Atezolizumab (NSCLC, first line)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Medical and scientific advice

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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

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

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Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
BSA	body surface area
CSR	clinical study report
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IV	intravenous
NCCN	National Comprehensive Cancer Network
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 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 23 September 2024.

Research question

The aim of this report is to assess the added benefit of atezolizumab in comparison with the appropriate comparator therapy (ACT) for first-line treatment of advanced non-small cell lung cancer (NSCLC) in adult patients who are ineligible for platinum-based therapy.

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

Table 2: Research questions of the benefit assessment of atezolizumab

Research question	Therapeutic indication[a]	ACT[b, c]
1	First-line treatment of advanced NSCLC in adult patients for whom platinum-based chemotherapy is not an option and whose tumours have no EGFR mutations or ALK translocations ▪ with PD-L1 expression ≥ 50% on tumour cells	▪ Pembrolizumab as monotherapy or ▪ cemiplimab as monotherapy
2	First-line treatment of advanced NSCLC in adult patients for whom platinum-based chemotherapy is not an option and whose tumours have no EGFR mutations or ALK translocations ▪ with PD-L1 expression < 50% on tumour cells	▪ Gemcitabine as monotherapy or ▪ vinorelbine as monotherapy

a. For the present therapeutic indication, it is assumed as per G-BA that there is neither a therapeutic indication for definitive radiochemotherapy nor for definitive local therapy. In addition, it is assumed that molecularly stratified therapy (directed against BRAF, KRAS G12C, METex14, RET, or ROS1) is not an option for the patients at the time of treatment with atezolizumab as monotherapy.
b. Presented is the respective ACT specified by the G-BA.
c. The approval and dosing information of the drugs' SPCs must be adhered to, and any deviations justified separately.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MET: mesenchymal-epithelial transition factor; METex14: MET gene exon 14; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1; SPC: Summary of Product Characteristics

In the present assessment, the following terms are used for the patient populations of the 2 research questions:

- Research question 1: patients with programmed cell death ligand 1 (PD-L1) expression ≥ 50% on tumour cells
- Research question 2: patients with PD-L1 expression < 50% on tumour cells

The company followed the specification of the ACT for both research questions.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive the added benefit. This concurs with the company's inclusion criteria.

Research question 1: patients with PD-L1 expression ≥ 50% on tumour cells

Results

No data are available for the assessment of the added benefit of atezolizumab in comparison with the ACT for first-line treatment of advanced NSCLC in adult patients with PD-L1 expression ≥ 50% on tumour cells who are ineligible for platinum-based chemotherapy. There is no hint of an added benefit of atezolizumab in comparison with the ACT; an added benefit for these patients is therefore not proven.

Results on added benefit

Because no relevant study is available for answering the present research question, there is no hint of added benefit of atezolizumab in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: patients with PD-L1 expression < 50% on tumour cells

Evidence presented by the company – IPSOS study

The IPSOS study is a multicentre, open-label RCT comparing atezolizumab with vinorelbine or gemcitabine. The study included adult patients with histologically or cytologically confirmed diagnosis of Stage IIIB or IV NSCLC (classification as per the American Joint Committee on Cancer [AJCC] 7th edition) without epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation. Patients were enrolled regardless of PD-L1 expression status of the tumour cells. However, at enrolment, PD-L1 expression of the tumour tissue was determined in an immunohistochemical test by a central laboratory in order to stratify based on PD-L1 expression. According to the study protocol, platinum-based combination chemotherapy had to be unsuitable for the patients included in the study.

The IPSOS study included a total of 453 patients who were randomly allocated in a 2:1 ratio to treatment with atezolizumab (N = 302) or to chemotherapy with vinorelbine or gemcitabine (N = 151). Randomization was stratified by histology (squamous versus non-squamous), the presence of brain metastases (yes/no) and PD-L1 expression status (assessed by SP142 immunohistochemistry assay on tumour cells; positive/negative/unknown).

Treatment with atezolizumab was largely in compliance with the recommendations in the Summary of Product Characteristics (SPC) and was continued until disease progression, unacceptable toxicity or death. Contrary to the SPC recommendation, treatment with atezolizumab in the intervention arm was also possible after disease progression as determined by the Response Evaluation Criteria in Solid Tumours (RECIST). The monotherapies with vinorelbine and gemcitabine used in the comparator arm of the IPSOS study were not administered in compliance with the approval (see explanations below).

