# Atezolizumab (NSCLC, first line)

## Addendum to Project A24-97 (dossier assessment)[1]

**ADDENDUM**

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## List of abbreviations

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALK | anaplastic lymphoma kinase |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| EGFR | epidermal growth factor receptor |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 |
| EORTC QLQ-LC13 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer Module 13 |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NSCLC | non-small cell lung cancer |
| PD-L1 | programmed cell death ligand 1 |
| PT | Preferred Term |
| RCT | randomized controlled trial |
| SAE | serious adverse event |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SOC | System Organ Class |
| SPC | Summary of Product Characteristics |
| VAS | visual analogue scale |

# 1 Background

On 11 February 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-97 (Atezolizumab – Benefit assessment according to §35a Social Code Book V) [1].

The G-BA commissioned IQWiG to assess the IPSOS study on the basis of the data from the second prespecified final data cut-off from 30 April 2022, taking into account the information provided in the dossier [2].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

## 2 Assessment of the IPSOS study

In dossier assessment A24-97, 2 research questions resulted from the ACT specified by the G-BA.

Research question 1 was the assessment of the added benefit of atezolizumab in comparison with the appropriate comparator therapy (ACT) in the first-line treatment of advanced non-small cell lung cancer (NSCLC) in adult patients with programmed cell death ligand 1 (PD-L1) expression ≥ 50% on tumour cells for whom platinum-based chemotherapy is not an option and whose tumours have no epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocations. Concurring with the company, no data for the comparison with the ACT were available for this research question.

Research question 2 was the assessment of the added benefit of atezolizumab in comparison with the ACT in the first-line treatment of advanced NSCLC in adult patients with PD-L1 expression < 50% on tumour cells for whom platinum-based chemotherapy is not an option and whose tumours have no EGFR mutations or ALK translocations. The company presented the IPSOS study to answer this research question. This study is a randomized controlled trial (RCT) comparing atezolizumab with gemcitabine or vinorelbine. The study included adult patients with Stage IIIB to IV NSCLC without EGFR mutation or ALK translocation for whom platinum-based chemotherapy is not an option. 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.

A detailed description of the information retrieval and the IPSOS study [3-6] can be found in dossier assessment A24-97 [1].

The IPSOS study was not used for the benefit assessment because the majority of patients in the comparator arm of the study did not receive approval-compliant treatment with gemcitabine or vinorelbine (dose level and dosing frequency). However, based on the information presented in the commenting procedure, it is assumed that treatment of the patients in the comparator arm of the study was essentially appropriate. In particular, it is assumed that weekly administration of vinorelbine or gemcitabine without a break in the last week of the cycle is generally not an option for the relevant patient population [7-10]. The IPSOS study is therefore rated as relevant for the benefit assessment.

In addition, it became apparent during the commenting procedure that patients with unknown PD-L1 expression status are treated like patients with PD-L1 expression < 50% on tumour cells. These patients are therefore to be assigned to research question 2.

Furthermore, in the commenting procedure [10], the company presented an additional analysis of the data at the time of the last patient last visit on 26 October 2023. The company explained that this analysis, both for the outcome of overall survival and for adverse event (AE) outcomes, mainly contains updates for 15 patients in the intervention arm who continued treatment with atezolizumab until the end of the study. This data update is not taken into account for the benefit assessment.

To answer research question 2, the subpopulation presented by the company in the dossier (patients with PD-L1 expression < 50% on tumour cells and patients with unknown PD-L1 expression status) of the prespecified final data cut-off of 30 April 2022 is used for the benefit assessment.

The results of the relevant subpopulation of the IPSOS study are described and assessed below. The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

The present addendum is structured as follows: Section 2.1 describes the characteristics of the IPSOS study. Sections 2.2 and 2.3 present the results and the derivation of the overall conclusion on added benefit of atezolizumab in the present research question based on the IPSOS study. A summary of the benefit assessment is found in Section 2.4.

## 2.1 Study characteristics

A detailed description of the IPSOS study can be found in dossier assessment A24-97 [1] and its Appendix B.

### Planned duration of follow-up observation

Table 1 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 1: Planned duration of follow-up observation – RCT, direct comparison: atezolizumab vs. gemcitabine or vinorelbine

| **Study**<br>**Outcome category**<br>**Outcome** | **Planned follow-up observation** |
|---|---|
| **IPSOS** | |
| Mortality | |
| Overall survival | Until death, lost to follow-up, withdrawal of consent, or end of study |
| Morbidity | |
| Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13) | Until disease progression |
| Health status (EQ-5D VAS) | Until disease progression |
| Health-related quality of life (EORTC QLQ-C30) | Until disease progression |
| Side effects | |
| AEs/severe AEs | Up to 30 days after the last dose of the study medication or until initiation of a subsequent antineoplastic therapy (whichever occurred first)[a] |
| SAEs/AESIs[b] | Up to 90 days after the last dose of the study medication or until initiation of a subsequent antineoplastic therapy (whichever occurred first)[a] |

a. Beyond this period, only events were observed that could be potentially related to the study medication.
b. This includes the analyses on immune-mediated AEs presented by the company (as listed in Table 15).

AE: adverse event; AESI: AE of special interest; EORTC: European Organisation 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

The observation periods for the outcomes on morbidity, health-related quality of life and side effects are systematically shortened, as the outcomes on morbidity and health-related quality of life were only recorded until disease progression, and the outcomes on side effects were only recorded for the period of treatment with the study medication (plus 30 days for AEs/severe AEs and 90 days for serious AEs [SAEs] and AEs of special interest [AESIs]). Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

**Patient characteristics**

A detailed characterization of the relevant subpopulation as well as of study and treatment discontinuations can be found in dossier assessment A24-97 [1] and its Appendix B.

The patient characteristics were largely comparable between the treatment groups of the relevant subpopulation in the IPSOS study. Most patients were male (72% and 67% respectively), white, and on average 75 years old, whereby the proportion of patients aged ≥ 80 years was higher in the intervention arm (38%) than in the comparator arm (30%). The

proportion of patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 2 or 3 was 79% in the intervention arm and 88% in the comparator arm. Around 76% of patients in both treatment arms had more than 3 comorbidities.

**Information on the course of the study**

Table 2 shows the mean and median treatment durations of the patients and the median observation periods for individual outcomes in the subpopulation relevant to research question 2.

Table 2: Information on the course of the study – RCT, direct comparison: atezolizumab vs. gemcitabine or vinorelbine, research question 2

| **Study**<br>**Duration of the study phase**<br>**Outcome category/outcome** | **Atezolizumab**<br>**N = 229** | **Gemcitabine or vinorelbine**<br>**N = 115** |
|---|---|---|
| **IPSOS** | | |
| Treatment duration [months][a] | ND | ND |
| Observation period [months] | | |
| Overall survival[b] | | |
| Median [Q1; Q3] | 42.6 [39.8; 48.4] | 36.8 [34.3; 52.7] |
| Mean (SD) | ND | |
| Morbidity | ND | |
| Health-related quality of life | ND | |
| Side effects | N = 228 | N = 113 |
| AEs/severe AEs[c] | | |
| Median [Q1; Q3] | 4.3 [ND] | 3.1 [ND] |
| Mean (SD) | ND | |
| SAEs/AESIs[d] | | |
| Median [Q1; Q3] | 5.5 [ND] | 4.3 [ND] |
| Mean (SD) | ND | |

a. No data available for the relevant subpopulation; according to the CSR, the median treatment duration [min; max] for the total population of the IPSOS study was 3.5 [0; 51] months in the intervention arm and 2.3 [0; 21] months in the control arm.
b. The observation period was calculated on the basis of the inverse Kaplan-Meier method.
c. Calculated as time since start of treatment until the time point of the final data cut-off, death, lost to follow-up, withdrawal of consent, study discontinuation, until 30 days after the last dose of the study medication or until initiation of a subsequent anticancer therapy.
d. Calculated as time since start of treatment until the time point of the final data cut-off, death, lost to follow-up, withdrawal of consent, study discontinuation, until 90 days after the last dose of the study medication or until initiation of a subsequent anticancer therapy.

AE: adverse event; AESI: AE of special interest; CSR: clinical study report; max: maximum; min: minimum; N: number of analysed patients; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation

No information on treatment duration is available for the relevant subpopulation. The relevant subpopulation accounts for approx. 76% of the total population of the IPSOS study. For this reason, it can be assumed that the information on the treatment duration of the total population can also be used as an approximation to the relevant subpopulation. For the total population of the IPSOS study, the median treatment duration in the intervention arm (3.5 months) was longer than the median treatment duration in the comparator arm (2.3 months).

The median observation period for the outcome of overall survival was longer in the intervention arm than in the comparator arm. No information is available on the median observation periods for the morbidity and health-related quality of life outcomes. The median observation periods for side effects are slightly higher in the intervention arm than in the comparator arm, but notably shorter compared with overall survival.

**Subsequent therapies**

For the relevant subpopulation, no information is available on which subsequent (antineoplastic) therapies the patients received after discontinuation of the study medication. The current S3 guideline on the prevention, diagnosis, treatment and follow-up of lung cancer [11] provides no explicit recommendation on subsequent therapies for this fragile patient population. The following information on subsequent antineoplastic therapies is available for the patients in the total population of the IPSOS study: A total of 61 (20%) patients in the intervention arm and 45 (30%) patients in the comparator arm received subsequent therapy. Most patients received chemotherapy (16% versus 11%), followed by cancer immunotherapies (1% versus 19%) and tyrosine kinase inhibitors (3% versus 3%). The extent to which this information can be applied to the relevant subpopulation is unclear. Overall, however, there is no evidence that patients were not offered adequate subsequent treatment.

