b. Institute's calculation, percentages related to the entire control group N = 151 N: number of randomized patients in the relevant (sub)populations; ND: no data		

Dossier assessment A17-06 [8] provides detailed information on the administered platinum-based chemotherapies for the KEYNOTE 024 study. In its dossier, the company presented no detailed information for the relevant subpopulation of the IMpower110 study. There is hardly any information on the administered chemotherapies for the relevant subpopulation of the KEYNOTE 042 study.

Platinum component of the common comparator

In Module 4 A of the dossier, the company describes that in the IMpower110 study, an individual decision was made for each patient as to which platinum derivative he or she should

receive. This decision was made by the investigators within the framework of routine medical practice, which also had to take into account the toxicity profile and comorbidities in each case. Thus, the choice of the platinum component of the IMpower110 study was in accordance with the specifications for the off-label use of carboplatin in NSCLC. The individual decision of the investigator for the choice of one of the two substances was documented accordingly by a query in the case report of the study.

The statements of the company do not correspond to the information in the study protocol of IMpower110. There, the choice of the platinum component of the platinum-based chemotherapy was described as being "in accordance with local practice". There is no information on possible selection criteria of the platinum components in the studies KEYNOTE 024 and KEYNOTE 042; in each case, there is only the information that the choice took place on an individual basis prior to randomization.

Table 8 shows that cisplatin and carboplatin were used with similar frequency in the comparator arms of IMpower110 and KEYNOTE 024. In the KEYNOTE 042 study, only carboplatin was administered.

Chemotherapy component of the common comparator

In the IMpower110 study, patients with non-squamous histology could only receive pemetrexed in addition to the platinum component. In KEYNOTE 024, gemcitabine or paclitaxel could also be administered; however, it can be seen that the majority of patients (82%) received pemetrexed. There is no information for the relevant subpopulation of the KEYNOTE 042 study.

In the IMpower110 study, patients with squamous histology only received gemcitabine in addition to the platinum component. In KEYNOTE 024, paclitaxel could also be administered, however, most patients (81%) received gemcitabine. In the KEYNOTE 042 study, patients with squamous histology could only receive paclitaxel.

A total of 11% of the patients (with squamous and non-squamous histology) received paclitaxel in KEYNOTE 024.

Maintenance treatment in the common comparator

In the IMpower110 study, all patients with non-squamous histology received maintenance therapy with pemetrexed, whereas in the KEYNOTE 024 study, only 37% of these patients received maintenance therapy with pemetrexed, although this maintenance therapy was recommended according to the study documents. In the KEYNOTE 042 study, administration of a maintenance treatment was at the investigator's discretion and was recommended. There was no information for the relevant subpopulation.

Summary

The described differences (paclitaxel only on the comparator side of the indirect comparison, maintenance treatment with pemetrexed only mandatory on the intervention side, in the KEYNOTE 042 study only carboplatin as platinum component) between the platinum-based chemotherapies of the 3 studies did not result in a fundamental questioning of the similarity of the common comparators for the indirect comparison. These differences were considered in the interpretation of the results of the outcomes on side effects.

Data cut-offs

From all 3 studies (IMpower110 as well as KEYNOTE 024 and KEYNOTE 042), those data cut-offs that had been prespecified were used for the assessment.

- The prespecified first data cut-off of 10 September 2018, originally planned as an interim analysis, was used for the IMpower110 study. For the more recent data cut-off of 4 February 2020, the available documents provide no information on whether this data cut-off was prespecified.
- For KEYNOTE 024, the second interim analysis of 9 May 2016 was used. After this data cut-off, all patients in the comparator arm had the option to switch to monotherapy with pembrolizumab due to the superiority of pembrolizumab in "overall survival".
- For KEYNOTE 042, the second interim analysis of 26 February 2018 was used since the results for overall survival were final at this time.

Planned duration of follow-up observation

Table 9 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 9: Planned duration of follow-up observation – RCT, indirect comparison: atezolizumab vs. pembrolizumab: (multipage table)

Study **outcome category** **outcome**	**Planned follow-up observation**
Study with atezolizumab	
IMpower110	
Mortality	
Overall survival	Until death, lost to follow-up or termination of study
Morbidity	
Symptoms, health status (EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D VAS)	Until disease progression (or beyond progression as long as the patient benefits for atezolizumab), withdrawal of consent or end of study
Health-related quality of life (EORTC QLQ-C30)	Until disease progression (or beyond progression as long as the patient benefits for atezolizumab), withdrawal of consent or end of study
Side effects	
AEs	Up to 30 days after the last dose of the study medication or initiation of new antineoplastic treatment
SAEs and immune-related AEs	Up to 90 days after the last dose of the study medication or initiation of new antineoplastic treatment
Studies with pembrolizumab	
KEYNOTE 024	
Mortality	
Overall survival	Until death
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-LC13), health status (EQ-5D VAS)	▪ Until 30 days after the last dose of the study medication ▪ at the end of treatment before progression: until progression or initiation of new antineoplastic treatment
Health-related quality of life (EORTC QLQ-C30)	▪ Until 30 days after the last dose of the study medication ▪ at the end of treatment before progression: until progression or initiation of new antineoplastic treatment
Side effects	
AEs	Until 30 days after the last dose of the study medication
SAEs and immune-related AEs	Until 90 days after the last dose of the study medication (or until 30 days after the last dose of the study medication if new antineoplastic treatment was initiated, whichever occurred first)

