25 July 2024
EMA/CHMP/111305/2024
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Tecentriq

International non-proprietary name: Atezolizumab

Procedure No. EMEA/H/C/004143/II/0082

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# List of abbreviations

| | |
|---|---|
| ADA | Anti-drug antibody |
| ADR | Adverse drug reaction |
| AJCC | American Joint Committee on Cancer |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALK | Anaplastic lymphoma kinase |
| BSC | Best supportive care |
| CCOD | Clinical cutoff date |
| CNS | Central nervous system |
| CR | Complete response |
| CSR | Clinical study report |
| DOR | Duration of response |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| EGFR | Epidermal growth factor receptor |
| EMA | European Medicines Agency |
| EORTC | European Organisation for Research and treatment of Cancer |
| ESMO | European Society for Medical Oncology |
| ES-SCLC | End-stage small cell lung cancer |
| EU | European Union |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HA | Health Authority |
| HR | Hazard ratio |
| HRQoL | Health-related quality of life |
| IC | Tumor-infiltrating immune cells |
| ICH | International Conference on Harmonization |
| ICI | Immune checkpoint inhibitor |
| IDCC | Independent data coordinating centre |
| IDMC | Independent Data Monitoring Committee |
| Ig | Immunoglobulin |
| IHC | Immunohistochemistry |
| IV | Intravenous |
| ITT | Intent-to-treat |
| IxRS | Interactive voice/web response system |
| KM | Kaplan-Meier |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic resonance imaging |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NCCN | National Comprehensive Cancer Network |

| | |
|---|---|
| NSCLC | Non-small cell lung cancer |
| ORR | Objective response rate |
| OS | Overall survival |
| PD-1 | Programmed death-1 |
| PD-L1 | Programmed death-ligand 1 |
| PI | Product information |
| PK | Pharmacokinetic |
| PFS | Progression-free survival |
| PR | Partial response |
| PRO | Patient-reported outcome |
| PS | Performance status |
| q2w | Every 2 weeks |
| q3w | Every 3 weeks |
| q4w | Every 4 weeks |
| QLQ-C30 | Quality of life Questionnaire Core 30 |
| QLQ-LC13 | Quality of life Questionnaire Lung Cancer Module 13 |
| RCT | Randomized controlled trial |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SC | Subcutaneous |
| SCE | Summary of Clinical Efficacy |
| SCLC | Small cell lung cancer |
| SOC | System organ class |
| TC | Tumor cell |
| TNBC | Triple-negative breast cancer |
| TTCD | Time to confirmed deterioration |
| UC | Urothelial carcinoma |
| U.K. | United Kingdom |
| ULN | Upper limit of normal |
| U.S. | United States |
| 1L | First-line |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 24 August 2023 an application for a variation.

The following variation was requested:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I |

Extension of indication to include first-line treatment of adult patients with non-small cell lung cancer (NSCLC) who are ineligible for platinum-based chemotherapy and who do not have EGFR mutant or ALK-positive disease, who have: locally advanced unresectable NSCLC not amenable for definitive chemoradiotherapy, or metastatic NSCLC, for TECENTRIQ, based on final results from study MO29872 (IPSOS); this is a phase 3, open-label, multicenter, randomized study to investigate the efficacy and safety of atezolizumab compared with chemotherapy in patients with treatment naive advanced or recurrent (stage IIIB not amenable for multimodality treatment) or metastatic (stage IV) non-small cell lung cancer who are deemed unsuitable for platinum-containing therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. Version 29.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

The variation requested amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP).

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0207/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0207/2019 was completed.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## *Scientific advice*

The MAH did not seek Scientific Advice at the CHMP.

### 1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Aaron Sosa Mejia

| Timetable | Actual dates |
|---|---|
| Submission date | 24 August 2023 |
| Start of procedure: | 16 September 2023 |
| CHMP Rapporteur Assessment Report | 9 November 2023 |
| PRAC Rapporteur Assessment Report | 20 November 2023 |
| Updated PRAC Rapporteur Assessment Report | 24 November 2023 |
| PRAC Outcome | 30 November 2023 |
| CHMP members comments | 4 December 2023 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 8 December 2023 |
| Request for supplementary information (RSI) | 14 December 2023 |
| Rapporteur's preliminary assessment report on the MAH's responses circulated on | 27 March 2024 |
| Rapporteur's updated assessment report on the MAH's responses circulated on | 18 April 2024 |
| 2nd request for supplementary information | 25 April 2024 |
| Rapporteur's preliminary assessment report on the MAH's responses circulated on | 27 June 2024 |
| Rapporteur's updated assessment report on the MAH's responses circulated on | 19 July 2024 |
| CHMP opinion | 25 July 2024 |

# 2. Scientific discussion

### 2.1. Introduction

This application seeks marketing authorisation for Tecentriq (atezolizumab) monotherapy for the first-line (1L) treatment of adult patients with non-small cell lung cancer (NSCLC) who are ineligible for platinum-based chemotherapy and who do not have epidermal growth factor receptor (EGFR) mutant or anaplastic lymphoma kinase (ALK)-positive disease, who have locally advanced, unresectable NSCLC not amenable for definitive chemoradiotherapy, or metastatic NSCLC based on results from Study MO29872 (hereafter referred to as IPSOS). This study is a Roche-sponsored, global, randomized controlled Phase III trial that compared the efficacy and safety of atezolizumab monotherapy versus single-agent chemotherapy (gemcitabine or vinorelbine as per investigator's choice) in patients with treatment-naïve locally advanced or metastatic NSCLC not harboring an EGFR mutation or ALK translocation and regardless of programmed death-ligand 1 (PD-L1) expression status who were deemed unsuitable for platinum-doublet chemotherapy. IPSOS enrolled 453 patients across 23 countries in North America, Central and South America, Asia Pacific, Europe and the Middle East.

## 2.1.1. Problem statement

### *Disease or condition*

The MAH applied for the following indication: *Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with NSCLC who are ineligible for platinum-based chemotherapy, and who do not have EGFR-mutant or ALK-positive NSCLC, who have:*

- *locally advanced, unresectable NSCLC not amenable for definitive chemoradiotherapy, or*
- *metastatic NSCLC (see section 5.1)*

### *Epidemiology*

Lung cancer remains the leading cause of cancer deaths worldwide; it is the most common cancer in men (together with prostate cancer) and the third most common cancer in women (after breast and colorectal cancer). It accounted for approximately 11% of all new cancers in 2020 with an estimated 2.2 million new cancer cases and 1.8 million death (Sung et al. 2021).

Half of all newly diagnosed NSCLC patients present with advanced disease (Stage IIIb or IV) (SEER 2023). In addition to advanced disease at diagnosis, patients could present with poor performance status (PS), advanced age and a history of unintentional weight loss (Bailey et al. 2023).

Platinum-based chemotherapy regimens are an efficacious standard of care, but can in some patients with substantial comorbidities or specific contraindications not be tolerated and therefore not an available treatment option (Quoix et al. 2011). For this reason, treatment tolerability is an important factor in treatment decisions for patients.

### *Management*

The current European Society for Medical Oncology (ESMO) treatment guidelines point out the lack of evidence for cancer immunotherapies in NSCLC patients with an Eastern Cooperative Oncology Group (ECOG) PS of ≥2 due to the exclusion of this patient population from clinical trials. The United Kingdom (U.K.) based, single arm, Phase II PePS2 trial studied pembrolizumab monotherapy in patients with advanced NSCLC and an ECOG PS of 2, regardless of PD-L1 expression level and number of previous lines of treatment. Based on these data, the ESMO panel states that this treatment option can be considered in patients with ECOG PS 2. Recommended therapies for the 1L treatment of patients with advanced NSCLC and an ECOG PS ≥2 are platinum based doublets in eligible patients, single agent chemotherapy with gemcitabine, vinorelbine, docetaxel or pemetrexed (for non-squamous NSCLC only), and best supportive care (BSC) in patients with an ECOG PS of 3 or 4. Similar to patients with an ECOG PS of 2, in elderly patients, single agent chemotherapy is superior to BSC (The Elderly Lung Cancer Vinorelbine Italian Study Group 1999) and carboplatin-based chemotherapy combinations are superior to non-platinum-based combinations or single-agent chemotherapy, though with increased toxicity (without significantly compromising QoL). Platinum based chemotherapy is the preferred option for elderly patients with PS 0-2 with adequate end organ function, while a single agent approach is recommended for the treatment of unfit or co-morbid patients.

Despite the limited survival benefit conferred by cytotoxic chemotherapy, platinum-based regimens remain the standard first-line option for most patients with locally advanced and metastatic NSCLC not harbouring an activating epidermal growth factor receptor (EGFR) mutation or ALK gene rearrangement. In particular, for newly diagnosed advanced stage non-squamous NSCLC, standard of care is a platinum-

doublet with either cisplatin or carboplatin and a taxane or pemetrexed, with or without bevacizumab. The combination of gemcitabine and a platinum analogue (either carboplatin or cisplatin) has also demonstrated efficacy as first-line treatment for NSCLC. Additionally, both vinorelbine and gemcitabine have been considered to have demonstrated improvement over BSC and are well tolerated.

In recent years, the use of immune checkpoint inhibitors (ICIs) has radically changed clinical practice and treatment paradigms in locally advanced, metastatic, and early-stage resectable NSCLC. Clinicians and researchers have pointed towards the lack of evidence-based treatment options for single-agent cancer immunotherapy in patients with poor PS and those ineligible for platinum-based therapy. These gaps provided the rationale for evaluating the benefits and risks of atezolizumab monotherapy in patients ineligible for platinum-based chemotherapy. Due to atezolizumab's well-established efficacy, safety, and pharmacokinetic (PK) profile, single agent atezolizumab was chosen to study its impact on OS in patients with 1L advanced or metastatic NSCLC deemed ineligible for platinum doublet therapy in the Phase III IPSOS trial.

### 2.1.2. About the product

Tecentriq (hereinafter atezolizumab) is a humanized immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab targets human programmed death-ligand 1 (PD L1) on tumor infiltrating immune cells (ICs) and tumor cells (TCs) and inhibits its interaction with its receptors, programmed death-1 (PD 1) and B7.1, both of which can provide inhibitory signals to T cells.

Atezolizumab is globally approved for the treatment of patients with metastatic squamous and non-squamous non-small cell lung cancer (NSCLC) as first-line (1L) therapy if their tumors are PD-L1 high (≥50%) or after prior chemotherapy (regardless of PD-L1 expression level), as well as 1L treatment of metastatic non-squamous NSCLC in combination with chemotherapy with or without bevacizumab. In addition, atezolizumab monotherapy is approved for adjuvant treatment of Stage II to IIIA NSCLC following resection and platinum-based chemotherapy in patients whose tumors have PD-L1 expression of ≥50%.

Atezolizumab is also globally approved for the treatment of a variety of other cancers, including extensive-stage small-cell lung cancer (ES-SCLC), urothelial cancer (UC), triple negative breast cancer (TNBC), melanoma, and hepatocellular carcinoma (HCC). In the US, atezolizumab is also approved for adult and pediatric patients 2 years of age and older with unresectable or metastatic alveolar soft part sarcoma (ASPS).

### 2.1.3. The development programme/compliance with CHMP guidance/scientific advice

**Table 1. Summary of Key Discussions with EMA and (Co-)Rapporteurs**

| Key request/agreements (if relevant) | Comment |
|---|---|
| The (Co-)Rapporteurs expressed concerns regarding the lack of PK sample collection in this fragile population and recommended preparing a robust justification to address this. | A rationale for not collecting PK data in IPSOS is provided in Section 2.3.2. |

| | |
|---|---|
| The (Co-)Rapporteurs raised concerns regarding the definition of platinum-ineligibility and the adequacy of the choice of chemotherapy for the comparator arm.<br><br>They recommended investigating efficacy endpoints according to chemotherapy. | Rationale for the population enrolled in IPSOS and for the choice of chemotherapy for the comparator arm is provided in Section 2.4.3. |
| The (Co-)Rapporteurs expressed interest in additional analyses by PD-L1 subgroups with both SP142 and SP263 assays to confirm the consistency of the treatment effect across PD-L1 subgroups. | The requested analyses are provided in Section 2.4.2. |
| The (Co-)Rapporteurs raised concerns regarding the safety data, in particular the higher proportion of SAEs and fatal AEs observed in the atezolizumab arm. | These data are discussed in Section 2.5.1. |
| AE = adverse event; PD-L1 = programmed death-ligand 1; PK = pharmacokinetic; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SAE = serious adverse event; | |

### 2.1.4. General comments on compliance with GCP

Phase III Study IPSOS was conducted in accordance with the principles of the "Declaration of Helsinki" and GCP. The appropriate Ethics Committees and Institutional Review Boards reviewed and approved the study.