**Risk of bias across outcomes (study level)**

Table 3 shows the risk of bias across outcomes (risk of bias at study level).

Table 3: Risk of bias across outcomes (study level) – RCT, direct comparison: atezolizumab vs. gemcitabine or vinorelbine

| 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 | | | |
| IPSOS | Yes | Yes | No | No | Yes | Yes | Low |
| RCT: randomized controlled trial | | | | | | | |

The risk of bias across outcomes is rated as low for the IPSOS study. Limitations resulting from the open-label study design are described in Section 2.2.2 under the outcome-specific risk of bias.

## 2.2 Results

### 2.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms, recorded using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer Module 13 (EORTC QLQ-LC13)
  - health status, recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - recorded using the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - immune-mediated SAEs
  - immune-mediated severe AEs
  - neutropenia (PT, severe AEs)
  - skin reactions (operationalized as skin and subcutaneous tissue disorders [System Organ Class (SOC), AEs])
  - gastrointestinal disorders (SOC, AEs)

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

Table 4 shows the outcomes for which data for research question 2 are available in the included study.

Table 4: Matrix of outcomes – RCT, direct comparison: atezolizumab vs. gemcitabine or vinorelbine, research question 2

| Study | Outcomes | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Overall survival | Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13) | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30) | SAEs | Severe AEs[a] | Discontinuation due to AEs | Immune-mediated SAEs and immune-mediated severe AEs[a] | Neutropenia (PT, severe AEs[a]) | Skin reactions[b] | Gastrointestinal disorders (SOC, AEs) |
| IPSOS | Yes | No[c] | No[c] | No[c] | Yes | Yes | Yes | No[c] | Yes | Yes | Yes |

a. Operationalized as CTCAE grade ≥ 3.
b. Operationalized as skin and subcutaneous tissue disorders (SOC, AEs).
c. No suitable data available; see section below for the reasoning.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; LC13: Quality of Life Questionnaire-Lung Cancer Module 13; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

**Notes on outcomes**

***Patient-reported outcomes on morbidity and health-related quality of life***

In the IPSOS study, patient-reported outcomes on symptoms (using EORTC QLQ-C30 and EORTC QLQ-LC13), health status (using EQ-5D VAS) and health-related quality of life (using EORTC QLQ-C30) were recorded every 6 weeks in the course of the study, until disease progression. However, a meaningful interpretation of the data presented by the company is not possible due to the strongly decreasing and differential response rates. By Week 18, the response rate was already around 56% in the intervention arm and around 37% in the comparator arm. It can be assumed that the early decline in response rates was largely due to the lack of outcome recording after disease progression planned in the study. Furthermore, due to the different treatment regimens between the intervention arm and the comparator arm (see Project A24-97 [1]), the patient-reported outcomes were also recorded at different time points within the treatment cycles in the 2 study arms. As a result, the study arms differ in terms of their representation of treatment-related burden over the course of the cycle. Additional analyses disregarding the recordings of these time points (with unequal treatment burden), for example, would be required to check the influence the different representations of the burden have on the results. For this purpose, a more frequent recording of patient-reported outcomes in the study would be more favourable for an assessment of the outcomes due to the different treatment regimens between the intervention arm and the comparator arm.

Due to the strongly decreasing and differential response rates as well as different time points of recording of the patient-reported outcomes within the treatment cycles, the results on the patient-reported outcomes cannot be interpreted meaningfully and are therefore not suitable for the benefit assessment.

***Immune-mediated SAEs and immune-mediated severe AEs***

The company did not present a summary analysis of immune-mediated events for immune-mediated AEs (SAEs and severe AEs). Instead, as part of the AESI analyses in Module 4 A, it only presented results for individual AESI categories, which only represent a part of the immune-mediated AEs. The analyses presented by the company are not suitable to provide a comprehensive reflection of the immune-mediated AEs. Thus, no suitable data are available for immune-mediated AEs (SAEs and severe AEs).

### 2.2.2 Risk of bias

Table 5 describes the risk of bias for the results of the relevant outcomes for research question 2.

Table 5: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: atezolizumab vs. gemcitabine or vinorelbine, research question 2

| Study | Study level | Outcomes | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Overall survival | Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13) | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30) | SAEs | Severe AEs[a] | Discontinuation due to AEs | Immune-mediated SAEs and immune-mediated severe AEs[a] | Neutropenia (PT, severe AEs[a]) | Skin reactions[b] | Gastrointestinal disorders (SOC, AEs) |
| IPSOS | L | L | –[c] | –[c] | –[c] | H[d] | H[d] | H[e] | –[c] | H[d] | H[d, e] | H[d, e] |

a. Operationalized as CTCAE grade ≥ 3.
b. Operationalized as skin and subcutaneous tissue disorders (SOC, AEs).
c. No suitable data available; see body of text in Section 2.2.1 for reasons.
d. Incomplete observations for potentially informative reasons.
e. Lack of blinding in subjective recording of outcomes.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer Module 13; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of the results on overall survival is rated as low.

No suitable data are available for the outcomes on symptoms (EORTC QLQ-C30, EORTC QLQ-LC13), health status (EQ-5D VAS), health-related quality of life (EORTC QLQ-C30, EORTC QLQ-C30) and the outcomes on immune-mediated SAEs and immune-mediated severe AEs (see Section 2.2.1).

The risk of bias of the results for the outcomes of SAEs, severe AEs, neutropenia (severe AEs), skin reactions (AEs), and gastrointestinal disorders (AEs) is rated as high. For the mentioned outcomes of the category of side effects, there are incomplete observations for potentially informative reasons due to the follow-up observation linked to the treatment duration. In addition, the risk of bias is rated as high for the outcomes of non-serious/non-severe AEs and for the outcome of discontinuation due to AEs due to the lack of blinding in the presence of subjective recording of outcomes.

**Summary assessment of the certainty of conclusions**

On the basis of the available information, at most indications can be derived for the outcome of overall survival and, due to the high risk of bias, at most hints, e.g. of added benefit, can be derived for the outcomes in the category of side effects.

### 2.2.3 Results

Table 6 summarizes the results of the comparison of atezolizumab with gemcitabine or vinorelbine as first-line treatment of advanced NSCLC in adult patients with PD-L1 expression < 50% on tumour cells for whom platinum-based chemotherapy is not an option and whose tumours have no EGFR mutations or ALK translocations. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

Kaplan-Meier curves on the presented time-to-event analyses can be found in Appendix A. Results on common AEs, SAEs, severe AEs, and discontinuations due to AEs are presented in Appendix B. A list of the AESIs on immune-mediated AEs provided by the company is presented as supplementary information in Appendix C. The company did not provide corresponding data for immune-mediated SAEs and immune-mediated severe AEs.

Table 6: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: atezolizumab vs. gemcitabine or vinorelbine, research question 2 (multipage table)

| Study<br>Outcome category<br>Outcome | Atezolizumab | | Gemcitabine or vinorelbine | | Atezolizumab vs. gemcitabine or vinorelbine |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value |
| **IPSOS (data cut-off 30 April 2022)** | | | | | |
| **Mortality** | | | | | |
| Overall survival | 229 | 10.2 [8.5; 12.0]<br>197 (86.0) | 115 | 8.0 [5.8; 10.9]<br>102 (88.7) | 0.76 [0.59; 0.97];<br>0.025[a] |
| **Morbidity** | | | | | |
| Symptoms (EORTC QLQ-C30 – time to first deterioration) | | | No suitable data[b] | | |
| Symptoms (EORTC QLQ-LC13 – time to first deterioration) | | | No suitable data[b] | | |
| Health status (EQ-5D VAS, time to first deterioration) | | | No suitable data[b] | | |
| **Health-related quality of life** | | | | | |
| EORTC QLQ-C30 – time to first deterioration | | | No suitable data[b] | | |
| **Side effects** | | | | | |
| AEs (supplementary information) | 228 | ND<br>212 (93.0) | 113 | ND<br>111 (98.2) | – |
| SAEs | 228 | ND<br>119 (52.2) | 113 | ND<br>44 (38.9) | 1.11 [0.78; 1.58];<br>0.560[d] |
| Severe AEs[c] | 228 | ND<br>135 (59.2) | 113 | ND<br>70 (61.9) | 0.66 [0.49; 0.89];<br>0.006[d] |
| Discontinuation due to AEs | 228 | ND<br>34 (14.9) | 113 | ND<br>17 (15.0) | 0.59 [0.32; 1.09];<br>0.089[d] |
| *Immune-mediated AEs (supplementary information)* | *228* | *ND*<br>*128 (55.7)* | *113* | *ND*<br>*26 (23.0)* | – |
| Immune-mediated SAEs | | | No suitable data[b] | | |
| Immune-mediated severe AEs[c] | | | No suitable data[b] | | |
| Neutropenia (PT, severe AEs[c]) | 228 | ND<br>2 (0.9) | 113 | ND<br>12 (10.6) | 0.05 [0.01; 0.23];<br>< 0.001[d] |
| Skin reactions[e] | 228 | ND<br>45 (19.7) | 113 | ND<br>16 (14.2) | 1.21 [0.68; 2.15];<br>0.522[d] |
| Gastrointestinal disorders (SOC, AEs) | 228 | ND<br>99 (43.4) | 113 | ND<br>61 (54.0) | 0.51 [0.37; 0.71];<br>< 0.001[d] |

Table 6: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: atezolizumab vs. gemcitabine or vinorelbine, research question 2 (multipage table)

| Study<br>Outcome category<br>Outcome | Atezolizumab | | Gemcitabine or vinorelbine | | Atezolizumab vs. gemcitabine or vinorelbine |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value |
| a. HR and 95% CI: Cox regression model, stratified by tumour histology (IxRS) and presence of brain metastases (IxRS); p-value: log-rank test.<br>b. See body of text for explanation.<br>c. Operationalized as CTCAE grade ≥ 3.<br>d. HR and 95% CI: unstratified Cox regression model; p-value: log-rank test.<br>e. Operationalized as skin and subcutaneous tissue disorders (SOC, AEs).<br>CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; IxRS: interactive voice/web response system; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer Module 13; RCT: randomized controlled trial; SOC: System Organ Class; VAS: visual analogue scale | | | | | |

On the basis of the available information, at most indications can be derived for the outcome of overall survival and, due to the high risk of bias, at most hints, e.g. of added benefit, can be derived for the outcomes in the category of side effects.