Table 9: Planned duration of follow-up observation – RCT, indirect comparison: atezolizumab vs. pembrolizumab: (multipage table)

Study **outcome category** **outcome**	**Planned follow-up observation**
KEYNOTE 042	
Mortality	
Overall survival	Until death
Morbidity	Not recorded
Health-related quality of life	Not recorded
Side effects	
AEs	Until 30 days after the last dose of the study medication or until initiation of a new antineoplastic treatment (whichever occurred first)
SAEs and immune-related AEs	Until 90 days after the last dose of the study medication (or until 30 days after the last dose of the study medication if new antineoplastic treatment was initiated, whichever occurred first)
AE: adverse event; EORTC: European Organization for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale	

In all 3 studies IMpower110, KEYNOTE 024 and KEYNOTE 042, the observation periods for the outcomes on morbidity, health-related quality of life and side effects were systematically shortened, as they were only recorded for the period of treatment with the study medication (until disease progression [only IMpower110 for outcomes on morbidity and health-related quality of life]; plus 90 days for SAEs and immune-mediated AEs or plus 30 days for AEs). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Patient characteristics

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

Table 10: Characteristics of the study populations – RCT, indirect comparison: atezolizumab vs. pembrolizumab, patients with high PD-L1 expression: (multipage table)

Study characteristic category	Study with atezolizumab		Studies with pembrolizumab			
	IMpower110		KEYNOTE 024		KEYNOTE 042	
	atezolizumab	platinum-based chemotherapy	pembrolizumab	platinum-based chemotherapy	pembrolizumab	platinum-based chemotherapy
	N = 134	N = 126	N = 154	N = 151	N = 299	N = 300
Age [years], mean (SD)	64 (9)	65 (9)	64 (10)	65 (10)	65 [33; 90][a]	66 [38; 85][a]
Sex [F/M], %	31/69	31/69	40/60	37/63	31/69	30/70
Family origin, n (%)						
White	109 (81)	107 (85)	125 (81)	126 (83)	ND	ND
Asian	22 (16)	16 (13)	ND	ND	ND	ND
Other	2 (2)	0 (0)	27 (18)	25 (17)	ND	ND
Unknown	1 (1)	3 (2)	2 (1)	0 (0)	ND	ND
Region, n (%)						
Europe	98 (73[b])[c]	99 (79[b])[c]	ND	ND	71 (24)	66 (22)
Rest of the world	36 (27)[b, d]	27 (21)[b, d]	ND	ND	228 (76)[b]	234 (78)[b]
Smoking status, n (%)						
Never-smoker	17 (13)	15 (12)	5 (3)	19 (13)	64 (21)	67 (22)
Active	36 (27)	34 (27)	34 (22)	31 (21)	57 (19)	59 (20)
Former	81 (60)	77 (61)	115 (75)	101 (67)	178 (60)	174 (58)
ECOG PS, n (%)						
0	40 (30)	44 (35)	54 (35)	53 (35)	96 (32)	91 (30)
1	94 (70)	82 (65)	99 (64)	98 (65)	203 (68)	209 (70)
Unknown	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Disease stage, n (%)						
IIIB	0 (0)	0 (0)	1 (1)	1 (1)	ND[e]	ND[e]
IV	134 (100)	126 (100)	153 (99)	150 (99)	ND	ND

Table 10: Characteristics of the study populations – RCT, indirect comparison: atezolizumab vs. pembrolizumab, patients with high PD-L1 expression: (multipage table)

Study characteristic category	Study with atezolizumab		Studies with pembrolizumab			
	IMpower110		KEYNOTE 024		KEYNOTE 042	
	atezolizumab	platinum-based chemotherapy	pembrolizumab	platinum-based chemotherapy	pembrolizumab	platinum-based chemotherapy
	N = 134	N = 126	N = 154	N = 151	N = 299	N = 300
Number of metastases at start of study						
Mean (SD)	3.0 (1.4)	3.2 (1.3)	ND	ND	ND	ND
Median [min; max]	3 [1; 8]	3 [1; 9]	ND	ND	ND	ND
Metastases, n (%)						
M0	ND	ND	1 (1)	1 (1)	ND	ND
M1	ND	ND	29 (19)	34 (23)	ND	ND
M1A	ND	ND	47 (31)	41 (27)	ND	ND
M1B	ND	ND	77 (50)	74 (49)	ND	ND
MX	ND	ND	0 (0)	1 (1)	ND	ND
Time since initial diagnosis [months]						
Mean (SD)	ND	ND	5.7 (13.4)	6.2 (23.7)	ND	ND
Median [min; max]	ND	ND	1.7 [0.7; 114.8]	1.7 [0.5; 230.8]	ND	ND
Tumour size at baseline [mm]						
Mean (SD)	92.1 (59.8)	111.0 (58.7)	90.9 (53.4)	99.8 (63.4)	ND	ND
Median [min; max]	81.5 [10.2; 390.0]	108.5 [17.0; 265.0]	82.0 [14.0; 322.0]	83.5 [14.0; 369.0]	ND	ND
Brain metastases, n (%)						
Yes	ND	ND	18 (12)	10 (7)	19 (6)	15 (5)
No	ND	ND	136 (88)	141 (93)	280 (94)	284 (95)
Histology, n (%)						
Squamous	34 (25)	38 (30)	29 (19)	27 (18)	107 (36)	114 (38)
Non-squamous	100 (75)	88 (70)	125 (81)	124 (82)	192 (64)	186 (62)