No audits were conducted for this study.

## *2.2. Non-clinical aspects*

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

### 2.2.1. Ecotoxicity/environmental risk assessment

Tecentriq (atezolizumab) is a protein and is therefore exempt from the Environmental Risk Assessment (ERA) requirements. This is compliant with the current Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00).

## *2.3. Clinical aspects*

### 2.3.1. Introduction

### GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has confirmed that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

**Table 2. A summary of atezolizumab studies utilised to support the summary of clinical pharmacology**

| Atezolizumab Monotherapy Studies | Phase | Indication | N Enrolled/PK evaluable (Total 3135/3079)[b] | Design/Dose/Primary Clinical Endpoint | How the study was utilized to support the SCP |
|---|---|---|---|---|---|
| PCD4989g (GO27831) | I | Multiple solid tumors | 481/473 | Dose-escalation/ up to 20 mg/kg q3w/ PK and safety | • Phase 1 popPK[a] (Section 3.2)<br>• Pooled monotherapy ER (Section 3.5)<br>• Age assessment (Section 3.3.2)<br>• Renal impairment assessment[a] (Section 3.3.1.1)<br>• Hepatic impairment assessment[a] (Section 3.3.1.2) |
| JO28944 | I | Multiple solid tumors | 6/6 | Dose-escalation/ 10 mg/kg and 20 mg/kg q3w/ PK and safety | • Phase 1 popPK[a] (Section 3.2)<br>• Pooled monotherapy ER (Section 3.5)<br>• Age assessment (Section 3.3.2)<br>• Renal impairment assessment[a] (Section 3.3.1.1)<br>• Hepatic impairment assessment[a] (Section 3.3.1.2) |
| IMvigor211 (GO29294) | III | 2L/3L mUC | 467/455 | 2-arm study/ 1200 mg q3w vs. vinflunine, paclitaxel, or docetaxel/OS | • Age assessment (Section 3.3.2) |
| POPLAR (GO28753) | II | 2L/3L NSCLC | 144/142 | 2-arm study/ 1200 mg q3w vs. docetaxel/ OS | • Age assessment (Section 3.3.2) |
| OAK (GO28915) | III | 2L/3L NSCLC | 613/606 | 2-arm study/ 1200 mg q3w vs. docetaxel/ OS | • Age assessment (Section 3.3.2) |
| IMpower110 (GO29431) | III | 1L NSCLC | 285/284 | 2-arm study/1200 mg q3w vs. cisplatin/carboplatin + pemetrexed/gemcitabine/OS | • Simulation comparison with IPSOS (Section 3.2.1) |
| IMvigor130 (WO30070) | III | 1L mUC | 803/789 | 3-arm study/1200 mg q3w vs. 1200 mg q3w + carboplatin + gemcitabine or cisplatin + gemcitabine vs. placebo + carboplatin + gemcitabine or cisplatin + gemcitabine/OS | • Baseline ECOG PS assessment (Section 3.4.1) |
| IMbrave150 (YO40245) | III | 1L mHCC | 336/324 | 2-arm study/1200 mg q3w + bevacizumab 15 mg/kg q3w vs. sorafenib 400 mg BID/OS | • Hepatic impairment assessment (Section 3.3.1.2) |

1L=first-line; 2L=second-line; 2L +=second-line and beyond; BID=twice per day; CSR=Clinical Study Report; DFS=disease-free survival; mHCC=metastatic hepatocellular carcinoma; mRCC=metastatic renal cell carcinoma; mUC=metastatic urothelial carcinoma; NSCLC=non-small call lung cancer; ORR=overall response rate; q3w=every 3 weeks; OS=overall survival; PK=pharmacokinetic.

[a] The atezolizumab Phase 1 popPK (Report No. 1066935) also included assessments for renal and hepatic impairment

[b] For randomized studies (i.e., IMvigor211, POPLAR, OAK, IMpower110, IMvigor130, and IMbrave150), number enrolled corresponds to the number of patients enrolled into the arm that includes atezolizumab therapy.

Study MO29872 (IPSOS) is a global, randomised controlled Phase III trial that compared the efficacy and safety of atezolizumab monotherapy versus single-agent chemotherapy (gemcitabine or vinorelbine as per investigator's choice) in patients with treatment-naïve locally advanced or metastatic NSCLC, who were deemed unsuitable for platinum doublet chemotherapy. The main focus of this study was to evaluate efficacy and safety of atezolizumab monotherapy in this patient population and given the extensive information on pharmacokinetics (PK) and anti-drug antibodies (ADA) already available for

atezolizumab, PK and ADA samples were not collected in IPSOS.

## 2.3.2. Pharmacokinetics

**Estimation of PK in IPSOS**

Atezolizumab PK and ADA samples were not collected in IPSOS and thus, no bioanalysis information is available and no population PK analysis was conducted for IPSOS. Instead, atezolizumab popPK simulated concentrations using selected observed median covariate values from the IPSOS patient population were compared to atezolizumab simulations using observed median covariate values from the IMpower110 patient population in order to demonstrate PK similarity. The IMpower110 study was a study evaluating monotherapy atezolizumab in 1L NSCLC patients, similar to the IPSOS study, and chosen as the reference population.

The popPK model developed in Phase I patients (Atezolizumab Phase I PopPK Report 1066935) showed that albumin, body weight, tumour burden (sum of longest diameters of target lesions), sex, and presence of ADA are significant covariates of atezolizumab PK.

Two sets of median covariates representing IMpower110 and IPSOS were used to predict exposure metrics for each study. For IMpower110 median values of albumin, body weight and tumour burden were 40 g/L, 70 kg, and 80 mm; for IPSOS median values albumin, body weight and tumour burden were 38 g/L, 65 kg, and 83 mm for, respectively. The popPK simulations were done for male and ADA-negative patients at an atezolizumab dose of 1200 mg q3w at Cycle 1 and at steady-state (Table 3).

**Table 3. Typical exposures in IMpower110 and IPSOS after simulations using median covariates (in male with ADA negative patients) at 1200 mg Q3W**

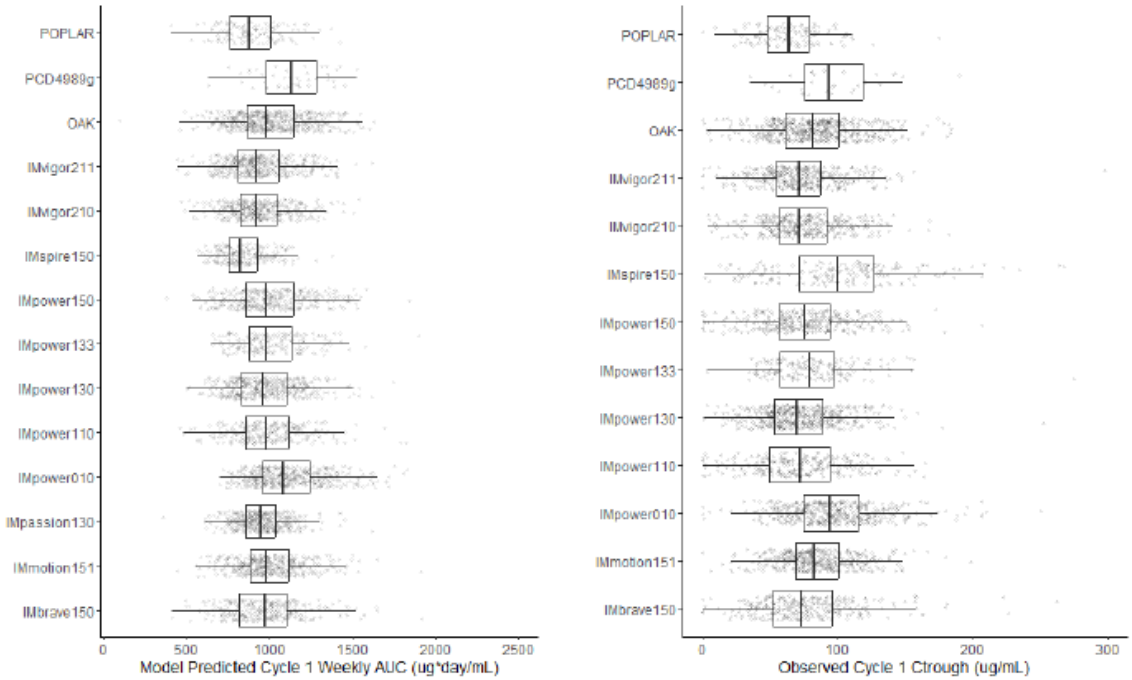
| | IMpower110 | IPSOS |
|---|---|---|
| **Cycle 1** | | |
| Typical CL (L/d) | 0.191 | 0.191 |
| $C_{max}$ (µg/mL) | 440 | 451 |
| $C_{min}$ (µg/mL) | 94.1 | 94.0 |
| AUC (µg·d/mL) | 3399 | 3422 |
| **Steady-state** | | |
| $C_{max}$ (µg/mL) | 631 | 640 |
| $C_{min}$ (µg/mL) | 190 | 188 |
| AUC (µg·d/mL) | 6282 | 6268 |

ADA = anti-drug antibody; AUC = area under the concentration-time curve; $C_{min}$ = minimum concentration; $C_{max}$ = maximum concentration
Note: Median albumin, body weight and tumor burden of 40 g/L, 70 kg and 80 mm, respectively, in IMpower110 and 38 g/L, 65 kg and 83 mm, respectively, in IPSOS.

**ADME characteristics**

Atezolizumab in both monotherapy and combination has been evaluated across a number of indications and has exhibited similar PK across all of these studies.

**Figure 1. Cross-study Box Plot of atezolizumab 1200 mg Q3W observed $C_{trough}$ (right) and Model-predicted weekly AUC (left) at Cycle 1**




AUC=area under the concentration-time curve; $C_{trough}$=pre-dose trough concentration.
For observed $C_{trough}$, x-axis is capped at 300 µg/mL, actual data extends to ~600 µg/mL.
Included in the plot are the studies of approved Tecentriq indications for mUC: IMvigor210, IMvigor211; NSCLC: IMpower010, IMpower110, IMpower130, IMpower150, OAK; SCLC: IMpower133; TNBC: IMpassion130; NSCLC: POPLAR; melanoma: IMsipre150; HCC: IMbrave150; RCC: IMmotion151. In addition, the 1200 mg Q3W cohort from FIH study PCD4989g was included. Observed Cycle 1 $C_{trough}$ (µg/mL) is not available for IMpassion130.

Model predicted CL for IMpower110 and IPSOS of 0.191 L/d were similar to the CL in the atezolizumab SmPC of 0.2 L/d.

## *Special populations*

### Organ impairment

There are no clinically important differences in atezolizumab clearance in patients with mild or moderate hepatic or renal impairment compared with patients with normal hepatic/renal function. Overall, 69% (208/300) of patients who received treatment with atezolizumab in IPSOS had renal impairment (51% [n =154] mild, 18% [n = 53] moderate and <1% [n = 1] severe). Overall, 9% (26/300) of patients who received treatment with atezolizumab in the IPSOS study had hepatic impairment as defined using National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria (8% [n =24] mild, <1% [n =2] moderate).

### Age

The IPSOS median age was 75 years versus atezolizumab monotherapy pooled median age of 64 years which was also the median age of IMpower110 population. No dose adjustment of Tecentriq is required in patients ≥ 65 years of age. In the atezolizumab arm of IPSOS, 15% of patients were <65 years of

age, 33% of patients were 65 - 74 years of age, 46% of patients were 75 - 84 years of age, and 5% of patients were ≥ 85 years of age.

**Baseline ECOG**

In the IPSOS patient population, there were more patients with baseline ECOG performance status 2 and 3, as compared to other atezolizumab monotherapy studies to date. The IMpower110 reference population included only 1L NSCLC patients with ECOG 0 or 1. Based on data from IMvigor130 which included patients with ECOG 2 status and sub-group analysis of safety data from IPSOS, baseline ECOG status is not expected to impact PK.