The primary outcome of the IPSOS study was overall survival. Further patient-relevant outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

As described above, only patients for whom platinum-based combination chemotherapy was not an option were enrolled in the IPSOS study. These were the following patients:

- Patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 2 or 3
- Patients who had an ECOG PS of 0 or 1 and were ≥ 70 years of age could be included if the following additional criteria were met:
  - substantial comorbidities and/or
  - contraindication(s) for platinum-based combination chemotherapy

According to the European Public Assessment Report (EPAR), in the approval procedure, the above criteria for unsuitability of platinum-based combination chemotherapy were considered by the European Medicines Agency (EMA) to be insufficient to represent the targeted fragile patient population. To address the EMA's criticism, the company subsequently defined further selection criteria in consultation with the EMA, based in part on the publications of De Marinis 2015 and Camerini 2022. Based on these criteria listed below, the company formed a subpopulation of the IPSOS study (referred to as "approval population" in the company's Module 4 A) from the total population:

- > 80 years, or
- ECOG PS 3, or
- ECOG PS 2 in combination with relevant comorbidities, or
- ≥ 70 years in combination with relevant comorbidities

A total of 405 of the 453 patients originally included in the study met the new criteria. The results of the approval population formed using the new criteria were considered robust enough by the EMA to be considered as supportive for the ultimately approved population of fragile patients who are ineligible for platinum-based combination chemotherapy.

The approval population formed by the company is considered sufficiently representative to represent the patient population who are ineligible for platinum-based combination chemotherapy.

From the approval population formed for the EMA, the company considered a subpopulation of patients whose tumours have a PD-L1 expression < 50% or an unknown PD-L1 expression status for research question 2 of the present benefit assessment. The subpopulation was formed on the basis of the results obtained with the Ventana PD-L1 (SP263) assay. The subpopulation presented by the company in Module 4 A comprises 229 (75.8%) of the 302 randomized patients in the intervention arm, and 115 (76.2%) of the 151 randomized patients in the control arm. The proportion of patients with unknown PD-L1 expression status totalled 8.7% of the presented subpopulation. The company did not explain to what extent the joint consideration of these patient groups is appropriate for research question 2.

IPSOS study unsuitable for the benefit assessment

No approval-compliant treatment in the comparator arm

Deviations for vinorelbine

According to the SPC, a once-weekly dosage is approved for monotherapy with vinorelbine in this therapeutic indication. According to the approval, the recommended regimen for oral administration of vinorelbine is 60 mg/m^2 of body surface area (BSA) for the first 3 administrations; for subsequent administrations, it is recommended to increase the dose to 80 mg/m^2 BSA, based on the measured neutrophil count. For the intravenous (IV) administration of vinorelbine, a dose of 25 to 30 mg/m^2 BSA once a week is recommended. In the IPSOS study, 84 (57%) of the patients in the comparator arm received vinorelbine monotherapy (oral or IV).

The doses specified in the study protocol of 60 mg/m^2 with an increase to 80 mg/m^2 BSA after 3 administrations (oral) and 25 to 30 mg/m^2 BSA (IV) for weekly dosing correspond to the information provided in the SPC. It can be inferred from version 1 of the study protocol (February 2017) that treatment had to be administered in compliance with the SPCs. However, as of version 3 of the study protocol (January 2018), it is stated that cyclical treatment regimens of either 21 days (dosing on Days 1 and 8) or 28 days (dosing on Days 1, 8 and 15) should be used for vinorelbine (oral or IV). The cyclical treatments of 21 or 28 days, which include a treatment-free week at the end of each cycle, do not correspond to the weekly dosing regimen recommended in the SPC. It is also unclear to what extent the doses of 60 mg/m^2 BSA for the first 3 administrations and 80 mg/m^2 BSA for the subsequent administrations, recommended for oral administration according to the SPC, were provided for in the cyclical treatment regimen.

The information on the total population in the clinical study report (CSR) shows that 64 of the 84 (76%) patients who received vinorelbine were treated in a 21- or 28-day cycle (with a one-week break at the end of each cycle), which deviates from the SPC. There is no information available on the proportion in the subpopulation of the IPSOS study presented by the company for research question 2.