Table 10: Characteristics of the study populations – RCT, indirect comparison: atezolizumab vs. pembrolizumab, patients with high PD-L1 expression: (multipage table)

Study characteristic category	Study with atezolizumab		Studies with pembrolizumab			
	IMpower110		KEYNOTE 024		KEYNOTE 042	
	atezolizumab	platinum-based chemotherapy	pembrolizumab	platinum-based chemotherapy	pembrolizumab	platinum-based chemotherapy
	N = 134	N = 126	N = 154	N = 151	N = 299	N = 300
Prior therapies, n (%)						
Adjuvant prior therapy	ND	ND	6 (4)	3 (2)	8 (3)[f]	4 (1)[f]
Neoadjuvant prior therapy	ND	ND	3 (2)	1 (1)	< 1 (< 1)[f]	5 (2)[f]
Platinum-based chemotherapy, n (%)						
Cisplatin	NA	42 (33)[g]	NA	47 (31)[b]	NA	0 (0)
Carboplatin	NA	76 (60)[g]	NA	103 (68)[b]	NA	300 (100)
Treatment discontinuation, n (%)	85 (64)[h]	103 (82)[h, i]	80 (52[b])	106 (70[b])	217 (73[b])	194 (65[b])
Study discontinuation, n (%)	58 (43)[h]	71 (56)[bh]	47 (31)[b]	69 (46)[b]	ND	ND

a. Median [min; max].
b. Institute's calculation.
c. Europe and Middle East.
d. Summary: North America, South America and Asia-Pacific.
e. Data only available for locally advanced: 27 (9%) in the pembrolizumab arm and 35 (12%) in the chemotherapy arm, or metastatic: 272 (91%) in the pembrolizumab arm versus 265 (88%) in the chemotherapy arm.
f. Prior therapy for non-metastatic disease.
g. Data for patients who received at least 1 dose of the study medication (N = 114), percentages: Institute's calculation based on the randomized population.
h. Data cut-off 10 September 2018.
i. Data presumably for patients who discontinued at least on chemotherapy component [carboplatin 36/76 (47.4%), cisplatin 24/42 (57.1%), pemetrexed 68/79 (86.1%) and gemcitabine 17/36 (47.2%)]

ECOG: Eastern Cooperative Oncology Group; f: female; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; NA: not applicable; ND: no data; RCT: randomized controlled trial; SD: standard deviation

Information on the interesting patient characteristics are not available for all 3 studies. However, based on the available information, the populations can be assessed as sufficiently comparable both between the IMpower110, KEYNOTE 024 and KEYNOTE 042 studies and between the treatment arms in each of the individual studies.

The mean age of the patients included in the studies IMpower110, KEYNOTE 024 and KEYNOTE 042 was 65 years, most of them were male and white (information on the family origin were not available for the KEYNOTE 024 study). Almost all patients had disease stage IV (IMpower110, KEYNOTE 024) or were in the metastatic stage (KEYNOTE 042). The majority of the patients included in the studies KEYNOTE 024 and KEYNOTE 042 had no brain metastases; data on the number of brain metastases in the IMpower110 study are not available.

The major difference between the studies is due to the different treatment options within the framework of the platinum-based chemotherapy (see also the section on the similarity of the common comparator “platinum-based combination chemotherapy” in the above studies). In each of the studies IMpower110 and KEYNOTE 024, approx. 32% of the patients in the relevant subpopulation received cisplatin and the other patients received carboplatin. All patients of the relevant subpopulation of the KEYNOTE 042 study received carboplatin. This difference did not raise doubts about the suitability of KEYNOTE 042 for an indirect comparison, however.

Treatment duration and observation period

Table 11 shows the mean and median treatment durations of the patients and the median observation periods for individual outcomes.

Table 11: Information on the course of the study – RCT, indirect comparison: atezolizumab vs. pembrolizumab, patients with high PD-L1 expression

Study **duration of the study phase** **outcome category**	**Atezolizumab or pembrolizumab**	**Platinum-based chemotherapy**
Study with atezolizumab		
IMpower110 (data cut-off 18 September 2018)	N = 134	N = 126
Treatment duration [months]	ND[a]	ND[a]
Observation period [months]		
Overall survival		
Median [first quartile; third quartile]	15.2 [9.7; 18.8]	12.7 [8.9; 18.7]
Mean (SD)	ND	ND
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND	ND
Studies with pembrolizumab		
KEYNOTE 024 (data cut-off 6 May 2016)	N = 154	N = 150
Treatment duration [months]		
Median [min; max]	7.0 [0.0; 18.7]	3.5 [0.0; 16.8]
Mean (SD)	6.8 (4.8)	4.0 (3.5)
Observation period [months]	ND	ND
KEYNOTE 042	N = 299	N = 300
Treatment duration [months]	ND	ND
Observation period [months]	ND	ND

a. No data available for the relevant subpopulation.