## Mortality

### *Overall survival*

For the outcome of overall survival, a statistically significant difference was found in favour of atezolizumab in comparison with gemcitabine or vinorelbine. Notably, the Kaplan-Meier curves on this outcome cross (see Appendix A.1, Figure 1). In the first 3.5 months, the Kaplan-Meier curve falls more steeply in the atezolizumab arm than in the comparator arm. At about 5 months after study start, the Kaplan-Meier curves cross, and only in the further course does an advantage of atezolizumab become apparent. This suggests that some patient groups reap less benefit or no benefit at all from the intervention. The characteristics of this patient group cannot be determined on the basis of the data submitted by the company. The crossing of the Kaplan-Meier curves might be based on an effect modification, but no statistically significant interaction was found for any of the subgroup characteristics examined in the IPSOS study. The Summary of Product Characteristics (SPC) of atezolizumab [12] includes a corresponding warning on the use of atezolizumab as monotherapy for first-line treatment in metastatic

NSCLC, stating that physicians should consider the delayed onset of atezolizumab effect before initiating first-line treatment as monotherapy in patients with NSCLC.

Overall, there is an indication of added benefit of atezolizumab in comparison with the ACT.

**Morbidity**

***Symptoms (EORTC QLQ-C30 and EORTC QLQ-LC13)***

No suitable data are available for the outcomes on symptoms, measured with the EORTC QLQ-C30 and the EORTC QLQ-LC13 (see Section 2.2.1). There is no hint of an added benefit of atezolizumab in comparison with the ACT; an added benefit is therefore not proven.

***Health status (EQ-5D VAS)***

No suitable data are available for the outcome of health status, measured with the EQ-5D VAS (see Section 2.2.1). There is no hint of an added benefit of atezolizumab in comparison with the ACT; an added benefit is therefore not proven.

***Health-related quality of life (EORTC QLQ-C30)***

No suitable data are available for health-related quality of life, measured with the EORTC QLQ-C30 (see Section 2.2.1). There is no hint of an added benefit of atezolizumab in comparison with the ACT; an added benefit is therefore not proven.

**Side effects**

***SAEs***

No statistically significant difference between treatment groups was found for the outcome of SAEs. There is no hint of greater or lesser harm from atezolizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

***Severe AEs***

For the outcome of severe AEs, a statistically significant difference was found in favour of atezolizumab in comparison with gemcitabine or vinorelbine. There is a hint of lesser harm from atezolizumab in comparison with the ACT.

***Discontinuation due to AEs***

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. There is an effect modification by the characteristic of sex, however (see Section 2.2.4). For men, there is a hint of lesser harm from atezolizumab in comparison with the ACT. For women, there is no hint of greater or lesser harm from atezolizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

***Immune-mediated SAEs, immune-mediated severe AEs***

No suitable data are available for the outcomes of immune-mediated SAEs and immune-mediated severe AEs (see Section 2.2.1). For each of them, there is no hint of greater or lesser harm from atezolizumab in comparison with the ACT; greater or lesser harm is therefore not proven in either case.

***Neutropenia***

For the outcome of neutropenia (severe AEs), a statistically significant difference was found in favour of atezolizumab in comparison with gemcitabine or vinorelbine. There is a hint of lesser harm from atezolizumab in comparison with the ACT.

***Skin reactions***

No statistically significant difference between treatment groups was found for the outcome of skin reactions (AEs). There is no hint of greater or lesser harm from atezolizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

***Other specific AEs***

*Gastrointestinal disorders*

For the outcome of gastrointestinal disorders (AEs), a statistically significant difference was found in favour of atezolizumab in comparison with gemcitabine or vinorelbine. There is a hint of lesser harm from atezolizumab in comparison with the ACT.

### 2.2.4 Subgroups and other effect modifiers

The following subgroup characteristics are taken into account in the present benefit assessment:

- age (< 75 years versus ≥ 75 years)
- sex (male versus female)
- ECOG PS (0/1 versus 2 versus 3)

The characteristics mentioned were prespecified.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup. Subgroup results where the extent does not differ between subgroups are not presented.

The results are presented in Table 7. The Kaplan-Meier curves on the subgroup results are presented in Appendix A.3.

Table 7: Subgroups (side effects) – RCT, direct comparison: atezolizumab vs. gemcitabine or vinorelbine, research question 2

| Study<br>Outcome | Atezolizumab | | Gemcitabine or vinorelbine | | Atezolizumab vs. gemcitabine or vinorelbine | |
|---|---|---|---|---|---|---|
| Characteristic<br>Subgroup | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI][a] | p-value[b] |
| **IPSOS (data cut-off 30 April 2022)** | | | | | | |
| **Side effects** | | | | | | |
| **Discontinuation due to AE** | | | | | | |
| Sex | | | | | | |
| Male | 165 | ND<br>20 (12.1) | 75 | ND<br>13 (17.3) | 0.35 [0.17; 0.76] | 0.005 |
| Female | 63 | ND<br>14 (22.2) | 38 | ND<br>4 (10.5) | 1.63 [0.52; 5.11] | 0.398 |
| Total | | | | | Interaction: | 0.016[c] |

a. Unstratified Cox regression model.
b. Log-rank test.
c. Likelihood ratio test.

AE: adverse event; CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial

## Side effects

### *Discontinuation due to AEs*

There was an effect modification by the characteristic of sex for the outcome of discontinuation due to AEs.

For men, a statistically significant difference was found in favour of atezolizumab in comparison with gemcitabine or vinorelbine. There is a hint of lesser harm from atezolizumab in comparison with the ACT.

For women, there was no statistically significant difference between treatment arms. There is no hint of greater or lesser harm from atezolizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

## 2.3 Probability and extent of added benefit

The probability and extent of 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 [13].

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.

### 2.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.2 (see Table 8).

**Determination of the outcome category for the outcomes on side effects**

It cannot be inferred from the dossier whether the following outcomes were serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

***Outcome of discontinuations due to AEs***

For the outcome of discontinuation due to AEs, no information for the relevant subpopulation is available regarding the severity grades of the AEs that led to the discontinuation of treatment. According to the study documents, 73% of the AEs that led to discontinuation in the total population of the IPSOS study were severe AEs. Therefore, the outcome of discontinuation due to AEs is assigned to the outcome category of serious/severe side effects.

Table 8: Extent of added benefit at outcome level: atezolizumab vs. gemcitabine or vinorelbine, research question 2 (multipage table)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Atezolizumab vs. gemcitabine**<br>**Median time to event (months) or proportion of events (%)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Outcomes with observation over the entire study duration** | | |
| **Mortality** | | |
| Overall survival | 10.2 vs. 8.0 months<br>HR: 0.76 [0.59; 0.97]<br>p = 0.025<br>Probability: "indication" | Outcome category: mortality<br>Added benefit, extent: "minor" |
| **Outcomes with shortened observation period** | | |
| **Morbidity** | | |
| Symptoms (EORTC QLQ-C30 – time to first deterioration) | No suitable data[c] | Lesser/added benefit not proven |
| Symptoms (EORTC QLQ-LC13 – time to first deterioration) | No suitable data[c] | Lesser/added benefit not proven |
| Health status (EQ-5D VAS – time to first deterioration) | No suitable data[c] | Lesser/added benefit not proven |
| **Health-related quality of life** | | |
| EORTC QLQ-C30 – time to first deterioration | No suitable data[c] | Lesser/added benefit not proven |
| **Side effects** | | |
| SAEs | ND vs. ND<br>HR: 1.11 [0.78; 1.58]<br>p = 0.560 | Greater/lesser harm not proven |
| Severe AEs | ND vs. ND<br>HR: 0.66 [0.49; 0.89]<br>p = 0.006<br>Probability: "hint" | Outcome category: serious/severe side effects<br>$0.75 \leq CI_u < 0.90$<br>Lesser harm, extent: "considerable" |