## 2.3.3. Pharmacodynamics

### *Mechanism of action*

Programmed death-ligand 1 (PD-L1) may be expressed on tumour cells and/or tumour-infiltrating immune cells, and can contribute to the inhibition of the antitumour immune response in the tumour microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T-cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.

Atezolizumab is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to PD-L1 and provides a dual blockade of the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the antitumour immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab spares the PD-L2/PD-1 interaction allowing PD-L2/PD-1 mediated inhibitory signals to persist.

### *Primary and secondary pharmacology*

No pharmacodynamics studies were conducted for the current application. No PK and PD samples were collected in the IPSOS trial.

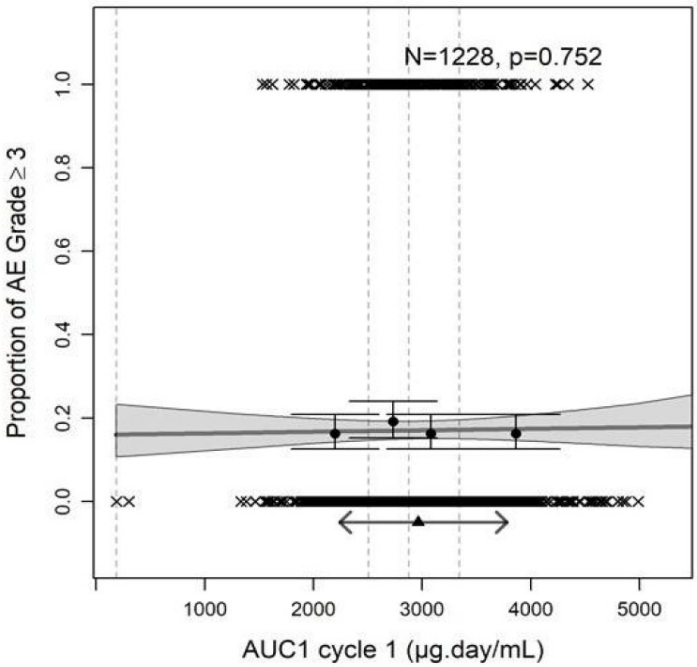
Analyses of exposure-response in the monotherapy setting

Exposure-response (ER) analyses were **not conducted** for the IPSOS study since no PK samples were collected; however, pooled ER analyses have been conducted for atezolizumab monotherapy across various indications (Atezolizumab pooled ER Report 1087176) submitted to the EMA as part of the Type II variation EMEA/H/C/004143/II/0022.

**Figure 2** and **Figure 3** represent the ER analysis conducted for safety from the **pooled atezolizumab monotherapy ER analysis**, evaluating the relationship between atezolizumab Cycle 1 AUC and the proportion of patients experiencing Grade ≥ 3 AEs, and atezolizumab Cycle 1 AUC and the proportion of patients experiencing AEs of special interest (AESI) of any grade, respectively.

**Figure 4** represents the ER analysis conducted for efficacy from the **pooled atezolizumab monotherapy ER analysis**, evaluating the relationship between atezolizumab Cycle 1 AUC and the objective response rate. **Figure 5** presents the ER analysis conducted for efficacy, which presents the overall survival distribution stratified over atezolizumab Cycle 1 AUC quartiles. The doses tested in the ER safety and efficacy analyses included patients who received atezolizumab 1200 mg q3w in **PCD4989g, IMvigor211 and OAK** (N=1056); patients from **PCD4989g** who received 10 to 20 mg/kg q3w (N=172); and one patient who received 1 mg/kg atezolizumab q3w from study **PCD4989g**.

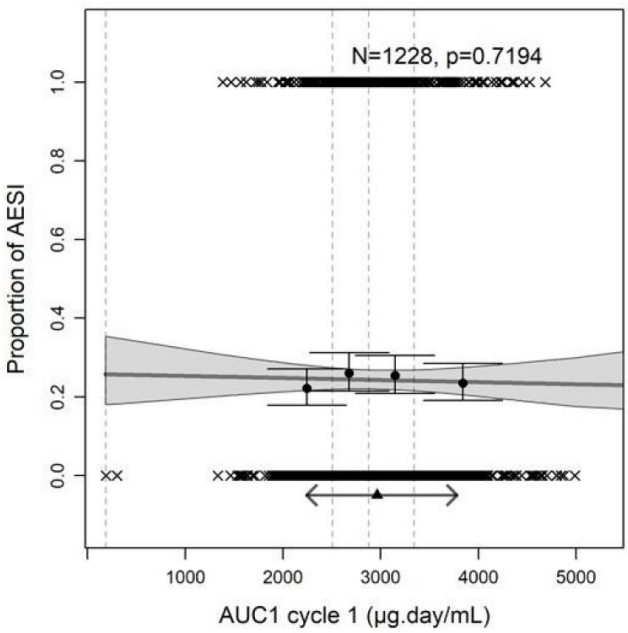
**Figure 2. Proportion of Patients Experiencing AE of Grade ≥ 3 vs. Cycle 1 AUC from Patients with NSCLC or UBC in Studies PCD4989g (NSCLC and mUC Cohorts), IMvigor211, and OAK**




AUC=area under the concentration-time curve; AE =adverse event; AEG35 =adverse events of Grade 3 to 5; CI =confidence interval; N =number of patients; NSCLC =non–small cell lung cancer; UBC = urothelial bladder cancer; p =p-value of Wald test in logistic regression of incidence versus exposure.

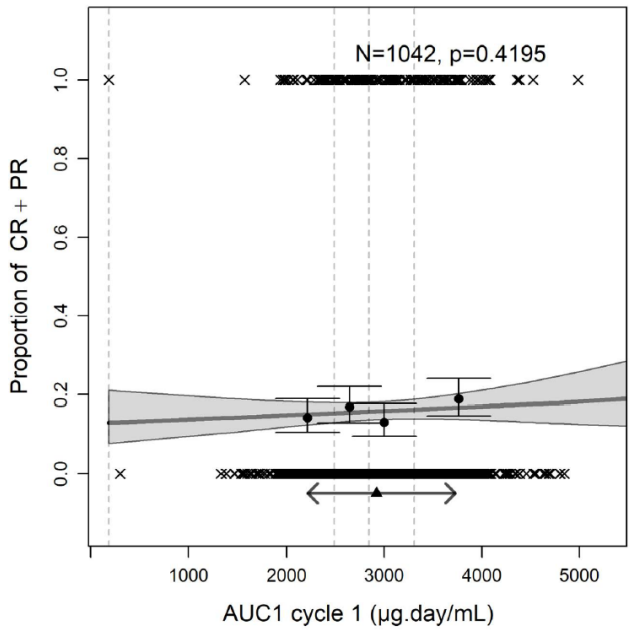
**Notes:** For legibility, two extreme AUC values (>15000 µg.day/mL) are not displayed on the plot. The data cutoff dates are 2 December 2014, 13 March 2017, and 7 July 2016 for Studies PCD4989g, IMvigor211 and OAK, respectively. The thick solid line and shaded area represent the logistic regression slope model and 95% prediction interval. The filled circles and error bar represent the incidence in exposure quartiles and 95% CI. The vertical lines are the limits of the exposure quartiles. The cross is AE events (0: No, 1: Yes). The triangle and two-headed arrow represent the mean exposure and exposure interval between the 10th and the 90th percentile for patients receiving 1200 mg atezolizumab, respectively.

**Figure 3. Proportion of Patients Experiencing AESI vs Cycle 1 AUC from Patients with NSCLC or mUC in Study PCD4989g (NSCLC and UBC cohorts), IMvigor211 and OAK**



AUC=area under the concentration-time curve; AESI =adverse events of special interest of any grade; CI =confidence interval; N =number of patients; NSCLC =non–small cell lung cancer; UBC = urothelial bladder cancer; p =p value of Wald test in logistic regression of incidence versus exposure.
**Notes:** For legibility, two extreme AUC values (>15000 µg.day/mL) are not displayed on the plot.
The data cutoff dates are 2 December 2014, 13 March 2017 and 7 July 2016 for PCD4989g, IMvigor211 and OAK, respectively. The thick solid line and shaded area represent the logistic regression slope model and 95% prediction interval. The filled circles and error bar represent the incidence in exposure quartiles and 95% CI. The vertical lines are the limits of the exposure quartiles. The cross is AE events (0: No, 1: Yes). The triangle and two-headed arrow represent the mean exposure and exposure interval between the 10th and the 90th percentile for patients receiving 1200 mg atezolizumab, respectively.

### Figure 4. Objective Response Rate vs. Atezolizumab AUC at Cycle 1– mUC and NSCLC Patients

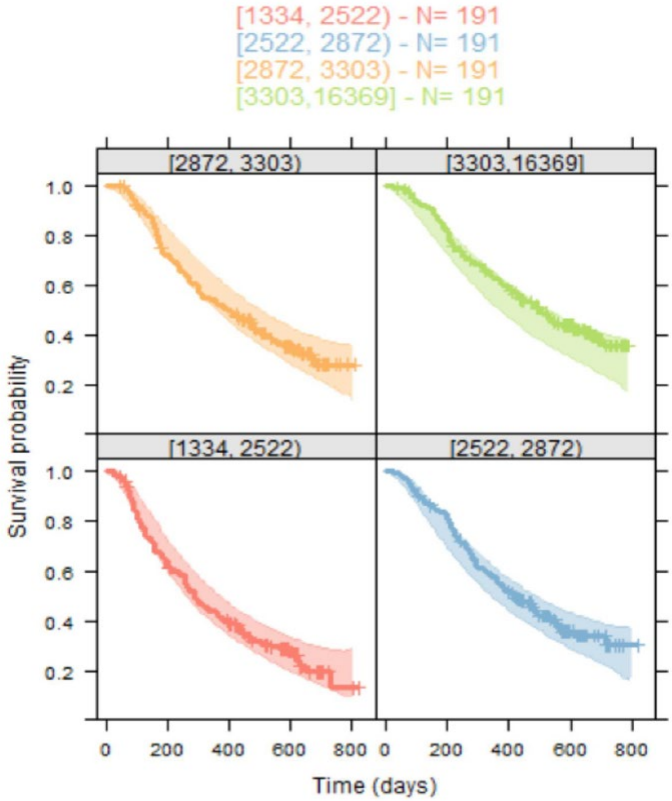



AUC =area under the curve; CI =confidence interval; CR =complete response; N =number of patients; p =p value of Wald test in logistic regression of proportion of responders versus exposure; PR =partial response; q3w =every three weeks

**Notes:** For legibility, one extreme AUC value (>15000 µg.day/mL) is not displayed on the plot.

The data cutoff dates are 2 December 2014, 13 March 2017 and 7 July 2016 for PCD4989g, IMvigor211 and OAK, respectively. The grey solid line and shaded area represent the logistic regression slope model and 95% prediction interval. The filled circles and error bar represent the proportion of responders in exposure quartiles and 95% CI. The vertical lines are the limits of the exposure quartiles. The crosses are the patient response events (0: No, 1: Yes). The triangle and two-headed arrow represent the mean exposure and exposure interval between the 10th and the 90th percentile for patients receiving 1200 mg atezolizumab, respectively.

**Figure 5. Evaluation of the Overall Survival Model in mUC and NSCLC Patients in Study IMvigor211 and OAK: Overall Survival Distribution Stratified by Quartile of AUC Cycle 1**




**Notes:** AUC Cycle 1 in μg/mL; [a, b) interval notation, a is included and b is excluded, (a≤x <b); bottom left panel: 1st quartile of AUC in atezolizumab arm N=191, bottom right panel: 2nd quartile of AUC in atezolizumab arm N=191, top left panel: 3rd quartile of AUC in atezolizumab arm N=191, upper right panel 4th quartile of AUC in atezolizumab arm N=191; Areas: 95% prediction interval of survival distributions; Line: Observed Kaplan-Meier distributions with censored data (crosses).

## 2.3.4. PK/PD modelling

Not applicable.

## 2.3.5. Discussion on clinical pharmacology

No **PK** or **ADA** samples were collected in Study IPSOS in 1L NSCLC patients. The patient population was similar to the patient population in IMpower110, which was used as reference. Exposure metrics for IMpower110 and IPSOS were predicted using the Phase I pop PK model using the study specific median values of covariates identified in the Phase I popPK model (baseline body weight, albumin, tumour burden, ADA, and gender) except for ADA status and gender. The median values of albumin, body weight and tumour burden from each study were highly comparable. The simulations were carried out in ADA negative male patients and were, as expected, highly comparable.