Deviations for gemcitabine

According to the SPC, a 28-day treatment cycle (dosing on Days 1, 8 and 15) with 1000 mg/m^2 BSA is approved for monotherapy with gemcitabine. Gemcitabine treatment also requires close haematological monitoring with determination of platelet and granulocyte counts before each dose.

In the IPSOS study, 63 (43%) of the patients in the comparator arm received gemcitabine monotherapy. The dose level was 1000 to 1250 mg/m^2 BSA. Administration of 1000 mg/m^2 BSA corresponds to the SPC recommendations for monotherapy. The dosage of 1250 mg/m^2 BSA also used in the study is only approved for platinum-based combination therapy with gemcitabine, according to the SPC. Information on the proportion of patients who received 1250 mg/m^2 BSA is neither available for the subpopulation presented by the company for research question 2 nor for the total population. In addition, as for vinorelbine, cyclical treatment regimens of either 21 days (dosing on Days 1 and 8) or 28 days (dosing on Days 1, 8 and 15) were also used for gemcitabine. However, gemcitabine monotherapy is only approved for a 28-day treatment cycle. The 21-day cycle is only approved for platinum-based combination therapy with gemcitabine.

The information on the total population in the CSR shows that 57 out of 63 (90%) patients received gemcitabine in a 21-day cycle, which deviates from the SPC. In addition, there is no information available either for the total population or for the subpopulation as to which dose level (1250 mg/m^2 BSA or 1000 mg/m^2 BSA) was administered in which treatment cycle (21 or 28 days). It is therefore unclear how many patients were treated with an approval-compliant dose of 1000 mg/m^2 BSA in a 28-day treatment cycle.

Failure to administer the comparator therapy in compliance with the approval in the IPSOS study affects all patient-relevant outcomes

Overall, at least 82% (121 of 147) of the patients in the comparator arm of the study were not treated in compliance with the respective approval of vinorelbine or gemcitabine. Corresponding information on the number of patients in the subpopulation presented by the company for research question 2 is not available.

It cannot be ruled out that a lower dosing frequency than weekly administration is better tolerated for some of the patients in the fragile patient population under consideration (reduced general condition [ECOG PS ≥ 2] and/or advanced age [> 70 years] and/or

comorbidities). However, it would then be expected that vinorelbine treatment would be started with weekly dosing in compliance with the approval and that the dose and/or dosing frequency would be adjusted depending on toxicity and tolerability – as recommended in the SPC. Neither the IPSOS study documents nor the information in Module 4 A explain why some of the patients received weekly treatment, but the majority received cyclical treatment (21- or 28-day treatment cycle with a 1-week break). There is also no information in the study documents on the criteria used to decide in favour of or against the respective treatment regimens. Neither the current national S3 guideline nor the National Comprehensive Cancer Network (NCCN) provide recommendations regarding the dose level or dosing frequency of vinorelbine. Thus, there is no evidence that the study treatments deviating from the approval correspond to a standard in everyday practice.

With regard to gemcitabine administration, it should be noted that the higher dosage used in the IPSOS study than recommended in the SPC (1250 mg/m^2 BSA instead of 1000 mg/m^2 BSA) appears questionable in this fragile patient population. Neither the current national S3 guideline nor the NCCN provide any recommendations regarding the dose level or dosing frequency for monotherapy with gemcitabine in this therapeutic indication, either. As with vinorelbine, there is therefore no evidence that the administration of gemcitabine in the study, which deviated from the approval, corresponds to a standard in everyday practice.

Overall, a large proportion of patients in the comparator arm of the IPSOS study were not treated in compliance with the approval. The systematic deviation from the approval taking place in the comparator arm has a relevant influence on all outcomes (overall survival, morbidity, health-related quality of life, and side effects). The effect on the outcomes cannot be estimated. Therefore, the data presented by the company are disregarded for the benefit assessment.

Results on added benefit

Because no relevant study is available for answering the present research question, there is no hint of added benefit of atezolizumab in comparison with the ACT; an added benefit is therefore not proven.