Table 8: Extent of added benefit at outcome level: atezolizumab vs. gemcitabine or vinorelbine, research question 2 (multipage table)

| **Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Atezolizumab vs. gemcitabine**<br>**Median time to event (months) or proportion of events (%)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| Discontinuation due to AEs<br>Sex<br>Male | ND vs. ND<br>HR: 0.35 [0.17; 0.76]<br>p = 0.005<br>Probability: "hint" | Outcome category: serious/severe side effects<br>$0.75 \leq CI_u < 0.90$<br>Lesser harm, extent: "considerable" |
| Female | ND vs. ND<br>HR: 1.63 [0.52; 5.11]<br>p = 0.398 | Greater/lesser harm not proven |
| Immune-mediated SAEs | No suitable data[c] | Greater/lesser harm not proven |
| Immune-mediated severe AEs | No suitable data[c] | Greater/lesser harm not proven |
| Neutropenia (severe AEs) | ND vs. ND<br>HR: 0.05 [0.01; 0.23]<br>p < 0.001<br>Probability: "hint" | Outcome category: serious/severe side effects<br>$CI_u < 0.75$, risk ≥ 5%<br>Lesser harm, extent: "major" |
| Skin reactions (AEs) | ND vs. ND<br>HR: 1.21 [0.68; 2.15]<br>p = 0.522 | Greater/lesser harm not proven |
| Gastrointestinal disorders (AEs) | ND vs. ND<br>HR: 0.51 [0.37; 0.71]<br>p < 0.001<br>Probability: "hint" | Outcome category: non-serious/non-severe side effects<br>$CI_u < 0.80$<br>Lesser harm, extent: "considerable" |

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval ($CI_u$).
c. See body of text in Section 2.2.1 for reasons.

AE: adverse event; CI: confidence interval; $CI_u$: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer Module 13; SAE: serious adverse event; VAS: visual analogue scale

### 2.3.2 Overall conclusion on added benefit

Table 9 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 9: Positive and negative effects from the assessment of atezolizumab in comparison with the ACT, research question 2

| **Positive effects** | **Negative effects** |
|---|---|
| **Outcomes with observation over the entire study duration** | |
| Mortality<br>▪ Overall survival: indication of an added benefit – extent: "minor" | – |
| **Outcomes with shortened observation period** | |
| Serious/severe side effects<br>▪ Severe AEs: hint of lesser harm – extent: "considerable"<br>▫ Neutropenia (severe AEs): hint of lesser harm – extent: "major"<br>▪ Discontinuation due to AEs<br>▫ Sex (male): hint of lesser harm – extent "considerable" | – |
| Non-serious/non-severe side effects<br>▪ Gastrointestinal disorders (AEs): hint of lesser harm – extent: "considerable" | – |
| No suitable data are available on the outcomes of morbidity, health-related quality of life, as well as immune-mediated SAEs, and immune-mediated severe AEs. | |
| ACT: appropriate comparator therapy; AE: adverse event; SAE: serious adverse event | |

Overall, only positive effects were found for atezolizumab in comparison with gemcitabine or vinorelbine. There is an indication of a minor added benefit for the outcome of overall survival. For the outcome category of serious/severe side effects, there are hints of lesser harm of considerable to major extent. For the outcome of discontinuation due to AEs, the hint of lesser harm exists only for men. For the outcome of gastrointestinal disorders in the outcome category of non-serious/non-severe side effects, there is a hint of lesser harm of considerable extent.

No suitable data are available for the patient-reported outcomes in the categories of morbidity and health-related quality of life. In addition, suitable analyses of immune-mediated SAEs and immune-mediated severe AEs are lacking. It is not assumed that the existing positive effects are completely called into question by potentially negative effects in the outcomes of immune-mediated SAEs and immune-mediated severe AEs.

In summary, there is an indication of a minor added benefit of atezolizumab compared with the ACT for patients with advanced NSCLC with PD-L1 expression < 50% on tumour cells for whom platinum-based chemotherapy is not an option and whose tumours have no EGFR mutations or ALK translocations.

## 2.4 Summary

The information presented in the commenting procedure and the oral hearing on the use (dose level and dosing frequency) of gemcitabine and vinorelbine in the comparator arm changes the conclusion on the added benefit of atezolizumab from dossier assessment A24-97 for research question 2. For research question 1, there is no change in comparison with dossier assessment A24-97.

The following Table 10 shows the result of the benefit assessment of atezolizumab under consideration of dossier assessment A24-97 and the present addendum.

Table 10: 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<br>▪ with PD-L1 expression ≥ 50% on tumour cells | ▪ Pembrolizumab as monotherapy<br>or<br>▪ 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<br>▪ with PD-L1 expression < 50% on tumour cells | ▪ Gemcitabine as monotherapy<br>or<br>▪ vinorelbine as monotherapy | Indication of minor added benefit |

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 References

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

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# Appendix A Kaplan-Meier curves

## A.1 Mortality

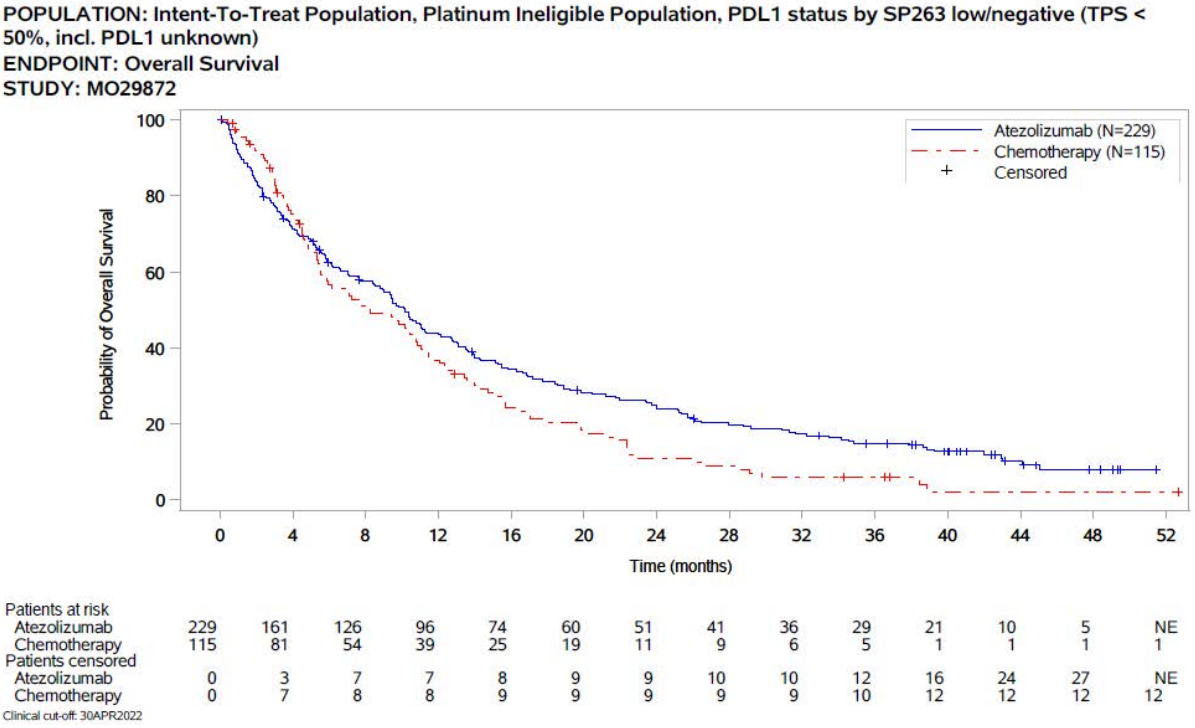


Figure 1: Kaplan-Meier curves for the outcome of overall survival (data cut-off 30 April 2022), research question 2

## A.2 Side effects

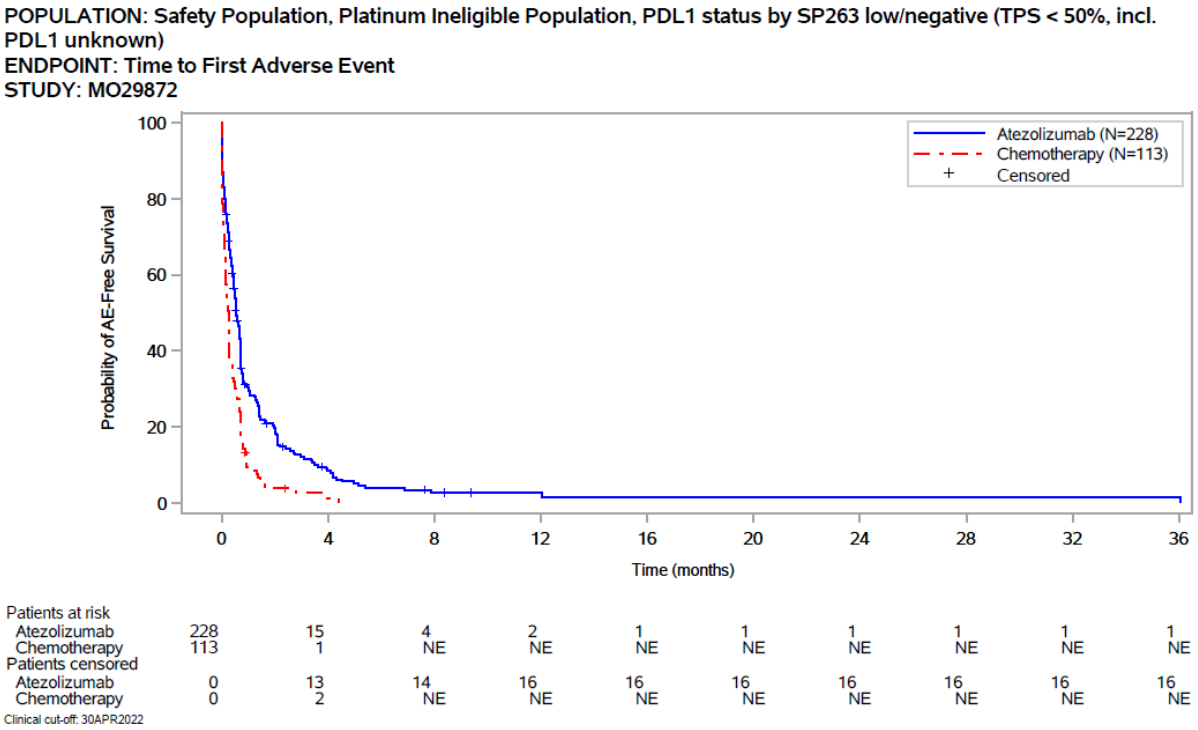


Figure 2: Kaplan-Meier curves for the outcome of AEs (supplementary presentation) (data cut-off 30 April 2022), research question 2