max: maximum; min: minimum; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

For the IMpower110 study, information on the observation period is only available for the outcome "overall survival". This was about 3 months longer in the intervention arm than in the comparator arm. For the KEYNOTE 024 study, information is only available for the treatment duration. This was about twice as long as in the comparator arm. The observation period for side effects in the KEYNOTE 024 study can be estimated on the basis of the data on median treatment duration because the recording of AEs was planned for up to 30 or of SAEs up to 90 days after the last study medication. For the KEYNOTE 042 study, information was neither available for the treatment duration nor for the observation period. The similarity of the studies in terms of treatment durations and observation periods cannot be investigated due to the lack of information.

Subsequent therapies

Available data on the subsequent therapies that patients in the studies received in the indirect comparison after discontinuation of the study medication are incomplete.

No information on subsequent therapies in the relevant subpopulation was available for the IMpower110 study. There is only the information that 29 (30%) of the patients from the comparator arm received immunotherapy as subsequent therapy at the relevant data cut-off of 10 September 2018. However, this information refers to the population with high PD-L1 expression according to the SP142 assay (TC3/IC3).

At the time point of the second interim analysis of 9 May 2016, the proportion of patients with subsequent therapy was 22.7% in the intervention arm and 16.6% in the comparator arm of the KEYNOTE 024 study. In the comparator arm, 66 (43.7%) patients had switched to monotherapy with pembrolizumab.

No information on concrete subsequent therapies in the relevant subpopulation was available for the KEYNOTE 042 study. At the time point of the data cut-off of 26 February 2018, the proportion of patients with antineoplastic subsequent therapy in the entire subpopulation was 37.7% (N = 240) in the intervention arm and 44.0% (N = 280) in the comparator arm. In the comparator arm, 28 (4.4%) patients had switched to monotherapy with pembrolizumab.

The similarity of the studies in terms of subsequent therapies cannot be assessed due to the lack of information.

Summary of the similarities of the studies in the adjusted indirect comparison

Similarity is a key requirement for the consideration of studies in the adjusted indirect comparison. The 3 studies IMpower110, KEYNOTE 024 and KEYNOTE 042 have a very similar study design and the patient populations are also sufficiently similar. Differences between the studies (IMpower110, KEYNOTE 024 and KEYNOTE 042) are particularly found in the common comparator platinum-based chemotherapy (paclitaxel only on the comparator side of the indirect comparison, maintenance treatment with pemetrexed only mandatory on the intervention side, in KEYNOTE 042 only carboplatin as platinum component). Certain aspects cannot be assessed due to missing data (treatment and observation periods, subsequent therapies). Overall, the similarity assumption for the indirect comparison is not rejected. However, the described differences between the platinum-based chemotherapies of the studies were taken into account when interpreting the results on AEs.

The homogeneity assumption is another key requirement for the consideration of studies in the adjusted indirect comparison. For the atezolizumab side, an investigation of homogeneity was not possible as only one study was available. For both pembrolizumab studies included, heterogeneity was checked in the framework of the meta-analytical summary for the outcome “overall survival”. No important heterogeneity was determined for the results of this outcome.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, indirect comparison: atezolizumab vs. pembrolizumab

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
Atezolizumab vs. chemotherapy							
IMpower110	Yes	Yes	No	No	Yes	No	Low
Pembrolizumab vs. chemotherapy							
KEYNOTE 024	Yes	Yes	No	No	Yes	No	Low
KEYNOTE 042	Yes	Yes	No	No	Yes	No	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the studies considered. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.3.1.2 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

For the studies IMpower110, KEYNOTE 024 and KEYNOTE 042, the company stated that the patient populations in the studies were comparable to typical patients in Germany, so that their results could be transferred to the German healthcare context. The company based these statements on demographic and disease-specific characteristics, such as the study populations being predominantly Caucasian (IMpower110, KEYNOTE 024) and male, and the majority having an ECOG PS of 1 at baseline. Moreover, the comparator therapy administered in the 3 studies, platinum-based chemotherapy with or without bevacizumab, was recommended by relevant guidelines at the time of conception and at the start of the study and thus corresponded to the German healthcare context at the time.

The company considered the results of the 3 studies IMpower110, KEYNOTE 024 and KEYNOTE 042 to be transferable to the German healthcare context. Thus, overall, the results of the indirect comparison could also be transferred to the German health care context.

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

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - overall survival
- Morbidity
  - health status recorded with the VAS of the EQ-5D questionnaire
  - symptoms, recorded with the EORTC QLQ-C30 and EORTC QLQ-LC13
- Health-related quality of life
  - health-related quality of life, recorded with the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - immune-related AEs
  - further specific AEs, if any

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

Table 13 shows for which outcomes data were available in the studies included.