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

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

Table 3: Atezolizumab – probability and extent of added benefit

Research question	Therapeutic indication[a]	ACT[b, c]	Probability and extent of added benefit
1	First-line treatment of advanced NSCLC in adult patients for whom platinum-based chemotherapy is not an option and whose tumours have no EGFR mutations or ALK translocations ▪ with PD-L1 expression ≥ 50% on tumour cells	▪ Pembrolizumab as monotherapy or ▪ cemiplimab as monotherapy	Added benefit not proven
2	First-line treatment of advanced NSCLC in adult patients for whom platinum-based chemotherapy is not an option and whose tumours have no EGFR mutations or ALK translocations ▪ with PD-L1 expression < 50% on tumour cells	▪ Gemcitabine as monotherapy or ▪ vinorelbine as monotherapy	Added benefit not proven

a. For the present therapeutic indication, it is assumed as per G-BA that there is neither a therapeutic indication for definitive radiochemotherapy nor for definitive local therapy. In addition, it is assumed that molecularly stratified therapy (directed against BRAF, KRAS G12C, METex14, RET, or ROS1) is not an option for the patients at the time of treatment with atezolizumab as monotherapy.
b. Presentation of the ACT specified by the G-BA.
c. The approval and dosing information of the drugs' SPCs must be adhered to, and any deviations justified separately.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MET: mesenchymal-epithelial transition factor; METex14: MET gene exon 14; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1; SPC: Summary of Product Characteristics

The G-BA decides on the added benefit.

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

I 2 Research question

The aim of this report is to assess the added benefit of atezolizumab in comparison with the ACT for first-line treatment of advanced NSCLC in adult patients who are ineligible for platinum-based therapy.

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

Table 4: Research questions of the benefit assessment of atezolizumab

Research question	Therapeutic indication[a]	ACT[b, c]
1	First-line treatment of advanced NSCLC in adult patients for whom platinum-based chemotherapy is not an option and whose tumours have no EGFR mutations or ALK translocations ▪ with PD-L1 expression ≥ 50% on tumour cells	▪ Pembrolizumab as monotherapy or ▪ cemiplimab as monotherapy
2	First-line treatment of advanced NSCLC in adult patients for whom platinum-based chemotherapy is not an option and whose tumours have no EGFR mutations or ALK translocations ▪ with PD-L1 expression < 50% on tumour cells	▪ Gemcitabine as monotherapy or ▪ vinorelbine as monotherapy

a. For the present therapeutic indication, it is assumed as per G-BA that there is neither a therapeutic indication for definitive radiochemotherapy nor for definitive local therapy. In addition, it is assumed that molecularly stratified therapy (directed against BRAF, KRAS G12C, METex14, RET, or ROS1) is not an option for the patients at the time of treatment with atezolizumab as monotherapy.
b. Presented is the respective ACT specified by the G-BA.
c. The approval and dosing information of the drugs' SPCs must be adhered to, and any deviations justified separately.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MET: mesenchymal-epithelial transition factor; METex14: MET gene exon 14; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1; SPC: Summary of Product Characteristics

In the present assessment, the following terms are used for the patient populations of the 2 research questions:

- Research question 1: patients with PD-L1 expression ≥ 50% on tumour cells
- Research question 2: patients with PD-L1 expression < 50% on tumour cells

The company followed the specification of the ACT for both research questions.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive the added benefit. This concurs with the company's inclusion criteria.

I 3 Research question 1: patients with PD-L1 expression ≥ 50% on tumour cells

I 3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on atezolizumab (status: 13 August 2024)
- bibliographical literature search on atezolizumab (last search on 12 August 2024)
- search in trial registries/trial results databases for studies on atezolizumab (last search on 19 August 2024)
- search on the G-BA website for atezolizumab (last search on 19 August 2024)
- bibliographical literature search on the ACT (last search on 12 August 2024)
- search in trial registries/trial results databases for studies on the ACT (last search on 13 August 2024)
- search on the G-BA website for the ACT (not conducted)

To check the completeness of the study pool:

- search in trial registries for studies on atezolizumab (last search on 15 October 2024); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check identified no relevant study allowing a direct comparison of atezolizumab versus the ACT. Since the company did not identify any RCTs for direct comparisons, it conducted an information retrieval for RCTs on the intervention and on the ACT for indirect comparisons, but again did not identify any studies based on this information retrieval.