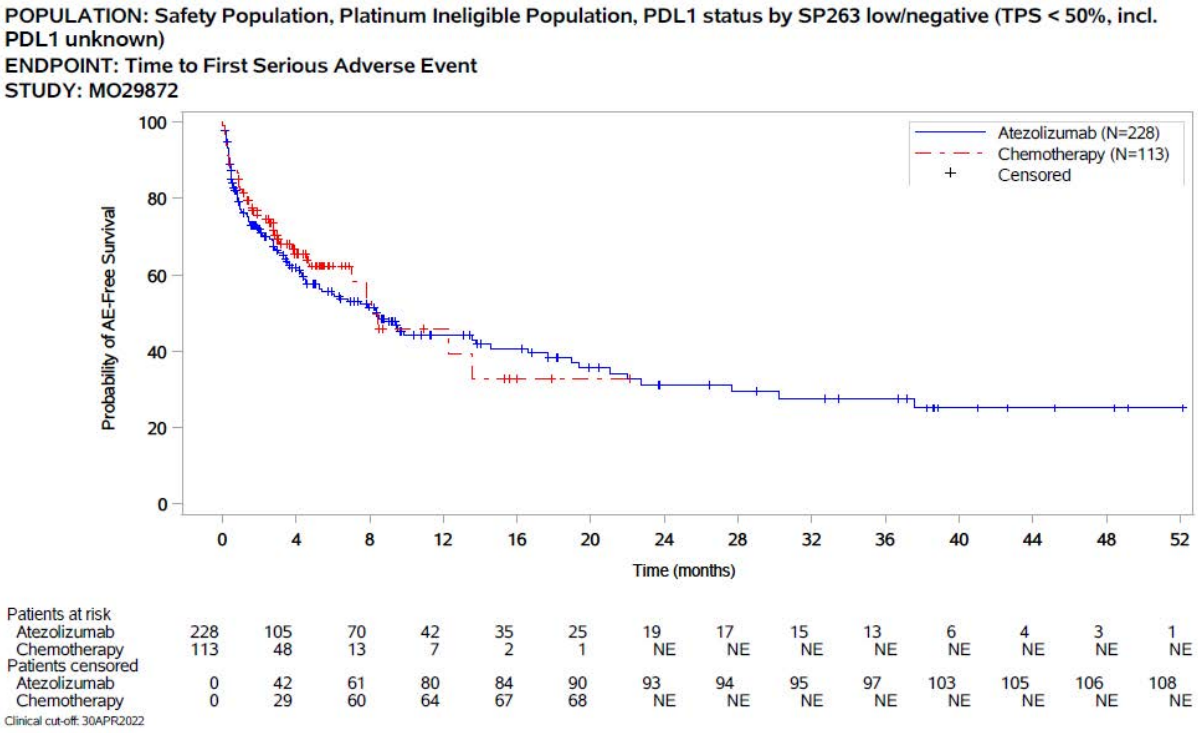


Figure 3: Kaplan-Meier curves for the outcome of SAEs (data cut-off 30 April 2022), research question 2

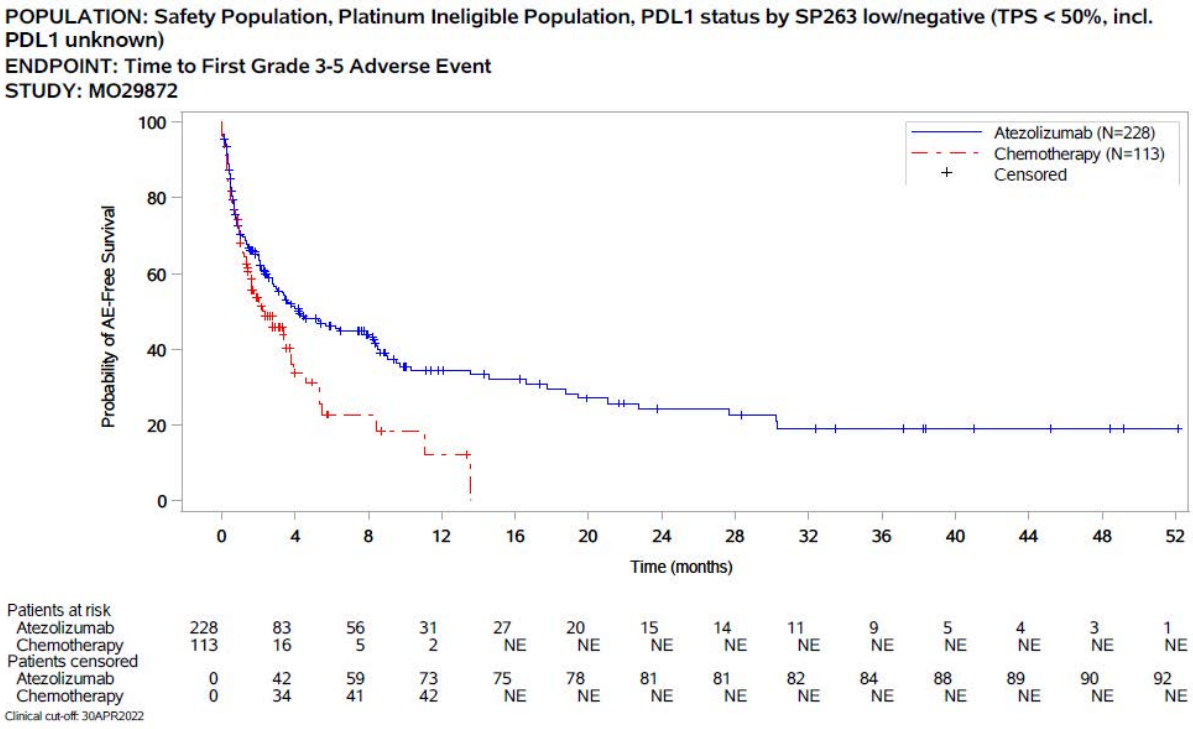


Figure 4: Kaplan-Meier curves for the outcome of severe AEs (data cut-off 30 April 2022), research question 2

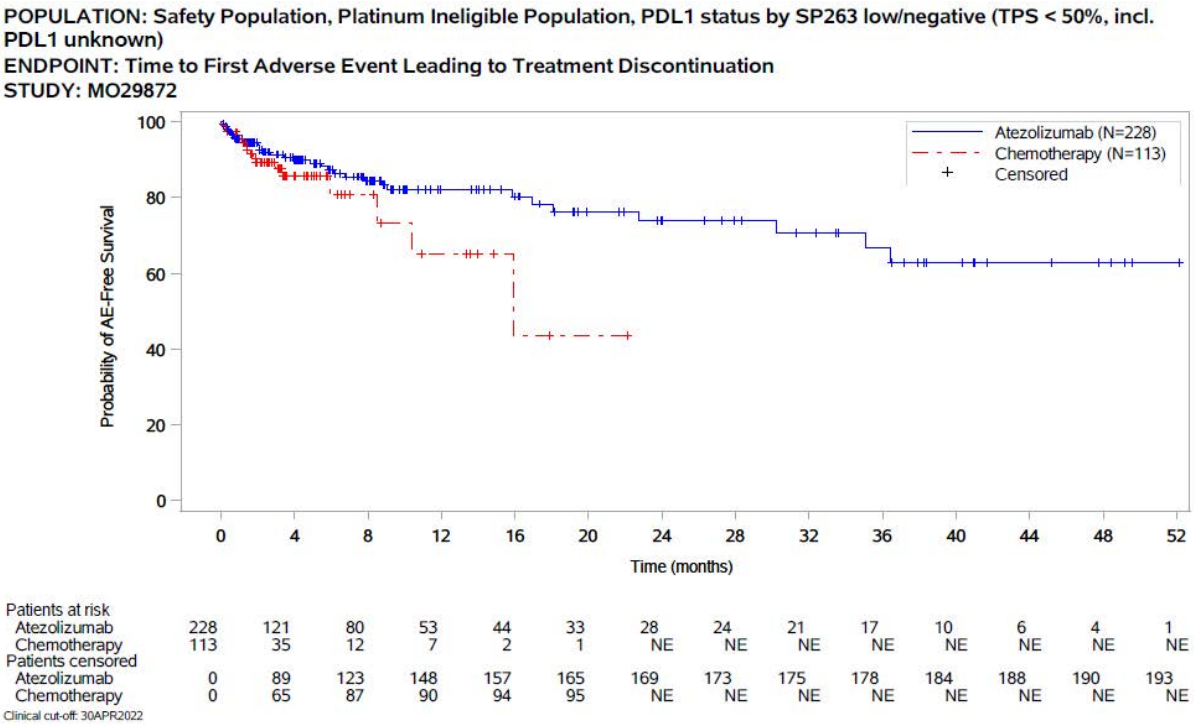


Figure 5: Kaplan-Meier curves for the outcome of discontinuation due to AEs (data cut-off 30 April 2022), research question 2