Table 13: Matrix of outcomes – RCT, indirect comparison: atezolizumab vs. pembrolizumab

Study	Outcomes								
	Overall survival	Health status (EQ-5D VAS)	Symptoms (EORTC QLQ-C30, QLQ-LC13)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-related AEs	Further specific AEs
Atezolizumab vs. chemotherapy									
IMpower110	Yes	No[b]	No[b]	No[b]	Yes	Yes	Yes	No[b]	No[c]
Pembrolizumab vs. chemotherapy									
KEYNOTE 024	Yes	No[d]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
KEYNOTE 042	Yes	No[e]	No[e]	No[e]	No[f]	No[f]	No[f]	No[f]	No[c]
Indirect comparison possible	Yes	No[g]	No[g]	No[g]	No[h]	No[h]	No[h]	No[g]	No[g]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. No data available for the relevant subpopulation.
c. Analyses on AEs are not available, therefore, a choice of specific AEs was impossible.
d. No usable data available.
e. Outcome not recorded.
f. No data available.
g. Not possible as results are not available for at least 1 edge of the indirect comparison.
h. Requirement for the certainty of results to perform an adjusted indirect comparison is not met (see Section 2.3.2.2).

ACT: appropriate comparator therapy; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

An indirect comparison could not be performed for the outcomes "health status", outcomes on symptoms, health-related quality of life and immune-related AEs, as the company did not provide data for the relevant subpopulation of the IMpower110 study and thus no results were available for at least one edge of the indirect comparison. Since, due to the open-label design of the included studies, the results for the outcomes on health status, symptoms and health-related quality of life had a high risk of bias, these could not be used for the indirect comparison even if they were available (see also the following Section 2.3.2.2). For the outcome "health status", no usable data are available for the KEYNOTE 024 study either, and this outcome was not recorded in the KEYNOTE 042 study.

The choice of further specific AEs based on the frequency and differences between the treatment arms for the indirect comparison was not possible because no data on common AEs were available for the relevant subpopulations of the studies IMpower110 and KEYNOTE 042.

2.3.2.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – indirect comparison: atezolizumab vs. pembrolizumab

Study	Study level	Outcomes								
		Overall survival	Health status (EQ-5D VAS)	Symptoms (EORTC C30, EORTC QLQ-LC-13)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-related AEs	Further specific AEs[b]
Atezolizumab vs. chemotherapy										
IMpower110	N	N	–[b]	–[b]	–[b]	H[c]	H[c]	H[d]	–[b]	–[e]
Pembrolizumab vs. chemotherapy										
KEYNOTE 024	N	N	–[f]	–[f]	–[f]	H[g]	H[g]	H[d]	–[f]	–[f]
KEYNOTE 042	N	N	–[h]	–[h]	–[h]	–[i]	–[i]	–[i]	–[i]	–[e]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. No data available for the relevant subpopulation.
c. High proportion of incomplete observations for potentially informative reasons, as AEs or SAEs were only followed up until 30 or 90 days after administration of the last study medication.
d. Lack of blinding in subjective recording of outcomes.
e. Analyses on AEs are not available, therefore, a choice of specific AEs was impossible.
f. Not assessed, as indirect comparison not calculable.
g. High proportion of incomplete observations for potentially informative reasons (48% of the patients in the pembrolizumab arm and 64% in the control arm discontinued treatment prematurely).
h. Outcome not recorded.
i. No data available.

ACT: appropriate comparator therapy; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and Treatment of Cancer; H: high; L: low; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The outcome-specific risk of bias of the results on the outcome "overall survival" was rated as low for each of the studies IMpower110, KEYNOTE 024 and KEYNOTE 042. This concurs with the company's assessment.

For the results on the outcomes "SAEs" and "severe AEs", the risk of bias was rated as high for both the IMpower110 study and the KEYNOTE 024 study. This is due to incomplete observations in both studies because of incomplete follow-up observation for potentially informative reasons after treatment discontinuation. The high risk of bias of the results on the outcome "discontinuation due to AEs" results from the lack of blinding in both studies against the background of the subjective recording of the outcome. The assessment of the risk of bias for the results of the mentioned outcomes is consistent with the company's assessment.

If only one study is available on one edge of an indirect comparison and results of individual outcomes of this study have a high risk of bias, the certainty of results required to conduct an adjusted indirect comparison is insufficient. Thus, there is no sufficient certainty of results for an adjusted indirect comparison for any of the outcomes of the side effects category for which usable data are available in the individual studies. Data for the present assessment that allow a meaningful adjusted indirect comparison are only available for overall survival. This deviates from the approach of the company, which, in addition to the outcome "overall survival", also used the outcomes "AEs", "SAEs", "discontinuation due to AEs" and "severe AEs" for an adjusted indirect comparison.

2.3.2.3 Results

Table 15 summarizes the results on the comparison of atezolizumab with pembrolizumab for research question 1 of the present benefit assessment. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Kaplan-Meier curves on the outcome "overall survival" and on the outcomes on side effects can be found in Appendix B of the full dossier assessment. The forest plots of the meta-analyses calculated by the Institute can be found in Appendix C of the full dossier assessment. Results on common AEs are not available for the respective relevant subpopulations of the studies IMpower110 and KEYNOTE 042. For the KEYNOTE 024 study, information on common AEs can be found in the Appendix of dossier assessment A17-06 [8].