I 3.2 Results on added benefit

No data are available for the assessment of the added benefit of atezolizumab in comparison with the ACT for first-line treatment of advanced NSCLC in adult patients with PD-L1 expression ≥ 50% on tumour cells who are ineligible for platinum-based chemotherapy. There is no hint of an added benefit of atezolizumab in comparison with the ACT; an added benefit for these patients is therefore not proven.

I 3.3 Probability and extent of added benefit

Since the company presented no data for the assessment of the added benefit of atezolizumab in comparison with the ACT for first-line treatment of advanced NSCLC in adult patients with PD-L1 expression ≥ 50% on tumour cells who are ineligible for platinum-based chemotherapy, an added benefit for these patients is not proven.

I 4 Research question 2: patients with PD-L1 expression < 50% on tumour cells

I 4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on atezolizumab (status: 13 August 2024)
- bibliographical literature search on atezolizumab (last search on 12 August 2024)
- search in trial registries/trial results databases for studies on atezolizumab (last search on 19 August 2024)
- search on the G-BA website for atezolizumab (last search on 19 August 2024)
- bibliographical literature search on the ACT (last search on 12 August 2024)
- search in trial registries/trial results databases for studies on the ACT (last search on 13 August 2024)
- search on the G-BA website for the ACT (not conducted)

To check the completeness of the study pool:

- search in trial registries for studies on atezolizumab (last search on 15 October 2024); for search strategies, see I Appendix A of the full dossier assessment

For the direct comparison of atezolizumab versus the ACT, the company identified the RCT MO29872 [3-6] (hereinafter referred to as IPSOS for short). The IPSOS study is unsuitable for the derivation of the added benefit of atezolizumab. This is due in particular to the fact that treatment in the comparator arm of the study largely deviated from the specifications of the approval (for detailed reasons, see the following sections).

The check for completeness of the study pool identified no relevant RCT for the direct comparison of atezolizumab versus the ACT for research question 2.

I 4.1.1 Evidence provided by the company

IPSOS study

The IPSOS study is a multicentre, open-label RCT comparing atezolizumab with vinorelbine or gemcitabine. The study included adult patients with histologically or cytologically confirmed diagnosis of Stage IIIB or IV NSCLC (classification as per the AJCC 7th edition) without EGFR mutation or ALK translocation. Patients were enrolled regardless of PD-L1 expression status of the tumour cells. However, at enrolment, PD-L1 expression of the tumour tissue was determined in an immunohistochemical test by a central laboratory in order to stratify based

on PD-L1 expression. The test was done with the Ventana PD-L1 (SP142) assay (hereinafter referred to as SP142 assay). As of protocol version 5 (December 2019), the Ventana PD-L1 (SP263) assay (hereinafter referred to as SP263 assay) was also used to test the tumour samples of all patients included in the IPSOS study for PD-L1 expression of the tumour tissue in addition to testing with the SP142 assay. According to the study protocol, platinum-based combination chemotherapy had to be unsuitable for the patients included in the study (see below for the criteria specified in the study).

No prior systemic treatment for advanced, recurrent or metastatic disease was allowed. However, prior treatments with curative intent for an earlier, non-metastatic stage of NSCLC were allowed, provided they had been completed 6 months prior to study inclusion (see Table 7 of the full dossier assessment). Patients with asymptomatic brain metastases were allowed to participate in the study.

The IPSOS study included a total of 453 patients who were randomly allocated in a 2:1 ratio to treatment with atezolizumab (N = 302) or to chemotherapy with vinorelbine or gemcitabine (N = 151). Randomization was stratified by histology (squamous versus non-squamous), the presence of brain metastases (yes/no) and PD-L1 expression status (assessed by SP142 immunohistochemistry assay on tumour cells; positive/negative/unknown).

Treatment with atezolizumab was largely in compliance with the recommendations in the SPC [7] and was continued until disease progression, unacceptable toxicity or death. Contrary to the SPC recommendation, treatment with atezolizumab in the intervention arm was also possible after disease progression as determined by RECIST. This was possible with the patient's written informed consent if, in the opinion of the investigator, there was a clinical benefit and no unacceptable toxicity, no decline in ECOG PS due to disease progression and no tumour progression at critical anatomical sites. A total of 86 (29%) patients in the atezolizumab arm continued treatment after disease progression. The monotherapies with vinorelbine and gemcitabine used in the comparator arm of the IPSOS study were not administered in compliance with the approval. A detailed explanation can be found in Section I 4.1.2.