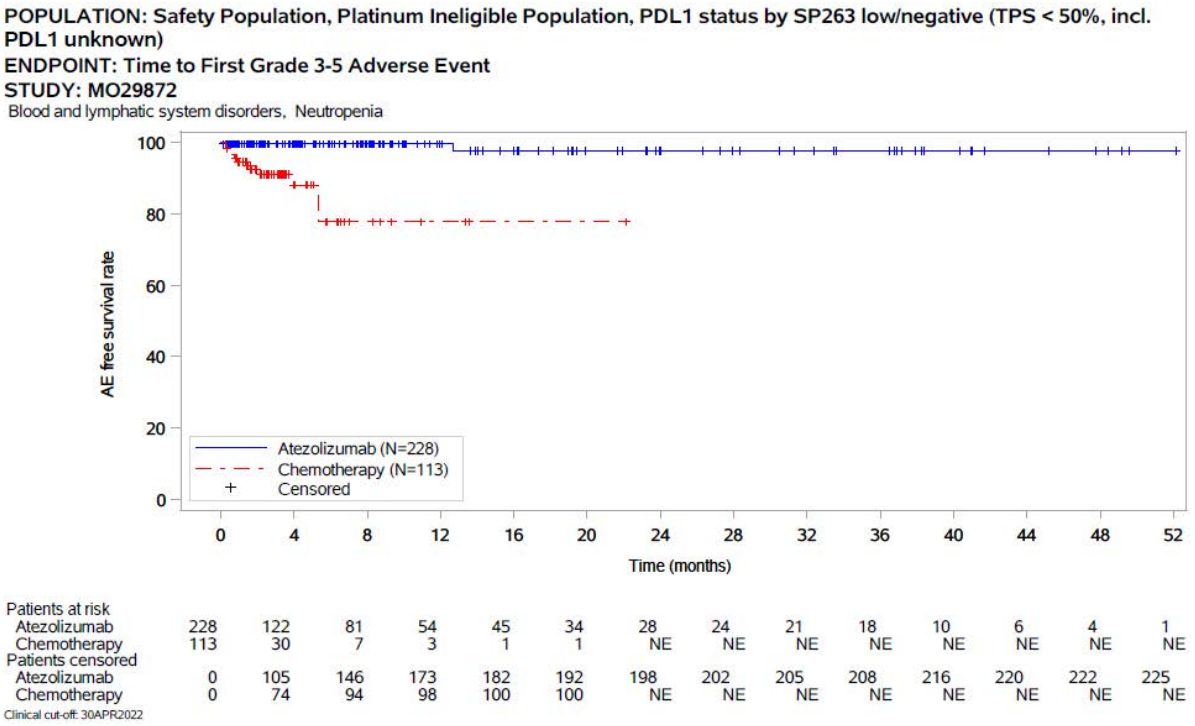


Figure 6: Kaplan-Meier curves for the outcome of neutropenia (severe AEs) (data cut-off 30 April 2022), research question 2

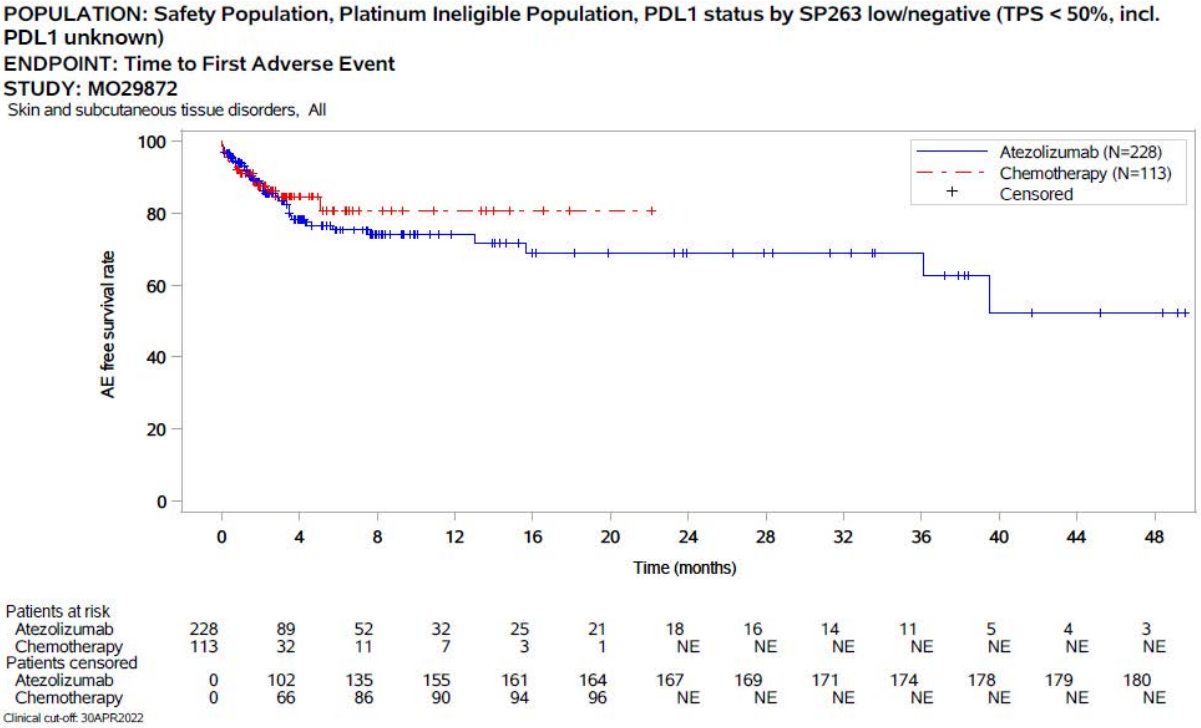


Figure 7: Kaplan-Meier curves for the outcome of skin reactions (AEs) (data cut-off 30 April 2022), research question 2

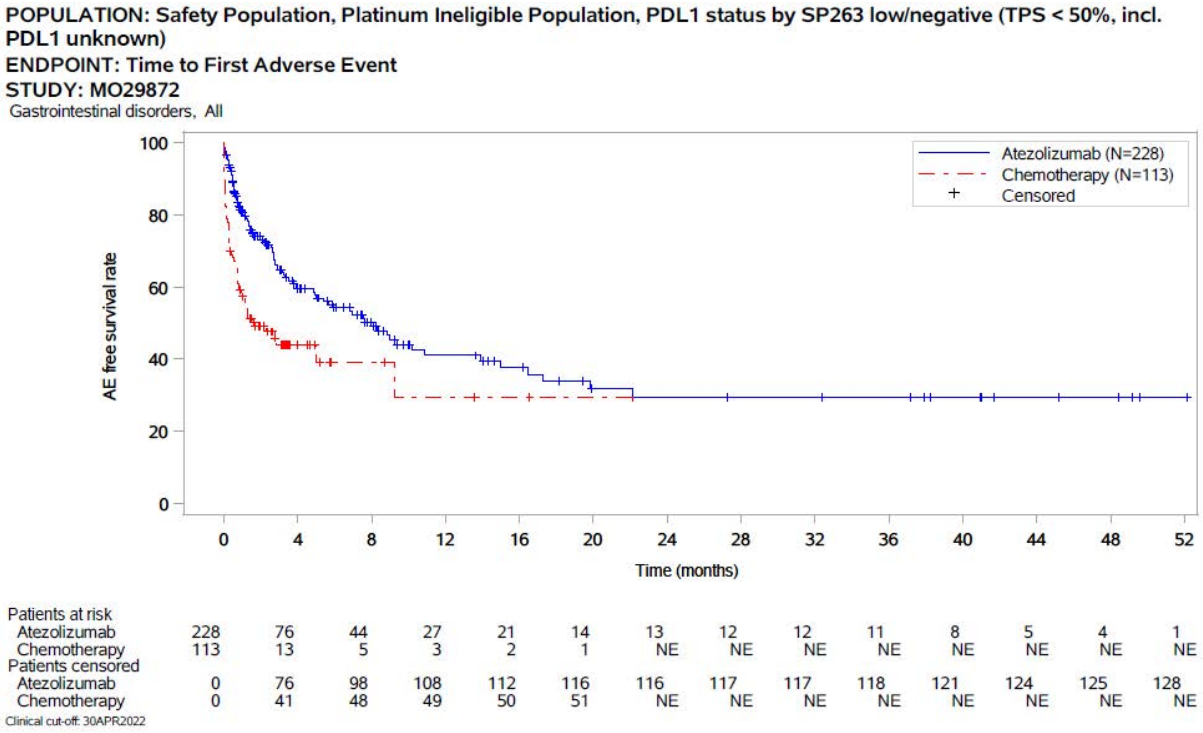


Figure 8: Kaplan-Meier curves for the outcome of gastrointestinal disorders (AEs) (data cut-off 30 April 2022), research question 2