No difference in **ADME** parameters are expected in the IPSOS patient population compared to other patients receiving atezolizumab monotherapy.

No study specific **intrinsic factors** of the IPSOS patient population are expected to have impact on atezolizumab PK.

No statistically significant atezolizumab ER relationship was identified with any of the tested efficacy and safety endpoints. Therefore, while it is **expected that IPSOS patients have similar atezolizumab PK as the already characterised atezolizumab PK** across different monotherapy indications, slight increases (or decreases) in atezolizumab exposure are not expected to be clinically meaningful due to the lack of ER (for both safety and efficacy) for atezolizumab monotherapy.

Overall, the atezolizumab monotherapy PK has been extensively characterised and is not expected to be different in the IPSOS patient population. In addition, because no statistically significant ER relationship has been identified, any potential minor differences in atezolizumab PK is not expected to be clinically meaningful.

The following four **dosing regimens** are recommended for atezolizumab when administered as a monotherapy:

- Atezolizumab 1200 mg q3w administered intravenously (IV); or
- Atezolizumab 840 mg q2w administered intravenously; or
- Atezolizumab 1680 mg q4w administered intravenously; or
- Atezolizumab 1875 mg q3w administered subcutaneously (SC).

The rationale to support the 1200 mg q3w regimen is based on the clinical data from the IPSOS study showing a positive benefit-risk of atezolizumab 1200 mg q3w in patients with treatment-naïve locally advanced or metastatic NSCLC who were deemed unsuitable for platinum-doublet chemotherapy (see Clinical Efficacy section). The rationale to support the 840 mg q2w and 1680 mg q4w dosing regimens is based on PK modeling and simulation, ER assessments, and safety analyses submitted to the EMA as part of the Type II variation EMEA/H/C/004143/II/0022. In the EU, these dosing regimens have been approved for the 1L NSCLC, 2L NSCLC, and UC monotherapy indications (Tecentriq SmPC).

Following the positive outcome of the Tecentriq X-76 procedure (CHMP positive opinion 09 Nov 2023 and EC decision 11 Jan 2024), Tecentriq 1875 mg SC q3w demonstrated non-inferiority when compared with the dose regimen of Tecentriq 1200 mg IV q3w. Consequently, it was concluded that the line extension for atezolizumab SC would include all current and future approved indications for atezolizumab IV (see EPAR Tecentriq X/76).

### 2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology data supports the use of atezolizumab in the applied indication, by means of PK determined in other studies.

## *2.4. Clinical efficacy*

### 2.4.1. Dose response study(ies)

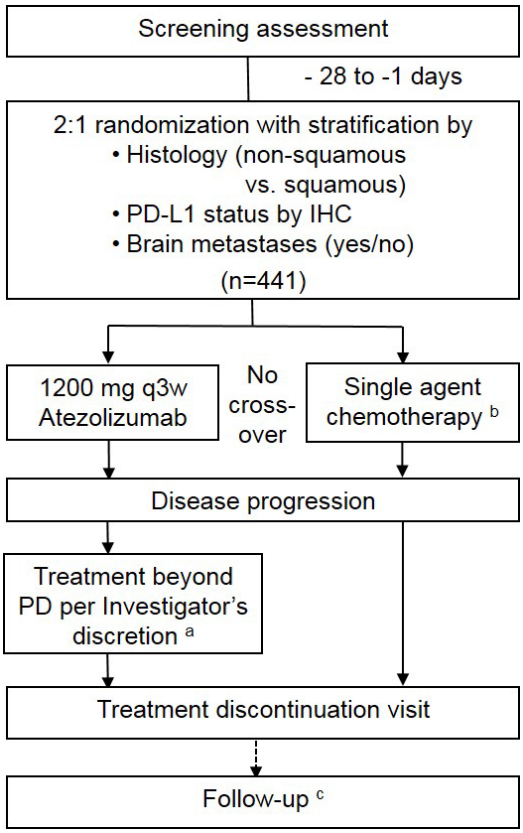
Please see 'Pharmacodynamics' section above.

## 2.4.2. Main study

### Title of Study

**IPSOS (MO29872). A Phase III, open-label, multicentre, randomised study to investigate the efficacy and safety of atezolizumab compared with chemotherapy in patients with treatment naive advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) non-small cell lung cancer who are deemed ineligible for platinum-containing therapy.**

**Figure 6. IPSOS (MO29872) - Study Design**




IHC = immunohistochemistry; NSCLC = non-small cell lung cancer; PD = disease progression; PD-L1 = programmed cell death-ligand 1; q3w = every 3 weeks

[a] Patients in the experimental arm with atezolizumab who show evidence of clinical benefit, could continue atezolizumab treatment after disease progression (RECIST v 1.1).

[b] Single-agent chemotherapy (vinorelbine, oral or intravenous, or gemcitabine, intravenous) based on investigator's choice was administered per relevant local guidelines and SmPC management. Chemotherapy cycles could be 3-weekly or 4-weekly.

[c] Follow-up information, including subsequent anticancer therapies and any treatment related adverse events, was collected via telephone calls and/or clinic visits every 2 months (± 5 days) until death, withdrawal of consent, loss to follow-up, study termination by the Sponsor, or protocol-defined end of study, whichever came first

## *Methods*

## Study participants

**Key Inclusion and Exclusion Criteria**

Patients who were treatment-naïve for locally advanced or metastatic NSCLC and who were deemed unsuitable for any platinum-doublet chemotherapy were enrolled in IPSOS. Key criteria relevant to efficacy are summarized below.

**Key Inclusion Criteria Relevant for Efficacy**

- Histologically or cytologically confirmed diagnosis of advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC as per the American Joint Committee on Cancer (AJCC) 7th edition.
- No sensitizing EGFR mutation (L858R or exon 19 deletions) or ALK fusion oncogene detected.
- No prior systemic treatment for advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC.
- Life expectancy ≥ 8 weeks
- Deemed unsuitable by the investigator for any platinum-doublet chemotherapy due to poor performance status (ECOG PS of 2 or 3). However, patients ≥ 70 years of age who had an ECOG PS of 0 or 1 could be included due to:

  a) substantial comorbidities
  b) contraindication(s) for any platinum-doublet chemotherapy.

- Patients with treated, asymptomatic central nervous system (CNS) metastases were eligible, provided they met all of the following criteria:

  a) Measurable disease outside CNS

  b) Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)

  c) No ongoing requirement for corticosteroids as therapy for CNS disease; anticonvulsants at a stable dose allowed

  d) No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomization

  e) No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

  Patients with new asymptomatic CNS metastases detected at screening had to receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients could then be eligible without the need for an additional brain scan prior to randomization, if all other criteria were met, including clinical confirmation of no evidence of interim disease progression

- Measurable disease (by RECIST v1.1)
  - Previously irradiated lesions could only be considered as measurable disease if disease progression had been unequivocally documented at that site since radiation and the previously irradiated lesion was not the only site of disease.

**Key Exclusion Criteria**

- Patients younger than 70 years who had an ECOG PS of 0 or 1
- Active or untreated CNS metastases as determined by CT or magnetic resonance imaging (MRI) evaluation of the brain during screening and prior radiographic assessments

  a) Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for >2 weeks prior to randomization

  b) Leptomeningeal disease

  c) History of CNS metastases intracranial haemorrhage
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L or calcium > 12 mg/dL or corrected serum calcium > ULN)
- Patients who had received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months from randomization since the last chemotherapy, radiotherapy, or chemoradiotherapy.
- Administration of a live, attenuated vaccine within 4 weeks before randomisation or anticipation that such a live attenuated vaccine would be required during the study.
- Treatment with systemic immunostimulatory agents (including but not limited to interferons, interleukin-2 [IL-2]) within 4 weeks or 5 half-lives of the drug, whichever was shorter, prior to randomisation.
- Treatment with systemic corticosteroids or other immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumor necrosis factor [anti-TNF] agents)

**PD-L1 testing**

Eligible patients had to provide a tumour tissue specimen for central assessment of PD-L1 expression by IHC at a central laboratory. Patients were tested prospectively using the SP142 assay for stratification and retrospectively by the SP263 assay. PD-L1 subgroup analyses by SP263 is a secondary endpoint introduced in Protocol amendment v5. The study enrolled all patients regardless of PD-L1 expression status.

Randomisation was stratified by PD-L1 expression levels determined in human formalin fixed, paraffin-embedded tumour tissue, using a specific anti-PD-L1 (SP142) rabbit monoclonal primary antibody IHC assay system (VENTANA PD-L1 SP142 Assay); efficacy analyses based on this assay were exploratory in nature.

The PD-L1 IHC assay and scoring criteria were developed to measure PD-L1-specific signals on both TCs and ICs. Four levels of TC expression (TC0, TC1, TC2, TC3) and four levels of IC expression (IC0, IC1, IC2, IC3) were determined by trained pathologists and used for the assessment of PD-L1 expression in NSCLC patients.

The protocol and statistical analysis plan (SAP) used outdated terminology, namely 'PD-L1 positive' to define TC3 or IC3 which is now known as 'PD-L1 high', and 'PD-L1 negative' to define TC0/1/2 and IC0/1/2 which is now known as 'PD-L1 low and negative', to define the PD-L1 strata. For clarity,

throughout the SCE, the use of the terms 'positive' and 'negative' has been replaced by the actual TC and IC cut-off levels for both PD-L1 assays used in the study.

**Table 4. Criteria for PD-L1 Expression Assessment in NSCLC Studies for the VENTANA PD-L1 (SP142) Assay**

| **Description of IHC Scoring Criteria** | **PD-L1 Expression Level** |
|---|---|
| Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in ICs covering < 1% of tumour area occupied by tumour cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma | IC0 |
| Presence of discernible PD-L1 staining of any intensity in ICs covering between ≥ 1% and < 5% of tumour area occupied by tumour cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma | IC1 |
| Presence of discernible PD-L1 staining of any intensity in ICs covering between ≥ 5% and < 10% of tumour area occupied by tumour cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma | IC2 |
| Presence of discernible PD-L1 staining of any intensity in ICs covering ≥ 10% of tumour area occupied by tumour cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma | IC3 |
| Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in < 1% TCs | TC0 |
| Presence of discernible PD-L1 staining of any intensity in ≥ 1% and < 5% TCs | TC1 |
| Presence of discernible PD-L1 staining of any intensity in ≥ 5% and < 50% TCs | TC2 |
| Presence of discernible PD-L1 staining of any intensity in ≥ 50% TCs | TC3 |

IC = tumour-infiltrating immune cell; IHC = immunohistochemistry; PD-L1 = programmed death–ligand 1; TC = tumour cell.

Protocol version 5 (19 December 2019) added the secondary endpoints of OS and PFS by RECIST v1.1 in patients with PD-L1 expression defined by the VENTANA PD-L1 SP263 IHC assay. To assess PD-L1 status, sections from tumour specimens were stained using the PD-L1 SP263 assay and trained pathologists scored these tumour specimens for tumour cell expression according to a scoring algorithm measuring PD-L1 on tumour cells (TC <1%, TC ≥ 1%, TC 1-49%, or TC ≥ 50% of tumour cells with membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control).

**Table 5. Nomenclature of PD-L1 Subgroups**

| **PD-L1 subgroup** | **Categories/cut-off by PD-L1 SP142 assay** | **Categories/cut-off by PD-L1 SP263 assay** |
|---|---|---|
| PD-L1 negative | TC0 and IC0 | < 1% |
| PD-L1 positive | TC1/2/3 or IC1/2/3 | ≥ 1% |
| PD-L1 low | [TC1/2 and IC0/1/2] or [TC0 and IC1/2] | 1 – 49% |
| PD-L1 low and negative | TC0/1/2 and IC0/1/2 | < 50% |

| PD-L1 subgroup | Categories/cut-off by PD-L1 SP142 assay | Categories/cut-off by PD-L1 SP263 assay |
|---|---|---|
| PD-L1 high | TC3 or IC3 | ≥ 50% |

IC = tumor-infiltrating immune cells; PD-L1 = programmed death-ligand 1; TC = tumor cells

## Treatments

Atezolizumab was administered at a **fixed dose of 1200 mg intravenously** on Day 1 of each 21-day cycle.

Patients randomised to receive **single-agent chemotherapy** (**vinorelbine, oral or IV** or **gemcitabine IV** based on investigator's choice) received chemotherapy per relevant local guidelines and prescribing information. Doses and dose modifications for the selected single-agent chemotherapy were according to local standard of care and SmPCs.