The primary outcome of the IPSOS study was overall survival. Further patient-relevant outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

Data cut-offs

Two data cut-offs are available for the IPSOS study:

- 15 May 2020 (prespecified interim analysis of overall survival after 304 events)

- 30 April 2022 (prespecified final analysis of overall survival after 379 events in the total study population)

For the benefit assessment, the company used the final data cut-off for all outcomes.

Further information on the IPSOS study characteristics, the interventions used, and the included patients can be found in I Appendix B of the full benefit assessment.

Subpopulation presented by the company

As described above, only patients for whom platinum-based combination chemotherapy was not an option were enrolled in the IPSOS study. These were the following patients:

- Patients with ECOG PS 2 or 3
- Patients who had an ECOG PS of 0 or 1 and were ≥ 70 years of age could be included if the following additional criteria were met:
  - substantial comorbidities and/or
  - contraindication(s) for platinum-based combination chemotherapy

According to the EPAR, in the approval procedure, the above criteria for unsuitability of platinum-based combination chemotherapy were considered by the EMA to be insufficient to represent the targeted fragile patient population [8]. To address the EMA's criticism, the company subsequently defined further selection criteria in consultation with the EMA, based in part on the publications of De Marinis 2015 and Camerini 2022 [9,10]. Based on these criteria listed below, the company formed a subpopulation of the IPSOS study (referred to as "approval population" in the company's Module 4 A) from the total population:

- > 80 years, or
- ECOG PS 3, or
- ECOG PS 2 in combination with relevant comorbidities, or
- ≥ 70 years in combination with relevant comorbidities

Relevant comorbidities were defined here as cardiac disorders, nervous system disorders, psychiatric disorders, vascular disorders, renal disorders, metabolism and nutrition disorders, or pulmonary disorders contraindicating treatment with platinum-based therapy, as assessed by the treating physician. Specific thresholds for when the conditions mentioned were actually categorized as relevant comorbidities were not defined in the study documents.

A total of 405 of the 453 patients originally included in the study met the new criteria. The results of the approval population formed using the new criteria were considered robust

enough by the EMA to be considered as supportive for the ultimately approved population of fragile patients who are ineligible for platinum-based combination chemotherapy.

Neither the German S3 guideline on the prevention, diagnosis, treatment and follow-up of lung cancer nor the NCCN guideline contain specific, generally applicable criteria for unsuitability of platinum-based chemotherapy [11,12]. In the S3 guideline, recommendations for platinum-free monotherapy are only considered for patients with an ECOG PS 2 in combination with comorbidities or advanced age. In addition, the S3 guideline points out that advanced age (> 75 years) alone should not be a reason to exclude patients from platinum-based combination therapy [11].

Overall, the approval population formed by the company is considered sufficiently representative to represent the patient population who are ineligible for platinum-based combination chemotherapy.

From the approval population formed for the EMA, the company considered a subpopulation of patients whose tumours have a PD-L1 expression < 50% or an unknown PD-L1 expression status for research question 2 of the present benefit assessment. The subpopulation was formed on the basis of the results of the SP263 assay. The subpopulation presented by the company in Module 4 A comprises 229 (75.8%) of the 302 randomized patients in the intervention arm, and 115 (76.2%) of the 151 randomized patients in the control arm. The proportion of patients with unknown PD-L1 expression status totalled 8.7% of the presented subpopulation. According to the information in the study documents, the PD-L1 expression status could not be determined in these patients due to insufficient tumour material. The company did not explain to what extent the joint consideration of these patient groups is appropriate for research question 2.

I 4.1.2 No approval-compliant treatment in the comparator arm

Deviations for vinorelbine

According to the SPC, a once-weekly dosage is approved for monotherapy with vinorelbine in this therapeutic indication [13,14].