## A.3 Subgroups analyses

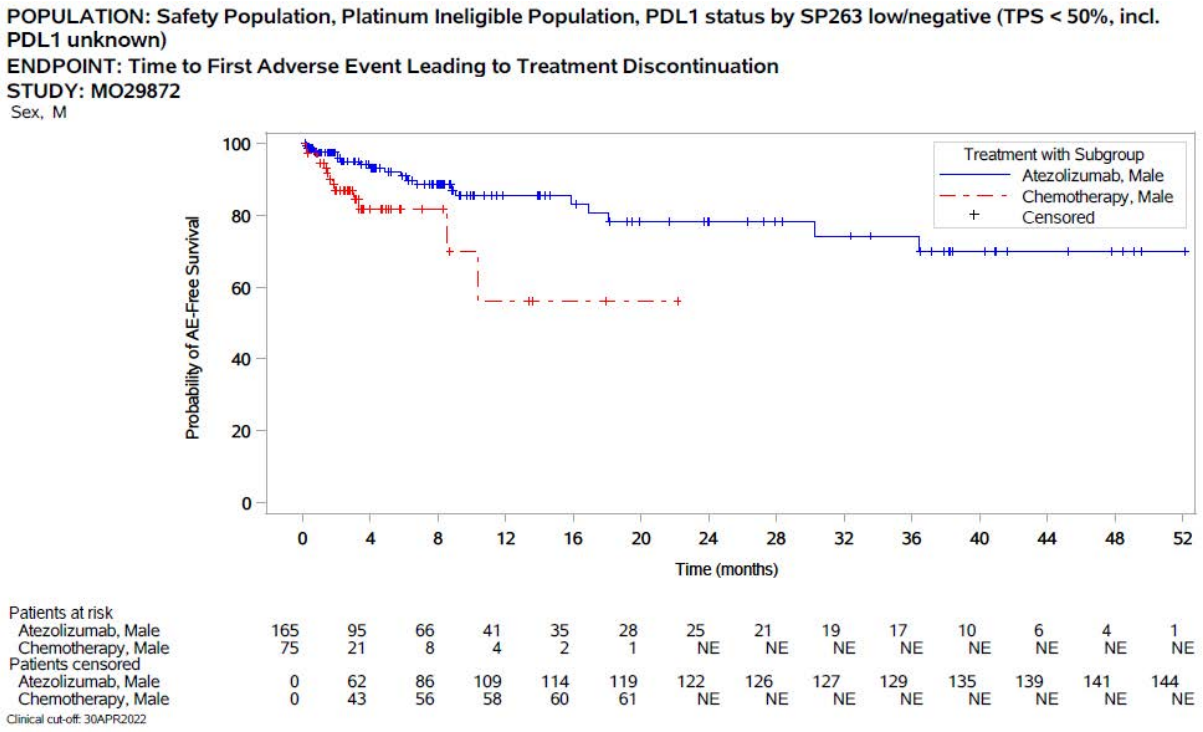


Figure 9: Kaplan-Meier curves for the outcome of discontinuation due to AEs, subgroup: male (data cut-off 30 April 2022), research question 2

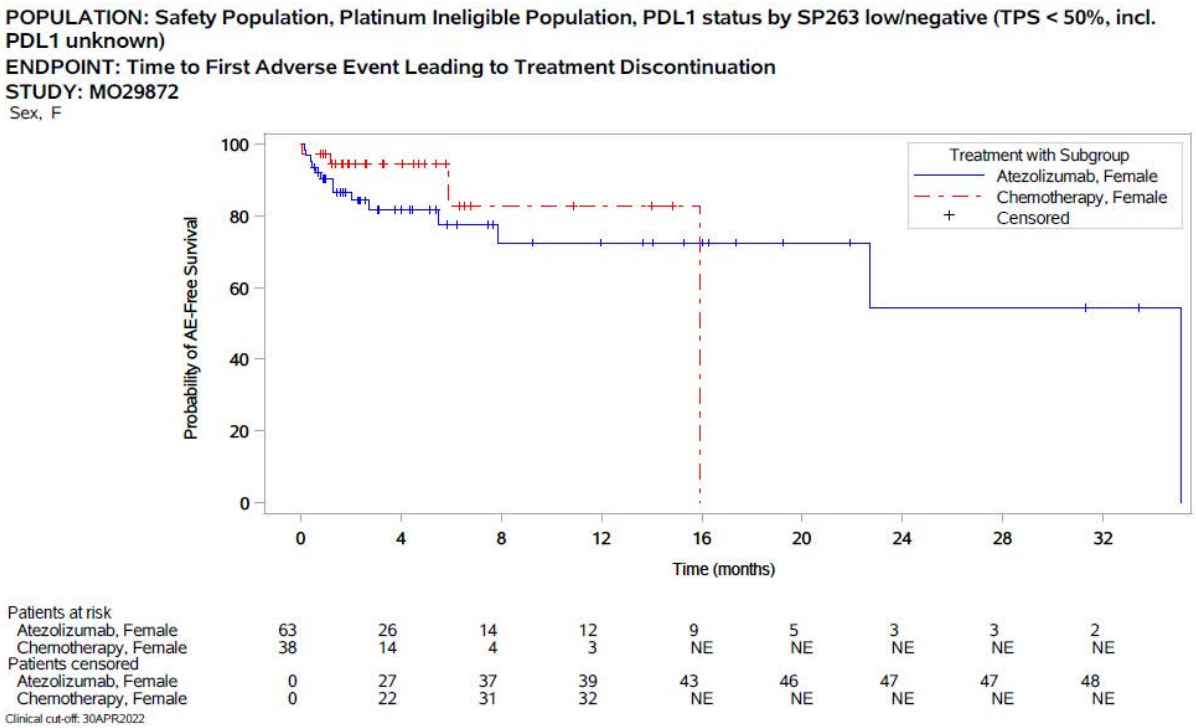


Figure 10: Kaplan-Meier curves for the outcome of discontinuation due to AEs, subgroup: female (data cut-off 30 April 2022), research question 2

## Appendix B Results on side effects

For the overall rates of AEs, SAEs, and severe AEs (CTCAE grade ≥ 3), the following tables present events for SOCs and Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- Overall rate of AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- Overall rates of severe AEs (e.g. CTCAE grade ≥ 3) and SAEs: events that occurred in at least 5% of patients in one study arm
- In addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

For the outcome of discontinuation due to AEs, all events that occurred in ≥ 2 patients in at least one study arm are presented.

Table 11: Common AEs[a] – RCT, direct comparison: atezolizumab vs. gemcitabine or vinorelbine, research question 2 (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | Atezolizumab N = 228 | Gemcitabine or vinorelbine N = 113 |
| **IPSOS** | | |
| **Overall AE rate** | 212 (93.0) | 111 (98.2) |
| Blood and lymphatic system disorders | 45 (19.7) | 54 (47.8) |
| Anaemia | 34 (14.9) | 39 (34.5) |
| Leukopenia | 3 (1.3) | 10 (8.8) |
| Neutropenia | 2 (0.9) | 16 (14.2) |
| Cardiac disorders | 33 (14.5) | 6 (5.3) |
| Atrial fibrillation | 12 (5.3) | 3 (2.7) |
| Endocrine disorders | 17 (7.5) | 2 (1.8) |
| Hypothyroidism | 14 (6.1) | 0 (0.0) |
| Eye disorders | 12 (5.3) | 3 (2.7) |
| Gastrointestinal disorders | 99 (43.4) | 61 (54.0) |
| Constipation | 35 (15.4) | 19 (16.8) |
| Diarrhoea | 26 (11.4) | 20 (17.7) |
| Nausea | 29 (12.7) | 30 (26.5) |
| Vomiting | 21 (9.2) | 21 (18.6) |
| General disorders and administration site conditions | 113 (49.6) | 55 (48.7) |
| Asthenia | 31 (13.6) | 15 (13.3) |
| Fatigue | 51 (22.4) | 26 (23.0) |
| Oedema peripheral | 17 (7.5) | 6 (5.3) |
| Pyrexia | 21 (9.2) | 7 (6.2) |
| Infections and infestations | 117 (51.3) | 43 (38.1) |
| Lower respiratory tract infection | 14 (6.1) | 7 (6.2) |
| Nasopharyngitis | 11 (4.8) | 2 (1.8) |
| Pneumonia | 40 (17.5) | 14 (12.4) |
| Upper respiratory tract infection | 12 (5.3) | 3 (2.7) |
| Urinary tract infection | 21 (9.2) | 12 (10.6) |
| Injury, poisoning and procedural complications | 27 (11.8) | 7 (6.2) |
| Fall | 12 (5.3) | 2 (1.8) |
| Investigations | 66 (28.9) | 32 (28.3) |
| Blood creatinine increased | 11 (4.8) | 3 (2.7) |
| Neutrophil count decreased | 1 (0.4) | 12 (10.6) |
| Weight decreased | 17 (7.5) | 8 (7.1) |
| White blood cell count decreased | 1 (0.4) | 10 (8.8) |