- Vinorelbine: IV infusion at 25-30 mg/m$^2$ or oral administration at 60-80 mg/m$^2$ on Days 1 and 8 of each 21-day cycle or on Days 1, 8 and 15 of each 28-day cycle or weekly administration or
- Gemcitabine: IV infusion at 1 000-1 250 mg/m$^2$ on Days 1 and 8 of each 21-day cycle or on Days 1, 8 and 15 of each 28-day cycle

**Table 6. Randomised First-Line Single-agent Chemotherapy Trials Including Patients Deemed Unsuitable for Platinum-based Chemotherapy**

| Single-Agent Chemotherapy | Reference (Trial name) | Phase | Sample size | Region (Country) | Key eligibility criteria related to platinum-unsuitability | PS 0/1 (%)[§] | PS 2 (%)[§] | PS 3 (%)[§] | Median Age (years)[§] | mOS (months)[§] |
|---|---|---|---|---|---|---|---|---|---|---|
| **Gemcitabine** | Cappuzzo et al. 2006 | II | 117 | Italy | KPS ≥50 (ECOG PS 0-2)* Further inclusion criteria details relevant to platinum-ineligibility population: Presence of neuropathy or kidney disease or any other condition for which the use of platinum compounds was contraindicated | KPS 100: 18 (SIT) / 16 (LIT) KPS 90-80: 55 (SIT) / 51 (LIT) KPS 70-60: 23 (SIT) / 30 (LIT) KPS 50: 4 (SIT) / 3 (LIT) | | 0 | 72 (SIT) / 73 (LIT) | 9.8 (SIT) / 9.8 (LIT) |
| **Vinorelbine** | Camerini et al. 2021 (Tempo Lung) | II | 167 | Europe | ECOG PS of 0-1 or 2; Patients unfit to receive platinum-based chemotherapy had at least one (or more) of the following criteria: previous adjuvant platinum-based chemotherapy, creatinine clearance <60 ml/min, heart failure New York Heart Association class II-III, hearing loss >grade 2 and medical condition impairing platinum-based chemotherapy according to physician's opinion | 62 (SOV) / 66 (MOV) | 38 (SOV) / 34 (MOV) | 0 | 77 (SOV) / 77 (MOV) | 7.6 (SOV) / 7.1 (MOV) |
| **Docetaxel** | Hainsworth et al. 2007 | III | 350 | US | Patients were required to be older than 65 years of age or to be poor candidates for standard platinum-based chemotherapy regimens because of either coexistent medical illness or poor performance status | 67 | 33 | 0 | 74 | 5.1* |
| **Pemetrexed** | Gridelli et al. 2007 | II | 87 | Europe | Age ≥70 years or <70 years for patients who, in the investigator's opinion, were ineligible for platinum-based chemotherapy because of poor PS or comorbidities; an Eastern Cooperative Oncology Group PS of 0 to 2 | 68 | 32 | 0 | 73 | 4.7** |

ECOG=Eastern Cooperative Oncology Group; KPS=Karnofsky Performance Scale; LIT=Low infusion time; mOS=median overall survival; MOV=Metronomic oral vinorelbine; PS=performance status; SIT=Standard infusion time; SOV=Standard Oral Vinorelbine; US=United States.
* Performance status was reported as Karnofsky performance status (KPS) for this trial; the range in ECOG PS is based on the performance scales comparison of Karnofsky and ECOG Scores in the ESMO Practice Tools. The ESMO practice tool considers KPS 100-90 as ECOG PS 0, KPS 80-70 as ECOG PS 1, KPS 60-50 as ECOG PS2, and a KPS of 40-30 as ECOG PS 3.
§ Percentages for Performance Status, median age and median OS are reported for the respective single-agent chemotherapy arm(s), as indicated.
* The trial investigated docetaxel versus docetaxel/gemcitabine (mOS: 5.5 months)
** The trial investigated pemetrexed versus sequential pemetrexed/gemcitabine (mOS: 5.4 months)

No crossover was allowed between treatment arms.

Tumour assessments were performed at baseline, every 6 weeks (± 5 days) following randomisation for 48 weeks, and every 9 weeks (± 5 days) thereafter, with additional scans as clinically indicated. Assessments continued until disease progression per RECIST v1.1.

Patients in the experimental arm with atezolizumab who showed evidence of clinical benefit, were permitted to continue treatment with atezolizumab beyond disease progression per RECIST v1.1 until loss of clinical benefit, unacceptable toxicity, patient or physician decision to discontinue, or death, if they met all of the following criteria:

- Evidence of clinical benefit (i.e., in the absence of symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results [if available], clinical status, and of laboratory values)
- Absence of unacceptable toxicity
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumour progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Patients for whom approved therapies exist must provide written consent to acknowledge deferring these treatment options in favour of continuing study treatment at the time of initial progression.

Patients randomised to atezolizumab who continued to receive atezolizumab following disease progression per RECIST v1.1 underwent tumour assessments until treatment discontinuation.

Tumour assessments were to continue regardless of whether patients discontinued study treatment or started new anti-cancer therapy in the absence of disease progression per RECIST v1.1 unless patients withdrew consent.

## Objectives

The primary efficacy objective was to evaluate the efficacy of atezolizumab compared with single-agent chemotherapy in patients with treatment-naïve locally advanced or metastatic NSCLC who are deemed unsuitable for any platinum-doublet chemotherapy, as measured by OS.

The secondary efficacy objectives of the study were to evaluate the efficacy of atezolizumab monotherapy compared with chemotherapy on the basis of the following outcome measures:

- OS rates at 6, 12, 18 and 24 months
- Investigator-assessed ORR using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1
- Investigator-assessed PFS using RECIST v1.1
- Investigator-assessed duration of response (DOR) using RECIST v1.1.
- OS and investigator-assessed PFS (using RECIST v1.1) in patients with PD-L1 expression defined by the VENTANA PD-L1 SP263 assay.

The patient-reported outcome (PRO) objective of the study was to evaluate and compare PROs of lung cancer symptoms, patient functioning, and health-related quality of life (HRQoL) between treatment arms as measured by the European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30).

Follow-up data capture, including subsequent anticancer therapies, continued for each patient until death, withdrawal of consent, loss to follow-up, or study termination by Sponsor, whichever occurred first.

Safety assessments included the incidence, nature, and severity of adverse events (AEs) and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events

(NCI CTCAE) v. 4.0. Laboratory safety assessments included the regular monitoring of haematology and blood chemistry.

An independent Data Monitoring Committee (IDMC) was employed to conduct periodic evaluations of safety data. In addition, the IDMC was also responsible for evaluating efficacy data at the pre-specified interim analysis prior to the Sponsor's unblinding. All analyses for the IDMC's review were prepared by an Independent Data Coordinating Centre (IDCC).

## Outcomes/endpoints

The primary efficacy outcome measure was the comparison of OS between the two treatment arms (atezolizumab versus chemotherapy) in the ITT population.

The secondary outcome measures were:

- OS rate at the 6-, 12-, 18-, and 24-month timepoints in the ITT population
- ORR in the ITT population, defined as a best overall response rate of confirmed CR or PR, as determined by the investigator with use of RECIST v1.1.
- PFS in the ITT population, defined as the time from randomization to the first documented disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs first.
- DOR, in the ITT population defined as the time from the first tumor assessment that supports the patient's objective response (CR or PR, whichever is first reported) to documented disease progression as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first, among patients who have a best overall response as CR or PR.
- OS and investigator-assessed PFS in patients with PD-L1 expression defined by the Ventana PD-L1 SP263 immunohistochemistry (IHC) assay (introduced in Protocol amendment v5).

The PRO measures were:

- Clinically meaningful change from baseline (defined as a ≥10-point change) in EORTC QLQ-C30 and EORTC QLQ-LC scores and TTCD defined as the time from randomization to the first confirmed clinically meaningful deterioration in EORTC QLQ-C30 and LC13 symptom scores. Confirmed clinically meaningful deterioration in lung cancer symptoms is defined as a ≥10-point increase above baseline in a symptom score that must be held for at least two consecutive assessments or an initial ≥10-point increase above baseline followed by either death within 6 weeks from the last assessment through Week 48 or death within 9 weeks from the last assessment from Week 48 thereafter.

## Sample size

Assuming a 10% withdrawal rate and accrual duration of 24 months, approximately 441 (in reality 453) patients will be randomised in a 2:1 ratio to atezolizumab (294 patients) or chemotherapy (147 patients). A total of 380 OS events will provide 90% power to detect a significant improvement in median OS with atezolizumab compared to chemotherapy from 7 months to 10 months (i.e. hazard ratio [HR] 0.7) using a log-rank test at an overall two-sided alpha level of 5% (using a two-look Lan-DeMets group sequential

design with an interim analysis at 80% of information fraction and O'Brien-Fleming type boundary at two-sided 5% level of significance).

## Randomisation

Randomisation to atezolizumab and chemotherapy arms will occur in a 2:1 ratio using permuted-block randomisation method. Randomisation will be stratified by the following factors:

- Histologic subtype (non-squamous vs. squamous)
- PD-L1 IHC status (positive vs. negative vs. unknown) according to assay VENTANA PD-L1 SP142
- Brain metastases (yes vs. no)

## Blinding (masking)

Not applicable, this study was open label.

Given the unique toxicities associated with chemotherapy (i.e., alopecia, hematologic toxicities), the pre-medications required (i.e., steroid, anti-emetics, and potentially growth factor support), the different dosing schedules for the chemotherapies and the option to administer vinorelbine either orally or intravenously, the study was open label.

## Statistical methods

### Analysis sets for the IPSOS study

**Intent-to-treat (ITT) Population**: all randomised patients irrespective of whether the assigned treatment was actually received. For analyses on ITT, patients will be grouped according to the treatment assigned at randomisation. The ITT population will be the population for the analysis of efficacy parameters.

**Safety-Evaluable Population:** all randomised patients who received any amount of study treatment. For analyses on Safety-Evaluable Population, patients will be grouped according to whether any amount of atezolizumab was received, including the case when atezolizumab was received in error. The Safety-Evaluable Population will be the population for the analysis of safety parameters.

**Hypotheses:** The overall type I error (α) for this study is 0.05 (two-sided). There will be no multiplicity adjustments for testing of secondary endpoints.

### Statistical methods

Treatment comparisons for the primary OS analysis were based on the stratified log-rank test based on the predefined randomisation stratification factors (see 'Randomisation'). The hazard ratio (HR) was estimated with use of a stratified Cox regression model, including a two-sided 95% CI. Kaplan-Meier methodology was used to estimate the median OS for each treatment arm and Kaplan-Meier (KM) curves were produced. Brookmeyer-Crowley methodology was used to construct the two-sided 95% CI for the median OS for each treatment arm. OS rates for 6-, 12, 18- and 24-month landmark analyses were estimated by the Kaplan-Meier methodology for each treatment arm, with two-sided 95% CIs calculated using Greenwood's formula.

Analysis of the secondary endpoints of PFS and TTCD was performed using the same methodology as with OS.

ORR and its 95% CI were estimated using the Clopper-Pearson method for each treatment arm. CIs for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution. The ORR was compared between the two arms using a Chi-square test.

Because the determination of DOR is based on a non-randomized subset of patients, formal hypothesis testing was not performed. Comparisons between treatment arms were made for descriptive purposes. The same methodologies detailed for the OS analysis were used for the DOR analysis.

**Interim analysis and final analysis**

There was one prespecified interim OS analysis performed by the iDMC after 304 deaths had occurred (CCOD: 15 May 2020), corresponding to 80% of the planned 380 events for the final analysis. The iDMC recommended that the study proceed to final analysis. To control the Type 1 error for OS, a Lan-DeMets group sequential design with an O'Brien Fleming type boundary was used. Final analysis of OS was conducted by the Sponsor when 379 OS events had been observed, 55 months after the first patient was randomised (CCOD: 30 April 2022). The planned information fraction and stopping boundaries at the time of each analysis were re-calculated using the actual number of events included in the analysis, and the nominal alpha level re-calculated accordingly so that the overall alpha level across both analyses was maintained at 5%. Boundaries can be seen below:

**Table 7. Timing and Stopping Boundaries for Interim and Final Analyses for Overall Survival**

| Interim and Final Analysis for OS | | | |
|---|---|---|---|
| Analysis Timing | Time from First Patient in (months) | Information Fraction (No. of events) | Stopping Boundary HR (p-value[1]) |
| Interim Analysis | 30 | 80% (304) | 0.76 ($p \leq 0.0244$) |
| Final Analysis | 42 | 100% (380) | 0.80 ($p \leq 0.0428$) |

**Censoring rules for primary endpoint, OS:** For OS, patients without a date of death will be censored on the date a patient was last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomization plus 1 day.