According to the approval, the recommended regimen for oral administration of vinorelbine is 60 mg/m^2 of BSA for the first 3 administrations; for subsequent administrations, it is recommended to increase the dose to 80 mg/m^2 BSA, based on the measured neutrophil count (see Table 7, I Appendix B of the full dossier assessment) [14]. For the IV administration of vinorelbine, a dose of 25 to 30 mg/m^2 BSA once a week is recommended [13]. For both oral and IV administration of vinorelbine, treatment should be carried out under close haematological monitoring (determination of haemoglobin concentration, as well as leucocyte, neutrophil and platelet counts before each dose); if necessary, the dose should be

modified if toxicity occurs. In the event of neutropenia, the dosage should be postponed until recovery [13,14].

In the IPSOS study, 84 (57%) of the patients in the comparator arm received vinorelbine monotherapy (oral or IV). The doses specified in the study protocol of 60 mg/m^2 with an increase to 80 mg/m^2 BSA after 3 administrations (oral) and 25 to 30 mg/m^2 BSA (IV) for weekly dosing correspond to the information provided in the SPC.

It can be inferred from version 1 of the study protocol (February 2017) that treatment had to be administered in compliance with the SPCs. However, as of version 3 of the study protocol (January 2018), it is stated that cyclical treatment regimens of either 21 days (dosing on Days 1 and 8) or 28 days (dosing on Days 1, 8 and 15) should be used for vinorelbine (oral or IV) (see Table 7, I Appendix B of the full dossier assessment).

The cyclical treatments of 21 or 28 days, which include a treatment-free week at the end of each cycle, do not correspond to the weekly dosing regimen recommended in the SPC. It is also unclear to what extent the doses of 60 mg/m^2 BSA for the first 3 administrations and 80 mg/m^2 BSA for the subsequent administrations, recommended for oral administration according to the SPC, were provided for in the cyclical treatment regimen.

The information on the total population in the CSR shows that 64 of the 84 (76%) patients who received vinorelbine were treated in a 21- or 28-day cycle (with a one-week break at the end of each cycle), which deviates from the SPC. There is no information available on the proportion in the subpopulation of the IPSOS study presented by the company for research question 2.

Deviations for gemcitabine

According to the SPC, a 28-day treatment cycle (dosing on Days 1, 8 and 15) with 1000 mg/m^2 BSA is approved for monotherapy with gemcitabine. Gemcitabine treatment also requires close haematological monitoring with determination of platelet and granulocyte counts before each dose. Depending on the platelet and granulocyte counts, the dose should be modified or treatment interrupted. In addition, the dose should be modified or interrupted also in case of non-haematological toxicity [15].

In the IPSOS study, 63 (43%) of the patients in the comparator arm received gemcitabine monotherapy. The dose level was 1000 to 1250 mg/m^2 BSA. Administration of 1000 mg/m^2 BSA corresponds to the SPC recommendations for monotherapy. The dosage of 1250 mg/m^2 BSA also used in the study is only approved for platinum-based combination therapy with gemcitabine, according to the SPC. Information on the proportion of patients who received 1250 mg/m^2 BSA is neither available for the subpopulation presented by the company for research question 2 nor for the total population. In addition, as for vinorelbine, cyclical

treatment regimens of either 21 days (dosing on Days 1 and 8) or 28 days (dosing on Days 1, 8 and 15) were also used for gemcitabine. However, gemcitabine monotherapy is only approved for a 28-day treatment cycle. The 21-day cycle is only approved for platinum-based combination therapy with gemcitabine.

The information on the total population in the CSR shows that 57 out of 63 (90%) patients received gemcitabine in a 21-day cycle, which deviates from the SPC. In addition, there is no information available either for the total population or for the subpopulation as to which dose level (1250 mg/m^2 BSA or 1000 mg/m^2 BSA) was administered in which treatment cycle (21 or 28 days). It is therefore unclear how many patients were treated with an approval-compliant dose of 1000 mg/m^2 BSA in a 28-day treatment cycle.

Failure to administer the comparator therapy in compliance with the approval in the IPSOS study affects all patient-relevant outcomes

Overall, at least 82% (121 of 147) of the patients in the comparator arm of the study were not treated in compliance with the respective approval of vinorelbine or gemcitabine. Corresponding information on the number of patients in the subpopulation presented by the company for research question 2 is not available.