Table 11: Common AEs[a] – RCT, direct comparison: atezolizumab vs. gemcitabine or vinorelbine, research question 2 (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | Atezolizumab N = 228 | Gemcitabine or vinorelbine N = 113 |
| Metabolism and nutrition disorders | 97 (42.5) | 38 (33.6) |
| Decreased appetite | 46 (20.2) | 27 (23.9) |
| Hypokalaemia | 15 (6.6) | 2 (1.8) |
| Hyponatraemia | 21 (9.2) | 5 (4.4) |
| Musculoskeletal and connective tissue disorders | 59 (25.9) | 33 (29.2) |
| Arthralgia | 20 (8.8) | 10 (8.8) |
| Back pain | 18 (7.9) | 8 (7.1) |
| Nervous system disorders | 47 (20.6) | 22 (19.5) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 10 (4.4) | 6 (5.3) |
| Dizziness | 13 (5.7) | 6 (5.3) |
| Psychiatric disorders | 36 (15.8) | 10 (8.8) |
| Insomnia | 16 (7.0) | 4 (3.5) |
| Renal and urinary disorders | 33 (14.5) | 7 (6.2) |
| Respiratory, thoracic and mediastinal disorders | 117 (51.3) | 44 (38.9) |
| Chronic obstructive pulmonary disease | 13 (5.7) | 3 (2.7) |
| Cough | 45 (19.7) | 10 (8.8) |
| Dyspnoea | 53 (23.2) | 12 (10.6) |
| Haemoptysis | 16 (7.0) | 9 (8.0) |
| Pleural effusion | 11 (4.8) | 3 (2.7) |
| Skin and subcutaneous tissue disorders | 45 (19.7) | 16 (14.2) |
| Dry skin | 12 (5.3) | 3 (2.7) |
| Pruritus | 19 (8.3) | 3 (2.7) |
| Rash | 22 (9.6) | 4 (3.5) |
| Vascular disorders | 30 (13.2) | 11 (9.7) |
| Hypertension | 14 (6.1) | 6 (5.3) |

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation taken from Module 4 without adaptation.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 12: Common SAEs[a] – RCT, direct comparison: atezolizumab vs. gemcitabine or vinorelbine, research question 2

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b] PT[b]** | **Atezolizumab** **N = 228** | **Gemcitabine or vinorelbine** **N = 113** |
| **IPSOS** | | |
| **Overall SAE rate** | 119 (52.2) | 44 (38.9) |
| Blood and lymphatic system disorders | 3 (1.3) | 6 (5.3) |
| Cardiac disorders | 15 (6.6) | 3 (2.7) |
| General disorders and administration site conditions | 17 (7.5) | 4 (3.5) |
| Infections and infestations | 55 (24.1) | 17 (15.0) |
| Pneumonia | 30 (13.2) | 10 (8.8) |
| Nervous system disorders | 10 (4.4) | 4 (3.5) |
| Respiratory, thoracic and mediastinal disorders | 33 (14.5) | 10 (8.8) |

a. Events that occurred in ≥ 10 patients in the intervention arm, or in ≥ 5% of patients in the comparator arm.
b. MedDRA version 25.0; SOC and PT notation taken from Module 4 without adaptation.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 13: Common severe AEs[a] – RCT, direct comparison: atezolizumab vs. gemcitabine or vinorelbine, research question 2

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b] PT[b]** | **Atezolizumab** | **Gemcitabine or vinorelbine** |
| | **N = 228** | **N = 113** |
| **IPSOS** | | |
| **Overall rate of severe AEs (CTCAE grade ≥ 3)** | 135 (59.2) | 70 (61.9) |
| Blood and lymphatic system disorders | 14 (6.1) | 24 (21.2) |
| Anaemia | 7 (3.1) | 6 (5.3) |
| Neutropenia | 2 (0.9) | 12 (10.6) |
| Cardiac disorders | 13 (5.7) | 2 (1.8) |
| Gastrointestinal disorders | 8 (3.5) | 7 (6.2) |
| General disorders and administration site conditions | 22 (9.6) | 8 (7.1) |
| Infections and infestations | 56 (24.6) | 18 (15.9) |
| Pneumonia | 28 (12.3) | 11 (9.7) |
| Investigations | 15 (6.6) | 13 (11.5) |
| Neutrophil count decreased | 0 (0) | 8 (7.1) |
| White blood cell count decreased | 0 (0) | 6 (5.3) |
| Metabolism and nutrition disorders | 32 (14.0) | 8 (7.1) |
| Hyponatraemia | 13 (5.7) | 4 (3.5) |
| Nervous system disorders | 8 (3.5) | 6 (5.3) |
| Respiratory, thoracic and mediastinal disorders | 44 (19.3) | 14 (12.4) |
| Dyspnoea | 14 (6.1) | 5 (4.4) |
| Vascular disorders | 13 (5.7) | 4 (3.5) |
| Hypertension | 10 (4.4) | 1 (0.9) |

a. Events that occurred in ≥ 10 patients in the intervention arm, or in ≥ 5% of patients in the comparator arm.
b. MedDRA version 25.0; SOC and PT notation taken from Module 4 without adaptation.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 14: Discontinuation due to AEs[a] – RCT, direct comparison: atezolizumab vs. gemcitabine or vinorelbine, research question 2

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Atezolizumab N = 228** | **Gemcitabine or vinorelbine N = 131** |
| **IPSOS** | | |
| **Overall rate of discontinuations due to AEs** | 34 (14.9) | 17 (15.0) |
| Blood and lymphatic system disorders | 0 (0.0) | 2 (1.8) |
| Gastrointestinal disorders | 2 (0.9) | 2 (1.8) |
| Diarrhoea | 0 (0.0) | 2 (1.8) |
| Vomiting | 0 (0.0) | 2 (1.8) |
| General disorders and administration site conditions | 4 (1.8) | 4 (3.5) |
| Hepatobiliary disorders | 4 (1.8) | 0 (0.0) |
| Infections and infestations | 5 (2.2) | 1 (0.9) |
| Pneumonia | 3 (1.3) | 1 (0.9) |
| Investigations | 1 (0.4) | 2 (1.8) |
| Musculoskeletal and connective tissue disorders | 3 (1.3) | 0 (0.0) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 2 (0.9) | 0 (0.0) |
| Nervous system disorders | 2 (0.9) | 2 (1.8) |
| Respiratory, thoracic and mediastinal disorders | 9 (3.9) | 4 (3.5) |
| Pneumonitis | 8 (3.5) | 2 (1.8) |

a. Events that occurred in ≥ 2 patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation taken from Module 4 without adaptation.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

## Appendix C Results on side effects in the category of immune-mediated AEs

Table 15: AESI categories of immune-mediated AEs[a] – RCT, direct comparison: Atezolizumab vs. gemcitabine or vinorelbine, research question 2 (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| Category[b] | Atezolizumab N = 228 | Gemcitabine or vinorelbine N = 113 |
| **IPSOS** | | |
| **Overall rate of immune-mediated AEs** | 128 (55.7) | 26 (23.0) |
| Autoimmune haemolytic anaemia | 0 (0) | 0 (0) |
| Haemophagocytic lymphohistiocytosis | 0 (0) | 0 (0) |
| Immune-mediated hepatitis (diagnosis, laboratory abnormalities) | 22 (9.6) | 5 (4.4) |
| Immune-mediated hepatitis (diagnosis) | 7 (3.1) | 0 (0) |
| Immune-mediated hepatitis (laboratory abnormalities) | 17 (7.5) | 5 (4.4) |
| Immune-mediated hyperthyroidism | 4 (1.8) | 2 (1.8) |
| Immune-mediated hypophysitis | 0 (0) | 0 (0) |
| Immune-mediated hypothyroidism | 21 (9.2) | 1 (0.9) |
| Immune-mediated colitis | 3 (1.3) | 0 (0) |
| Immune-mediated meningoencephalitis | 0 (0) | 0 (0) |
| Immune-mediated encephalitis | 0 (0) | 0 (0) |
| Immune-mediated meningitis | 0 (0) | 0 (0) |
| Immune-mediated myasthenia gravis | 1 (0.4) | 0 (0) |
| Immune-mediated myocarditis | 1 (0.4) | 0 (0) |
| Immune-mediated myositis + rhabdomyolysis | 0 (0) | 0 (0) |
| Immune-mediated myositis | 0 (0) | 0 (0) |
| Rhabdomyolysis | 0 (0) | 0 (0) |
| Immune-mediated adrenal insufficiency | 1 (0.4) | 0 (0) |
| Immune-mediated nephritis | 0 (0) | 1 (0.9) |
| Immune-mediated pancreatitis | 3 (1.3) | 0 (0) |
| Immune-mediated pneumonitis | 10 (4.4) | 3 (2.7) |
| Immune-mediated severe cutaneous reaction | 0 (0) | 0 (0) |
| Immune-mediated toxic eye inflammation | 0 (0) | 0 (0) |
| Immune-mediated vasculitis | 0 (0) | 0 (0) |
| Immune-mediated rash | 33 (14.5) | 9 (8.0) |
| Immune-mediated diabetes mellitus | 3 (1.3) | 0 (0) |
| Immune-mediated Guillain-Barre syndrome | 0 (0) | 0 (0) |
| Infusion related reaction | 1 (0.4) | 0 (0) |

a. The operationalizations for AEs of special interest (AESIs) presented by the company are shown.
b. Notation taken from Module 4 of the dossier.

AE: adverse event; AESI: AE of special interest; n: number of patients with at least one event; N: number of analysed patients; RCT: randomized controlled trial