**Censoring rules for key secondary time to event endpoints:**

Progression-Free Survival (PFS), defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurs first. Patients who were alive and who had not experienced disease progression will be censored at the date of the last tumor assessment or the date of randomization plus 1 day if no post-baseline tumor assessment was available.

Duration of Response (DOR), defined as the time from the first occurrence of a documented objective response to the time of disease progression, as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurs first. Patients who were alive and who had not experienced disease progression will be censored at the date of the last tumor assessment or the date of randomization plus 1 day if no post-baseline tumor assessment was available.

OS and Investigator-assessed PFS according to RECIST v1.1 in patients with PD-L1 expression defined by the SP142 and SP263 immunohistochemistry (IHC) assay

**Subgroup and Exploratory Analyses**

The consistency of OS and PFS results was investigated in pre-specified subgroup analyses by demographic and baseline disease characteristics and by PD-L1 expression by IHC (SP263 assay and SP142 assay).

Additional post-hoc analyses in response to health authority feedback have also been performed and include:

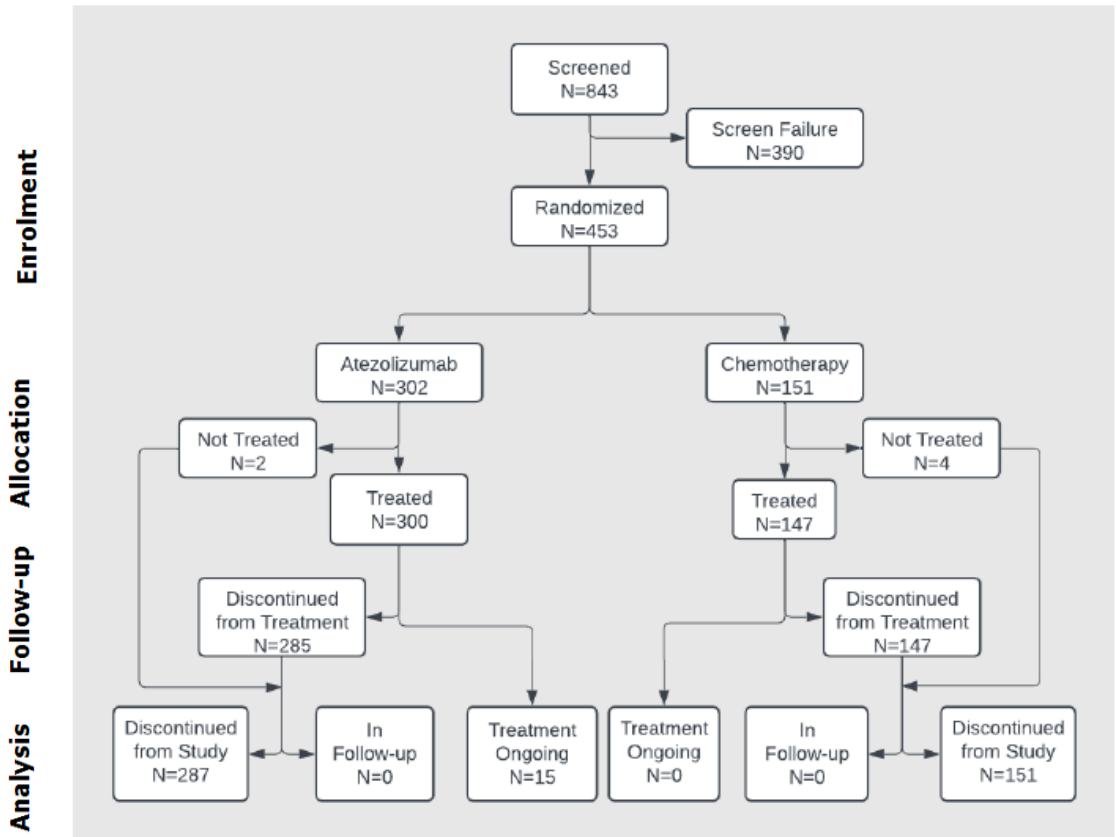
- A sensitivity analysis of OS performed to better characterise the impact of treatment discontinuation based on the investigator's decision. For patients who discontinued treatment with the reason documented as 'Physician decision', overall survival was censored at the time of the treatment discontinuation.
- Subgroup analyses of OS, PFS and ORR as well as description of baseline demographics and disease characteristics were performed according to: PD-L1 expression by the SP263 and SP142 IHC assays and investigator's choice of preferred chemotherapy (vinorelbine vs. gemcitabine)

Furthermore, a number of other sensitivity analyses were conducted. These are discussed under assessor's comment.

**Changes to the SAP:** Only changes from version 2 and 3 are disclosed in the SAP.

## *Results*

### Participant flow



## Recruitment

First Patient randomised: 11-Sep-2017.
Last patient randomised: 23 September 2019.
Data cut-off for Primary Analysis: 30-Apr-2022.

A total of 843 patients were screened for entry into the study and 390 patients failed screening based on information collected in the IxRS. The most common reasons for screen failure were failure to meet inclusion criteria, meeting one or more exclusion criteria, investigator or patient decision and insufficient tissue for analysis or lab result unavailable.

Patients were recruited from 85 centers across 23 countries. The number of patients randomized per region and country, followed by the number of centers (in parentheses), is summarized below in descending order:

- Europe and Middle East: Spain 48 patients (9 sites), United Kingdom 47 (7), Germany 42 (8), Poland 40 (2), Italy 30 (3), Switzerland 11 (3), Belgium 9 (4), Kazakhstan 8 (2), Romania 6 (3), Bulgaria 6 (2), Czech Republic 4 (1), Ireland 4 (2), Portugal 4 (2), Denmark 3 (1), Slovakia 3 (2).
- Asia Pacific: China 55 patients (7 sites), India 38 (7), Vietnam 15 (2).
- Central and South America: Brazil 20 patients (3 sites), Colombia 18 (4), Mexico 16 (3), Argentina 7 (3).
- North America: Canada 19 patients (5 sites)

Of the 453 enrolled patients, 302 patients were randomised to the atezolizumab monotherapy arm and 151 patients were randomised to the chemotherapy (gemcitabine or vinorelbine) arm. Of these 453 randomized patients, 447 patients received at least one dose of study treatment and comprised the safety-evaluable population.

As of the CCOD (30 April 2022), 95% of patients [287/302] in the atezolizumab arm vs. 100% of patients [151/151] in the chemotherapy arm had discontinued the study. The remaining 5% of patients [15/302] in the atezolizumab arm on study at the time of the CCOD were still on study treatment.

## Conduct of the study

**Table 8. Treatment discontinuation (Safety-Evaluable Population)**

| | Atezolizumab (N=300) | Chemotherapy (N=147) | Total (N=447) |
|---|---|---|---|
| Received at least One Dose of Study Drug, n(%) | 300 (100.0) | 147 (100.0) | 447 (100.0) |
| Treatment Status, n(%) | | | |
| Ongoing | 15 ( 5.0) | 0 ( 0.0) | 15 ( 3.4) |
| Discontinued from Treatment | 285 ( 95.0) | 147 (100.0) | 432 ( 96.6) |
| Primary Reason for Discontinuation from Treatment, n(%) | | | |
| Adverse Event | 38 ( 12.7) | 20 ( 13.6) | 58 ( 13.0) |
| Death | 60 ( 20.0) | 18 ( 12.2) | 78 ( 17.4) |
| Progressive disease | 151 ( 50.3) | 75 ( 51.0) | 226 ( 50.6) |
| Lost to follow-up | 1 ( 0.3) | 1 ( 0.7) | 2 ( 0.4) |
| Non-compliance | 3 ( 1.0) | 0 ( 0.0) | 3 ( 0.7) |
| Withdrawal by subject | 27 ( 9.0) | 12 ( 8.2) | 39 ( 8.7) |
| Study terminated by sponsor | 1 ( 0.3) | 0 ( 0.0) | 1 ( 0.2) |
| Physician decision | 3 ( 1.0) | 17 ( 11.6) | 20 ( 4.5) |
| Other | 1 ( 0.3) | 4 ( 2.7) | 5 ( 1.1) |
| Patients who Continued Treatment beyond Disease Progression, n(%) | 86 ( 28.7) | 0 ( 0.0) | 86 ( 19.2) |

**Table 9. Study discontinuation (ITT Population)**

| | Atezolizumab (N=302) | Chemotherapy (N=151) | Total (N=453) |
|---|---|---|---|
| Received at least One Dose of Study Drug, n(%) | 300 ( 99.3) | 147 ( 97.4) | 447 ( 98.7) |
| On-study Status, n(%) | | | |
| Alive: On Treatment | 15 ( 5.0) | 0 ( 0.0) | 15 ( 3.3) |
| Patients who Discontinued the Study, n(%) | 287 ( 95.0) | 151 (100.0) | 438 ( 96.7) |
| Primary Reason for Discontinuation from the Study, n(%) | | | |
| Death | 236 ( 78.1) | 127 ( 84.1) | 363 ( 80.1) |
| Lost to follow-up | 9 ( 3.0) | 3 ( 2.0) | 12 ( 2.6) |
| Withdrawal by subject | 26 ( 8.6) | 16 ( 10.6) | 42 ( 9.3) |
| Study terminated by sponsor | 15 ( 5.0) | 5 ( 3.3) | 20 ( 4.4) |
| Physician decision | 1 ( 0.3) | 0 ( 0.0) | 1 ( 0.2) |

**Table 10. Summary of Major Protocol Deviations (ITT Population)**

| Protocol Deviation Category<br>Protocol Deviation Subcategory | Atezolizumab (N=302)<br>n (%) | Chemotherapy (N=151)<br>n (%) | Total (N=453)<br>n (%) |
|---|---|---|---|
| Patients with Any Major Protocol Deviations | 89 ( 29.5) | 39 ( 25.8) | 128 ( 28.3) |
| Overall Total Number of Major Protocol Deviations | 113 | 53 | 166 |
| Exclusion Criteria | 13 ( 4.3) | 11 ( 7.3) | 24 ( 5.3) |
| Excluded CNS involvement | 1 ( 0.3) | 3 ( 2.0) | 4 ( 0.9) |
| Excluded autoimmune disease | 0 | 2 ( 1.3) | 2 ( 0.4) |
| Excluded concurrent or prior therapy | 6 ( 2.0) | 5 ( 3.3) | 11 ( 2.4) |
| Excluded medical condition | 6 ( 2.0) | 2 ( 1.3) | 8 ( 1.8) |
| Inclusion Criteria | 18 ( 6.0) | 7 ( 4.6) | 25 ( 5.5) |
| Failure to perform serum pregnancy test at screening | 1 ( 0.3) | 0 | 1 ( 0.2) |
| ICF deviation during screening | 3 ( 1.0) | 4 ( 2.6) | 7 ( 1.5) |
| Inadequate hematologic and end organ function | 8 ( 2.6) | 3 ( 2.0) | 11 ( 2.4) |
| No tumor tissue at screening | 1 ( 0.3) | 0 | 1 ( 0.2) |
| Prohibited prior systemic anticancer treatment | 2 ( 0.7) | 0 | 2 ( 0.4) |
| Symptomatic/untreated CNS mets | 3 ( 1.0) | 0 | 3 ( 0.7) |
| Medication | 14 ( 4.6) | 6 ( 4.0) | 20 ( 4.4) |
| Overdosage of IMP | 0 | 4 ( 2.6) | 4 ( 0.9) |
| Use of prohibited concomitant therapy during the course of the study | 14 ( 4.6) | 2 ( 1.3) | 16 ( 3.5) |
| Procedural | 56 ( 18.5) | 24 ( 15.9) | 80 ( 17.7) |
| Error with stratification | 11 ( 3.6) | 4 ( 2.6) | 15 ( 3.3) |
| Incorrect drug handling | 4 ( 1.3) | 0 | 4 ( 0.9) |
| Missed or incorrect study procedure | 35 ( 11.6) | 13 ( 8.6) | 48 ( 10.6) |
| Missed or incorrect tumor assessment | 12 ( 4.0) | 7 ( 4.6) | 19 ( 4.2) |

**Protocol amendments**

Version 1: 13 Feb 2017

Version 2: 29 Jun 2017

Exclusion criteria: Amended to exclude patients younger than 70 years with ECOG PS 0/1 in line with ESMO guidelines.