It cannot be ruled out that a lower dosing frequency than weekly administration is better tolerated for some of the patients in the fragile patient population under consideration (reduced general condition [ECOG PS ≥ 2] and/or advanced age [> 70 years] and/or comorbidities). However, it would then be expected that vinorelbine treatment would be started with weekly dosing in compliance with the approval and that the dose and/or dosing frequency would be adjusted depending on toxicity and tolerability – as recommended in the SPC. Neither the IPSOS study documents nor the information in Module 4 A explain why some of the patients received weekly treatment, but the majority received cyclical treatment (21- or 28-day treatment cycle with a 1-week break). There is also no information in the study documents on the criteria used to decide in favour of or against the respective treatment regimens. The amendment to the protocol version 3 of the IPSOS study only states that administration of the monotherapies in the comparater arm was changed to comply with both local guidelines and the SPC, as these may differ and the study was aimed at a more realistic setting. Neither the current national S3 guideline nor the NCCN provide recommendations regarding the dose level or dosing frequency of vinorelbine [11,12]. Thus, there is no evidence that the study treatments deviating from the approval correspond to a standard in everyday practice.

With regard to gemcitabine administration, it should be noted that the higher dosage used in the IPSOS study than recommended in the SPC (1250 mg/m^2 BSA instead of 1000 mg/m^2 BSA) appears questionable in this fragile patient population. Neither the current national S3

guideline nor the NCCN provide any recommendations regarding the dose level or dosing frequency for monotherapy with gemcitabine in this therapeutic indication, either [11,12]. As with vinorelbine, there is therefore no evidence that the administration of gemcitabine in the study, which deviated from the approval, corresponds to a standard in everyday practice.

Overall, a large proportion of patients in the comparator arm of the IPSOS study were not treated in compliance with the approval. The systematic deviation from the approval taking place in the comparator arm has a relevant influence on all outcomes (overall survival, morbidity, health-related quality of life, and side effects). The effect on the outcomes cannot be estimated. Therefore, the data presented by the company are disregarded for the benefit assessment.

I 4.2 Results on added benefit

No suitable data are available for the assessment of the added benefit of atezolizumab in comparison with the ACT for first-line treatment of advanced NSCLC in adult patients with PD-L1 expression < 50% on tumour cells who are ineligible for platinum-based chemotherapy. There is no hint of an added benefit of atezolizumab in comparison with the ACT; an added benefit for these patients is therefore not proven.

I 4.3 Probability and extent of added benefit

Since the company presented no suitable data for the assessment of the added benefit of atezolizumab in comparison with the ACT for first-line treatment of advanced NSCLC in adult patients with PD-L1 expression < 50% on tumour cells who are ineligible for platinum-based chemotherapy, an added benefit is not proven.

I 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 5.

Table 5: Atezolizumab – probability and extent of added benefit

Research question	Therapeutic indication[a]	ACT[b, c]	Probability and extent of added benefit
1	First-line treatment of advanced NSCLC in adult patients for whom platinum-based chemotherapy is not an option and whose tumours have no EGFR mutations or ALK translocations ▪ with PD-L1 expression ≥ 50% on tumour cells	▪ Pembrolizumab as monotherapy or ▪ cemiplimab as monotherapy	Added benefit not proven
2	First-line treatment of advanced NSCLC in adult patients for whom platinum-based chemotherapy is not an option and whose tumours have no EGFR mutations or ALK translocations ▪ with PD-L1 expression < 50% on tumour cells	▪ Gemcitabine as monotherapy or ▪ vinorelbine as monotherapy	Added benefit not proven

a. For the present therapeutic indication, it is assumed as per G-BA that there is neither a therapeutic indication for definitive radiochemotherapy nor for definitive local therapy. In addition, it is assumed that molecularly stratified therapy (directed against BRAF, KRAS G12C, METex14, RET, or ROS1) is not an option for the patients at the time of treatment with atezolizumab as monotherapy.
b. Presentation of the ACT specified by the G-BA.
c. The approval and dosing information of the drugs' SPCs must be adhered to, and any deviations justified separately.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MET: mesenchymal-epithelial transition factor; METex14: MET gene exon 14; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1; SPC: Summary of Product Characteristics

For the patients with PD-L1 expression ≥ 50% on tumour cells included in research question 1, the company did not consider the added benefit to be assessable. For research question 2, the assessment described above deviates from that of the company, which derived an indication of considerable added benefit for patients with PD-L1 expression < 50% on tumour cells.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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