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – atezolizumab vs. pembrolizumab, patients with high PD-L1 expression: (multipage table)

Outcome category **outcome** **comparison** **study**	**Atezolizumab or pembrolizumab** **N**	**median time to event in months [95% CI]** **patients with event n (%)**	**Platinum-based chemotherapy** **N**	**median time to event in months [95% CI]** **patients with event n (%)**	**Group difference** **HR [95% CI]; p-value**
Mortality					
All-cause mortality					
Atezolizumab vs. platinum-based chemotherapy					
IMpower110 (data cut-off 10 September 2018)	134	20.2 [13.3; NC] 53 (39.6)	126	11.0 [8.8; 16.5] 67 (53.2)	0.57 [0.39; 0.82]; 0.002[a]
Pembrolizumab vs. platinum-based chemotherapy					
KEYNOTE 024 (data cut-off 9 May 2016)	154	NA 44 (28.6)	151	NA [9.4; NC] 64 (42.4)	0.60 [0.41; 0.89]; 0.010[b]
KEYNOTE 042 (data cut-off 26 February 2018)	299	20.0 [15.4; 24.9]; ND	300	12.2 [10.4; 14.2]; ND	0.69 [0.56; 0.85]; < 0.001[c]
Total					0.67 [0.56; 0.80]; < 0.001[d]
Indirect comparison using common comparators[e]:					
Atezolizumab vs. pembrolizumab					0.85 [0.56; 1.29]; 0.449[f]
Morbidity					
Health status (EQ-5D VAS)	No usable data[g]				
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)	No usable data[g]				
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-LC13)	No usable data[g]				
Side effects					
AEs (supplementary information)					
Atezolizumab vs. platinum-based chemotherapy					
IMpower110 (data cut-off 10 September 2018)	134	ND 118 (88.1)	114	ND 104 (91.2)	–
Pembrolizumab vs. platinum-based chemotherapy					
KEYNOTE 024 (data cut-off 9 May 2016)	154	ND 148 (96.1)	150	ND 145 (96.7)	–
KEYNOTE 042 (data cut-off 26 February 2018)	299	ND	300	ND	–

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – atezolizumab vs. pembrolizumab, patients with high PD-L1 expression: (multipage table)

Outcome category outcome comparison study	Atezolizumab or pembrolizumab N	Atezolizumab or pembrolizumab median time to event in months [95% CI] patients with event n (%)	Platinum-based chemotherapy N	Platinum-based chemotherapy median time to event in months [95% CI] patients with event n (%)	Group difference HR [95% CI]; p-value
SAEs					
Atezolizumab vs. platinum-based chemotherapy					
IMpower110 (data cut-off 10 September 2018)	134	ND 39 (29.1)	114	ND 31 (27.2)	0.87 [0.54; 1.41]; 0.579[h]
Pembrolizumab vs. platinum-based chemotherapy					
KEYNOTE 024 (data cut-off 9 May 2016)	154	ND 68 (44.2)	150	ND 66 (44.0)	1.00 [0.71; 1.41]; 0.994[b]
KEYNOTE 042 (data cut-off 26 February 2018)	299	ND	300	ND	ND
Indirect comparison using common comparators[e]:					
Atezolizumab vs. pembrolizumab					_[i]
Severe AEs[j]					
Atezolizumab vs. platinum-based chemotherapy					
IMpower110 (data cut-off 10 September 2018)	134	ND 43 (32.1)	114	ND 62 (54.4)	0.37 [0.25; 0.56]; < 0.001[h]
Pembrolizumab vs. platinum-based chemotherapy					
KEYNOTE 024 (data cut-off 9 May 2016)	154	ND 82 (53.2)	150	ND 109 (72.7)	0.49 [0.36; 0.66]; < 0.001[b]
KEYNOTE 042 (data cut-off 26 February 2018)	299	ND	300	ND	ND
Indirect comparison using common comparators[e]:					
Atezolizumab vs. pembrolizumab					_[i]
Discontinuation due to AEs					
Atezolizumab vs. platinum-based chemotherapy					
IMpower110 (data cut-off 10 September 2018)	134	ND 5 (3.7)	114	ND 25 (21.9)	0.12 [0.05; 0.32]; < 0.001[h]
Pembrolizumab vs. platinum-based chemotherapy					
KEYNOTE 024 (data cut-off 9 May 2016)	154	ND 14 (9.1)	150	ND 21 (14)	0.60 [0.31; 1.19]; 0.144[b]
KEYNOTE 042 (data cut-off 26 February 2018)	299	ND	300	ND	ND
Indirect comparison using common comparators[e]:					
Atezolizumab vs. pembrolizumab					_[i]

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – atezolizumab vs. pembrolizumab, patients with high PD-L1 expression: (multipage table)