Amended to ensure exclusion of patients with illness or condition that may interfere with capacity or compliance with the study protocol.

Study population: Amended to include patients deemed 'unsuitable for any platinum doublet chemotherapy' as opposed to 'unsuitable for platinum containing therapy' to appropriately recruit cisplatin and carboplatin ineligible patients.

Study procedures: Increased frequency of on-treatment pregnancy tests and regular post-discontinuation visit pregnancy testing until at least 5 months after the last dose of atezolizumab or until at least 6 months after the last dose of chemotherapy.

Version 3: 16 Jan 2018

Inclusion criteria: Requirement for male contraception for atezolizumab patients removed as atezolizumab is not genotoxic.

Study procedures: PRO assessment frequency aligned with tumor assessments. Optional tumor biopsy at time of progression removed and replaced with serum sample. Initial tumor assessments and baseline laboratory assessments to be performed with 14 days prior to randomization. EGFR/ALK testing made mandatory only for patients with non-squamous NSCLC and squamous NSCLC who are never smokers or have mixed histology. Serum sampling for EBV removed. Week 6 plasma biomarker sampling amended to Week 7.

Concomitant medications: Immunostimulatory and-suppressive agents added to list of prohibited therapy.

Version 4: 14 Jan 2019

Inclusion criteria: Requirement for female patients of childbearing potential randomised to the atezolizumab arm to refrain from donating eggs was added.

Version 5: 19 Dec 2019

Inclusion criteria: Requirement for female patients of childbearing potential randomised to the atezolizumab arm to refrain from donating eggs was removed as study drug is not genotoxic.

Concomitant medications: Traditional herbal medicines used at investigator's discretion added.

Primary endpoints: Addition of interim analysis after 304 OS events (approximately 30 months from FPI). The final OS analysis will be conducted after 380 OS events (approximately 42 months after FPI) as opposed to after 372 OS events (approximately 40 months after FPI).

Secondary endpoints: Secondary objective to evaluate the efficacy (OS and INV-PFS [using RECIST v1.1]) of atezolizumab compared with single-agent chemotherapy in patients with PD-L1 expression defined by SP263 IHC assay added.

Version 6: 03 Feb 2021

Concomitant medications: Immunosuppressive medications removed from list of prohibited therapies and added to cautionary therapies section

Version 7: 22 Dec 2021

Primary endpoint: A time limit of at least 54 months after first patient enrolled was introduced as an alternative to the target 380 OS events for analysis of the primary endpoint, whichever should occur first.

**Follow-up**

Duration of survival follow-up was calculated using the reverse Kaplan-Meier estimate of OS. In the ITT population, the median duration of survival follow-up was 41.0 months and was comparable between the treatment arms (41.4 months in the atezolizumab arm versus 39.9 months in the chemotherapy arm)

**Table 11. Duration of Survival Follow-up (ITT Population)**

| | Atezolizumab (N=302) | Chemotherapy (N=151) | Total (N=453) |
|---|---|---|---|
| Kaplan-Meier Estimates of Duration of Survival Follow-Up (months) | | | |
| Events, n(%) | 53 (17.5%) | 21 (13.9%) | 74 (16.3%) |
| Censored, n(%) | 249 (82.5%) | 130 (86.1%) | 379 (83.7%) |
| 25th Pctl. (95% CI[1]) | 38.2 (33.9, 40.1) | 34.3 (34.3, 39.9) | 36.7 (34.3, 39.9) |
| Median (95% CI[1]) | 41.4 (40.0, 44.2) | 39.9 (36.5, 52.7) | 41.0 (39.9, 43.1) |
| 75th Pctl. (95% CI[1]) | 47.8 (43.1, 49.1) | 52.7 (36.8, NE) | 47.8 (43.1, 49.4) |
| Min, Max | 0.1, 51.5 | 0.1, 53.5 | 0.1, 53.5 |

The inverse Kaplan-Meier methodology was used to estimate the duration of survival follow-up.
[1] 95% Confidence Interval (CI) computed using the Brookmeyer and Crowley method.

## Baseline data

In the following sections, two efficacy datasets are presented:

**The intent-to-treat (ITT) population (N=453, 302 in the atezo arm and 151 in the chemo arm)** is constituted by all randomised patients irrespective of whether the assigned treatment was actually received. This population (N=453, from which 302 were in the atezo arm and 151 in the chemotherapy arm) was used for all the efficacy analysis per protocol.

**The platinum-ineligible population (N=405, 268 in the atezo arm and 137 in the chemo arm):** Considering the lax and relatively ambiguous per-protocol definition of platinum-ineligibility in the inclusion criteria from IPSOS, the CHMP questioned whether the observed results were robust enough to represent the targeted *fragile* patient population. The MAH acknowledged the lack of detailed information in IPSOS as to why study investigators assessed their patients to be ineligible for a platinum-based doublet and lack of severity grading for ongoing comorbidities and recognised that this information cannot be obtained in retrospect. Based on this, it was agreed with the MAH to assess which proportion of patients from IPSOS could meet "directly evaluable" criteria for platinum ineligibility according to *De Marinis et al. 2015*, i.e., age >80 years, Eastern Cooperative Oncology Group (ECOG) PS ≥3, and creatinine clearance <45 mL/min. In addition, the MAH assessed the proportion of patients with any ongoing comorbidities if they did not meet any of the three 'directly evaluable' criteria.

After the assessment, the following selection criteria were defined to select an ad hoc dataset of patients ('platinum-ineligible population'):

1. Age >80 years; and/or
2. ECOG PS 3; and/or
3. ECOG PS 2 in combination with relevant comorbidities; and/or
4. Age ≥70 years in combination with relevant comorbidities.

Relevant comorbidities are related to 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.

Efficacy results for the 'platinum ineligible population' are described in the Ancillary analyses section.

**Table 12. Summary of Baseline Demographic Characteristics (ITT Population)**

| | Atezolizumab (N=302) | Chemotherapy (N=151) | Total (N=453) |
|---|---|---|---|
| Age (years) | | | |
| n (missing) | 302 (0) | 151 (0) | 453 (0) |
| Mean (SD) | 73.6 (9.1) | 73.8 (8.5) | 73.7 (8.9) |
| Median | 75.0 | 75.0 | 75.0 |
| Min, Max | 33, 94 | 37, 89 | 33, 94 |
| Age Category (years), n(%) | | | |
| <65 | 46 ( 15.2) | 19 ( 12.6) | 65 ( 14.3) |
| 65-74 | 100 ( 33.1) | 51 ( 33.8) | 151 ( 33.3) |
| 75-84 | 141 ( 46.7) | 72 ( 47.7) | 213 ( 47.0) |
| >=85 | 15 ( 5.0) | 9 ( 6.0) | 24 ( 5.3) |
| Age Category (years), n(%) | | | |
| <70 | 80 ( 26.5) | 43 ( 28.5) | 123 ( 27.2) |
| >=70 | 222 ( 73.5) | 108 ( 71.5) | 330 ( 72.8) |
| Age Category (years), n(%) | | | |
| <80 | 205 ( 67.9) | 108 ( 71.5) | 313 ( 69.1) |
| >=80 | 97 ( 32.1) | 43 ( 28.5) | 140 ( 30.9) |
| Sex, n(%) | | | |
| Male | 220 ( 72.8) | 108 ( 71.5) | 328 ( 72.4) |
| Female | 82 ( 27.2) | 43 ( 28.5) | 125 ( 27.6) |
| Ethnicity, n(%) | | | |
| Hispanic or Latino | 47 ( 15.6) | 23 ( 15.2) | 70 ( 15.5) |
| Not Hispanic or Latino | 242 ( 80.1) | 125 ( 82.8) | 367 ( 81.0) |
| Not reported | 9 ( 3.0) | 3 ( 2.0) | 12 ( 2.6) |
| Unknown | 4 ( 1.3) | 0 | 4 ( 0.9) |
| Race, n(%) | | | |
| American Indian or Alaska Native | 12 ( 4.0) | 9 ( 6.0) | 21 ( 4.6) |
| Asian | 75 ( 24.8) | 38 ( 25.2) | 113 ( 24.9) |
| Indian subcontinent | 28 ( 9.3) | 10 ( 6.6) | 38 ( 8.4) |
| Other than Indian subcontinent | 47 ( 15.6) | 28 ( 18.5) | 75 ( 16.6) |
| Black or African American | 2 ( 0.7) | 1 ( 0.7) | 3 ( 0.7) |
| White | 203 ( 67.2) | 95 ( 62.9) | 298 ( 65.8) |
| Unknown | 4 ( 1.3) | 2 ( 1.3) | 6 ( 1.3) |
| Multiple | 6 ( 2.0) | 6 ( 4.0) | 12 ( 2.6) |
| Weight[1] (kg) at baseline | | | |
| n (missing) | 302 (0) | 151 (0) | 453 (0) |
| Mean (SD) | 65.72 (15.29) | 66.14 (15.75) | 65.86 (15.43) |
| Median | 65.00 | 65.00 | 65.00 |
| Min, Max | 31.0, 130.7 | 35.0, 128.5 | 31.0, 130.7 |
| ECOG Performance Status[1], n(%) | | | |
| 0 | 7 ( 2.3) | 0 | 7 ( 1.5) |
| 1 | 49 ( 16.2) | 19 ( 12.6) | 68 ( 15.0) |
| 2 | 228 ( 75.5) | 116 ( 76.8) | 344 ( 75.9) |
| 3 | 18 ( 6.0) | 16 ( 10.6) | 34 ( 7.5) |
| ECOG 0/1 and Age ≥ 70, n(%) | 56 ( 18.5) | 19 ( 12.6) | 75 ( 16.6) |
| Smoking Status, n(%) | | | |
| Never | 35 ( 11.6) | 20 ( 13.2) | 55 ( 12.1) |
| Current | 58 ( 19.2) | 28 ( 18.5) | 86 ( 19.0) |
| Previous | 209 ( 69.2) | 103 ( 68.2) | 312 ( 68.9) |

[1] Baseline evaluation is defined as the latest evaluation performed prior to or on the first dosing date (i.e. at visit Day 1).