Outcome category outcome comparison study	Atezolizumab or pembrolizumab N	Atezolizumab or pembrolizumab median time to event in months [95% CI] patients with event n (%)	Platinum-based chemotherapy N	Platinum-based chemotherapy median time to event in months [95% CI] patients with event n (%)	Group difference HR [95% CI]; p-value
Immune-related AEs					
Atezolizumab vs. platinum-based chemotherapy					
IMpower110 (data cut-off 10/09/2018)	134	ND	114	ND	
Pembrolizumab vs. platinum-based chemotherapy					
KEYNOTE 024 (data cut-off 9 May 2016)	154	–[k]	150	–[k]	
KEYNOTE 042 (data cut-off 26 February 2018)	299	ND	300	ND	

a. HR and 95% CI: Cox regression model, stratified by sex and baseline ECOG PS, p-value from log-rank test.
b. HR and 95% CI: Cox regression model, stratified by geographical region, ECOG PS and histology, p-value from Wald test.
c. HR and 95% CI: Cox regression model, stratified by geographical region, ECOG PS and histology, p-value from log-rank test.
d. Institute's calculation, meta-analysis with fixed effect (inverse variance).
e. Indirect comparison according to Bucher [3].
f. Institute's calculation.
g. Not possible as results are not available for at least 1 edge of the indirect comparison.
h. HR and 95% CI: unstratified analysis, p-value from log-rank test.
i. No presentation of effect estimations, as no hint, e.g. of an added benefit, is derived due to the outcome-specific high risk of bias in at least one of the studies of the indirect comparison and the resulting insufficient certainty of results of the indirect comparison (see Section 2.3.2.2).
j. Operationalized as CTCAE grade ≥ 3.
k. Results not presented, as an indirect comparison is not possible.

ACT: appropriate comparator therapy; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; ND: not data; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; VAS: visual analogue scale

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Moreover, the risk of bias of the results on the outcomes of the category "side effects" was rated as high in the studies IMpower110 and KEYNOTE 024. The certainty of results of the results from the indirect comparisons is therefore not sufficient. Therefore, no indirect comparison was performed for these outcomes, and no hint of an added benefit was derived. This assessment

does not concur with that of the company, which conducted indirect comparisons for all outcomes of the category “side effects” considered by it.

Mortality

Overall survival

The adjusted indirect comparison showed no statistically significant difference between the treatment groups for the outcome "overall survival". Hence, there was no hint of an added benefit of atezolizumab in comparison with pembrolizumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Module 4 A of the dossier provides no usable data for the outcomes of the morbidity category. Hence, there was no hint of an added benefit of atezolizumab in comparison with pembrolizumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

Module 4 A provides no usable data for the outcomes of the category "health-related quality of life". Hence, there was no hint of an added benefit of atezolizumab in comparison with pembrolizumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Side effects

Due to an insufficient certainty of results in the two studies IMpower110 and KEYNOTE 024, no indirect comparison was calculated for the outcomes “SAEs”, “severe AEs” and “discontinuation due to AEs”. The differences regarding the maintenance treatments in the common comparator arms (platinum-based chemotherapies) must be considered. Moreover, there are no usable data for the outcome “immune-related AEs” for the relevant subpopulation of the IMpower110 study. Hence, no usable data on the AE outcomes are available for the indirect comparison. This resulted in no hint of greater or lesser harm from atezolizumab in comparison with pembrolizumab; greater or lesser harm is therefore not proven.

For the outcomes “SAEs” and "severe AEs” this concurs with the assessment of the company. The company derived a hint of an added benefit for the outcome "discontinuation due to AEs”.

2.3.2.4 Subgroups and other effect modifiers

Module 4 A of the dossier provides no subgroup analyses for the indirect comparison. Thus, no conclusions on potential effect modifications are possible for the comparison of atezolizumab and pembrolizumab.

2.3.3 Probability and extent of added benefit

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

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

2.3.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.3.2 (see Table 16).

Table 16: Extent of added benefit at outcome level: atezolizumab vs. pembrolizumab

Outcome category outcome	**Atezolizumab vs. pembrolizumab effect estimation [95% CI]; p-value probability[a]**	**Derivation of extent**
Mortality		
Overall survival	Indirect comparison: HR: 0.85 [0.56; 1.29]; 0.449[b]	Lesser benefit/added benefit not proven
Morbidity		
Health status (EQ-5D VAS)	No sufficient data[c]	Lesser benefit/added benefit not proven
Symptoms (EORTC C30, EORTC QLQ-LC-13)	No sufficient data[c]	Lesser benefit/added benefit not proven
Health-related quality of life		
Health-related quality of life (EORTC QLQ-C30)	No sufficient data[c]	Lesser benefit/added benefit not proven
Side effects		
SAEs	No usable data[d]	Greater/lesser harm not proven
Severe AEs[e]	No usable data[d]	Greater/lesser harm not proven
Discontinuation due to AEs	No usable data[d]	Greater/lesser harm not proven
Immune-related AEs	No sufficient data[c]	Greater/lesser harm not proven
Further specific AEs	No sufficient data[c]	Greater/lesser harm not proven

a. Probability provided if statistically significant differences are present.
b. Institute's calculation.
c. Indirect comparison not possible as results are not available for at least 1 edge of the indirect comparison.
d. Effect estimation from indirect comparison not presented due to insufficient certainty of results.
e. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event

2.3.3.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of atezolizumab in comparison with pembrolizumab

Positive effects	Negative effects
–	–
For each of the outcomes of the categories “morbidity”, “health-related quality of life” and “side effects”, there are no usable data for the indirect comparison.	

Overall, based on the adjusted indirect comparison using the common comparator platinum-based chemotherapy, there are neither positive nor negative effects of atezolizumab in comparison with pembrolizumab.

However, it should be noted that usable results with sufficient certainty of results for an indirect comparison are only available for the outcome "overall survival”. There is no hint of an added benefit of atezolizumab for this outcome, as the indirect comparison showed no statistically significant difference. For the outcomes of the outcome categories of morbidity and health-related quality of life as well as for the outcomes “immune-related AEs” and further specific AEs, sufficient data are not available for at least 1 side of the indirect comparison. Usable data for an indirect comparison are not available for the outcomes "SAEs", "severe AEs” and “discontinuation due to AEs”, as the certainty of results was not sufficient for an indirect comparison. Moreover, the differences of the maintenance treatment in the platinum-based chemotherapies of the common comparators must be taken into account when interpreting the results on the outcomes of the side effects category. Balancing of benefit and harm is not possible as the results on the outcome categories “morbidity”, “health-related quality of life” and “side effects” are not usable.

In summary, for the first-line treatment of adult patients with metastatic NSCLC, there is no hint of an added benefit of atezolizumab compared to the ACT pembrolizumab for research question 1 of the present benefit assessment (TPS ≥ 50%); an added benefit is therefore not proven.

The assessment described above deviates from that of the company, which derived a non-quantifiable added benefit for all patients in the newly approved therapeutic indication of atezolizumab versus pembrolizumab as ACT - regardless of the presence of a TPS ≥ 50%.

2.4 Research question 2: patients with a TPS ≥ 1% and < 50% (PD-L1 expression)

2.4.1 Information retrieval and study pool

In Module 4 A of its dossier, the company did not consider research question 2, the assessment of the added benefit of atezolizumab in comparison with the ACT as first-line treatment of metastatic NSCLC in adult patients in the approved therapeutic indication of atezolizumab whose tumours had a TPS of ≥ 1% and < 50% (PD-L1 expression).

The RCT IMpower110 used by the company for research question 1 on the atezolizumab side, compares atezolizumab with a platinum-based combination chemotherapy (pemetrexed + cisplatin or carboplatin, gemcitabine + cisplatin or carboplatin). Thus, analyses of a subpopulation of the study population - patients in the approved therapeutic indication of atezolizumab whose tumours have a TPS of ≥ 1% and < 50% (PD-L1 expression) - could potentially be used for research question 2.

2.4.2 Results on added benefit

Module 4 A of the dossier provides no data for the assessment of the added benefit of atezolizumab in comparison with the ACT as first-line treatment of metastatic NSCLC in adult patients in the newly approved therapeutic indication of atezolizumab whose tumours have a TPS of ≥ 1% and < 50% (PD-L1 expression). Hence, there was no hint of an added benefit of atezolizumab in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

Module 4 A of the dossier provides no data for the assessment of the added benefit of atezolizumab in comparison with the ACT as first-line treatment of metastatic NSCLC in adult patients in the newly approved therapeutic indication of atezolizumab whose tumours have a TPS of ≥ 1% and < 50% (PD-L1 expression). An added benefit for these patients is therefore not proven.

This assessment deviates from the assessment of the company insofar as the company did not consider these patients of research question 2 in its assessment at all.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of atezolizumab in comparison with the ACT is summarized in Table 18.

Table 18: Atezolizumab – probability and extent of added benefit: (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
	First-line treatment of adult patients with metastatic NSCLC whose tumours express PD-L1 in ≥ 50% of the TCs or in ≥ 10% of the tumour-infiltrating ICs without EGFR mutations or ALK-positive NSCLC		
1	Patients with a TPS ≥ 50% (PD-L1 expression)[b]	Pembrolizumab as monotherapy	Added benefit not proven[c]
2	Patients with a TPS of ≥ 1% and < 50% (PD-L1 expression)[b]	▪ Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)[d] or ▪ 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[d] or ▪ carboplatin in combination with nab-paclitaxel or ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with non-squamous histology) or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with squamous histology) or ▪ monotherapy with gemcitabine or vinorelbine (only for patients with ECOG PS 2 as an alternative to platinum-based combination treatment)	Added benefit not proven

Table 18: Atezolizumab – probability and extent of added benefit: (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. It is assumed that the patients in the present therapeutic indication had no indication for definitive local therapy and that no molecularly stratified therapy (against EGFR, ALK, BRAF or ROS1) could be considered for the patients at the time of treatment with atezolizumab. It is also assumed that the patients were generally eligible for active antineoplastic therapy, which is why BSC was not considered as an ACT in the present case. c. Only patients with an ECOG PS of 0 or 1 were included in the studies for the indirect comparison. It remains unclear whether the observed results can be transferred to patients with an ECOG PS ≥ 2. d. On cisplatin/carboplatin in combination with a third-generation cytostatic agent: In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the two substances and on the existing comorbidities; see Appendix VI to Section K of the Pharmaceutical Directive. ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; 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; ROS1: c-ros oncogene 1; TC: tumour cells; TPS: Tumour Proportion Score			

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

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Please see full dossier assessment for full reference list.

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