**Table 13. Summary of Baseline Demographic Characteristics (Platinum-ineligible Population)**

| | Atezolizumab (N=268) | Chemotherapy (N=137) | Total (N=405) |
|---|---|---|---|
| Age (years) | | | |
| n (missing) | 268 (0) | 137 (0) | 405 (0) |
| Mean (SD) | 74.7 (8.0) | 74.4 (7.9) | 74.6 (7.9) |
| Median | 75.5 | 76.0 | 76.0 |
| Min, Max | 47, 94 | 49, 89 | 47, 94 |
| Age Category (years), n(%) | | | |
| <65 | 33 ( 12.3) | 15 ( 10.9) | 48 ( 11.9) |
| 65-74 | 87 ( 32.5) | 44 ( 32.1) | 131 ( 32.3) |
| 75-84 | 133 ( 49.6) | 69 ( 50.4) | 202 ( 49.9) |
| >=85 | 15 ( 5.6) | 9 ( 6.6) | 24 ( 5.9) |
| Age Category (years), n(%) | | | |
| <70 | 62 ( 23.1) | 38 ( 27.7) | 100 ( 24.7) |
| >=70 | 206 ( 76.9) | 99 ( 72.3) | 305 ( 75.3) |
| Age Category (years), n(%) | | | |
| <=80 | 192 ( 71.6) | 104 ( 75.9) | 296 ( 73.1) |
| >80 | 76 ( 28.4) | 33 ( 24.1) | 109 ( 26.9) |
| Sex, n(%) | | | |
| Male | 194 ( 72.4) | 96 ( 70.1) | 290 ( 71.6) |
| Female | 74 ( 27.6) | 41 ( 29.9) | 115 ( 28.4) |
| Ethnicity, n(%) | | | |
| Hispanic or Latino | 39 ( 14.6) | 21 ( 15.3) | 60 ( 14.8) |
| Not Hispanic or Latino | 217 ( 81.0) | 113 ( 82.5) | 330 ( 81.5) |
| Not reported | 8 ( 3.0) | 3 ( 2.2) | 11 ( 2.7) |
| Unknown | 4 ( 1.5) | 0 | 4 ( 1.0) |
| Race, n(%) | | | |
| American Indian or Alaska Native | 10 ( 3.7) | 8 ( 5.8) | 18 ( 4.4) |
| Asian | 52 ( 19.4) | 31 ( 22.6) | 83 ( 20.5) |
| Indian subcontinent | 14 ( 5.2) | 5 ( 3.6) | 19 ( 4.7) |
| Other than Indian subcontinent | 38 ( 14.2) | 26 ( 19.0) | 64 ( 15.8) |
| Black or African American | 2 ( 0.7) | 1 ( 0.7) | 3 ( 0.7) |
| White | 194 ( 72.4) | 91 ( 66.4) | 285 ( 70.4) |
| Unknown | 4 ( 1.5) | 2 ( 1.5) | 6 ( 1.5) |
| Multiple | 6 ( 2.2) | 4 ( 2.9) | 10 ( 2.5) |
| Weight[1] (kg) at baseline | | | |
| n (missing) | 268 (0) | 137 (0) | 405 (0) |
| Mean (SD) | 66.19 (15.79) | 66.60 (15.81) | 66.33 (15.78) |
| Median | 65.00 | 65.00 | 65.00 |
| Min, Max | 31.0, 130.7 | 35.0, 128.5 | 31.0, 130.7 |
| ECOG Performance Status[1], n(%) | | | |
| 0 | 6 ( 2.2) | 0 | 6 ( 1.5) |
| 1 | 49 ( 18.3) | 19 ( 13.9) | 68 ( 16.8) |
| 2 | 195 ( 72.8) | 102 ( 74.5) | 297 ( 73.3) |
| 3 | 18 ( 6.7) | 16 ( 11.7) | 34 ( 8.4) |
| ECOG 0/1 and Age ≥ 70, n(%) | 55 ( 20.5) | 19 ( 13.9) | 74 ( 18.3) |
| Smoking Status, n(%) | | | |
| Never | 30 ( 11.2) | 15 ( 10.9) | 45 ( 11.1) |
| Current | 56 ( 20.9) | 25 ( 18.2) | 81 ( 20.0) |
| Previous | 182 ( 67.9) | 97 ( 70.8) | 279 ( 68.9) |

[1] Baseline evaluation is defined as the latest evaluation performed prior to or on the first dosing date (i.e. at visit Day 1).
Relevant comorbidities defined as the following HLGTs: Cardiac arrhythmias, Coronary artery disorders, Heart failures, Myocardial disorders, Cardiac valve disorders, Arteriosclerosis, stenosis, vascular insufficiency and necrosis,
Vascular hypertensive disorders, Central nervous system vascular disorders, Mental impairment disorders, Neurological disorders NEC, Peripheral neuropathies, Increased intracranial pressure and hydrocephalus, Encephalopathies,
Deliria (incl confusion), Psychiatric disorders NEC, Dementia and amnestic conditions,
Nephropathies, Renal disorders (excl nephropathies), Electrolyte and fluid balance conditions,
Glucose metabolism disorders (incl diabetes mellitus), Appetite and general nutritional disorders,
Bronchial disorders (excl neoplasms), Lower respiratory tract disorders (excl obstruction and infection), Pulmonary vascular disorders.

**Table 14. Summary of Baseline Disease Characteristics (ITT Population)**

| | Atezolizumab (N=302) | Chemotherapy (N=151) | Total (N=453) |
|---|---|---|---|
| Histology[1], n(%) | | | |
| Squamous | 129 ( 42.7) | 64 ( 42.4) | 193 ( 42.6) |
| Non-squamous | 173 ( 57.3) | 87 ( 57.6) | 260 ( 57.4) |
| Adenocarcinoma | 156 ( 90.2) | 81 ( 93.1) | 237 ( 91.2) |
| Adenosquamous | 5 ( 2.9) | 0 | 5 ( 1.9) |
| Sarcomatoid | 2 ( 1.2) | 0 | 2 ( 0.8) |
| Large cell | 1 ( 0.6) | 0 | 1 ( 0.4) |
| Large cell with neuroendocrine differentiation | 0 | 1 ( 1.1) | 1 ( 0.4) |
| Poorly differentiated | 4 ( 2.3) | 1 ( 1.1) | 5 ( 1.9) |
| Mixed (not including small cell) | 1 ( 0.6) | 0 | 1 ( 0.4) |
| NSCLC/NOS | 4 ( 2.3) | 4 ( 4.6) | 8 ( 3.1) |
| Initial Diagnosis Staging, n(%) | | | |
| Stage IA | 12 ( 4.0) | 4 ( 2.6) | 16 ( 3.5) |
| Stage IB | 4 ( 1.3) | 4 ( 2.6) | 8 ( 1.8) |
| Stage IIA | 12 ( 4.0) | 1 ( 0.7) | 13 ( 2.9) |
| Stage IIB | 14 ( 4.6) | 2 ( 1.3) | 16 ( 3.5) |
| Stage IIIA | 13 ( 4.3) | 11 ( 7.3) | 24 ( 5.3) |
| Stage IIIB | 44 ( 14.6) | 26 ( 17.2) | 70 ( 15.5) |
| Stage IV | 187 ( 61.9) | 97 ( 64.2) | 284 ( 62.7) |
| Not Done | 1 ( 0.3) | 0 | 1 ( 0.2) |
| Unknown | 15 ( 5.0) | 6 ( 4.0) | 21 ( 4.6) |
| Current Disease Stage at Enrollment, n(%) | | | |
| Stage IIIB | 41 ( 13.6) | 21 ( 13.9) | 62 ( 13.7) |
| Stage IV | 261 ( 86.4) | 130 ( 86.1) | 391 ( 86.3) |
| Locations of Metastatic Disease at Enrollment[2], n(%) | | | |
| Adrenal gland | 42 ( 13.9) | 16 ( 10.6) | 58 ( 12.8) |
| Bone | 68 ( 22.5) | 23 ( 15.2) | 91 ( 20.1) |
| Brain | 27 ( 8.9) | 13 ( 8.6) | 40 ( 8.8) |
| Liver | 44 ( 14.6) | 26 ( 17.2) | 70 ( 15.5) |
| Lung | 204 ( 67.5) | 102 ( 67.5) | 306 ( 67.5) |
| Lymph node | 175 ( 57.9) | 90 ( 59.6) | 265 ( 58.5) |
| Mediastinum | 29 ( 9.6) | 11 ( 7.3) | 40 ( 8.8) |
| Pleural cavity | 70 ( 23.2) | 30 ( 19.9) | 100 ( 22.1) |
| Pericardial cavity | 16 ( 5.3) | 6 ( 4.0) | 22 ( 4.9) |
| Skin | 1 ( 0.3) | 1 ( 0.7) | 2 ( 0.4) |
| Chest wall | 6 ( 2.0) | 2 ( 1.3) | 8 ( 1.8) |
| Bronchus | 0 | 1 ( 0.7) | 1 ( 0.2) |
| Trachea | 5 ( 1.7) | 1 ( 0.7) | 6 ( 1.3) |
| Abdominal cavity | 6 ( 2.0) | 5 ( 3.3) | 11 ( 2.4) |
| Abdominal wall | 1 ( 0.3) | 0 | 1 ( 0.2) |
| Other | 28 ( 9.3) | 14 ( 9.3) | 42 ( 9.3) |
| Missing | 37 ( 12.3) | 19 ( 12.6) | 56 ( 12.4) |
| Number of Metastatic Sites at Enrollment | | | |
| n (missing) | 265 (37) | 132 (19) | 397 (56) |
| Mean (SD) | 2.7 (1.3) | 2.6 (1.2) | 2.7 (1.3) |
| Median | 3.0 | 2.0 | 3.0 |
| Min, Max | 1, 8 | 1, 7 | 1, 8 |

| | Atezolizumab (N=302) | Chemotherapy (N=151) | Total (N=453) |
|---|---|---|---|
| Time from Initial Diagnosis Date to Initial Dose Administered[3] (months) | | | |
| n (missing) | 293 (9) | 146 (5) | 439 (14) |
| Mean (SD) | 8.24 (15.93) | 10.65 (30.01) | 9.04 (21.65) |
| Median | 2.10 | 1.87 | 2.04 |
| Min, Max | 0.5, 118.2 | 0.5, 189.1 | 0.5, 189.1 |
| Time from Earliest Date of 1st Diag. of Locally Recurrent Disease or Locally Advanced Unresectable Disease or Metastatic Disease to Initial Dose Administered (months) | | | |
| n (missing) | 291 (11) | 145 (6) | 436 (17) |
| Mean (SD) | 4.14 (10.72) | 3.70 (7.95) | 3.99 (9.88) |
| Median | 1.71 | 1.64 | 1.68 |
| Min, Max | 0.1, 114.1 | 0.1, 76.8 | 0.1, 114.1 |
| EGFR Mutation[4], n(%) | | | |
| EGFR mutations other than L858R or exon 19 deletions | 1 ( 0.3) | 1 ( 0.7) | 2 ( 0.4) |
| No mutation | 269 ( 89.1) | 131 ( 86.8) | 400 ( 88.3) |
| Not Done | 32 ( 10.6) | 19 ( 12.6) | 51 ( 11.3) |
| ALK Rearrangement[4], n(%) | | | |
| No | 266 ( 88.1) | 130 ( 86.1) | 396 ( 87.4) |
| Not evaluable | 3 ( 1.0) | 1 ( 0.7) | 4 ( 0.9) |
| Not Done | 33 ( 10.9) | 20 ( 13.2) | 53 ( 11.7) |
| Baseline Target Tumor Sum Longest Diameter (mm) | | | |
| n (missing) | 302 (0) | 151 (0) | 453 (0) |
| Mean (SD) | 91.03 (48.65) | 87.84 (48.17) | 89.97 (48.46) |
| Median | 83.00 | 85.00 | 83.00 |
| Min, Max | 10.0, 317.0 | 13.0, 290.0 | 10.0, 317.0 |
| Baseline Target Tumor Sum Longest Diameter Category, n(%) | | | |
| <Median | 150 ( 49.7) | 73 ( 48.3) | 223 ( 49.2) |
| >=Median | 152 ( 50.3) | 78 ( 51.7) | 230 ( 50.8) |
| Lactate Dehydrogenase, n(%) | | | |
| High | 116 ( 38.4) | 52 ( 34.4) | 168 ( 37.1) |
| Normal | 169 ( 56.0) | 90 ( 59.6) | 259 ( 57.2) |
| Low | 13 ( 4.3) | 7 ( 4.6) | 20 ( 4.4) |
| Missing | 4 ( 1.3) | 2 ( 1.3) | 6 ( 1.3) |

1 Based on eCRF data.
2 A patient can be counted in more than one location (when multiple locations are checked).
3 Time from <diagnosis> to initial dose administered = (First treatment intake − <diagnosis> date + 1)/30.4375.
4 EGFR & ALK testing was not mandated for patients with squamous NSCLC.

**Table 15. Summary of Baseline Disease Characteristics (Platinum-ineligible Population)**

| | Atezolizumab (N=268) | Chemotherapy (N=137) | Total (N=405) |
|---|---|---|---|
| Histology[1], n(%) | | | |
| Squamous | 120 ( 44.8) | 58 ( 42.3) | 178 ( 44.0) |
| Non-squamous | 148 ( 55.2) | 79 ( 57.7) | 227 ( 56.0) |
| Adenocarcinoma | 133 ( 89.9) | 74 ( 93.7) | 207 ( 91.2) |
| Adenosquamous | 5 ( 3.4) | 0 | 5 ( 2.2) |
| Sarcomatoid | 2 ( 1.4) | 0 | 2 ( 0.9) |
| Large cell with neuroendocrine differentiation | 0 | 1 ( 1.3) | 1 ( 0.4) |
| Poorly differentiated | 3 ( 2.0) | 1 ( 1.3) | 4 ( 1.8) |
| Mixed (not including small cell) | 1 ( 0.7) | 0 | 1 ( 0.4) |
| NSCLC/NOS | 4 ( 2.7) | 3 ( 3.8) | 7 ( 3.1) |
| Initial Diagnosis Staging, n(%) | | | |
| Stage IA | 12 ( 4.5) | 3 ( 2.2) | 15 ( 3.7) |
| Stage IB | 4 ( 1.5) | 4 ( 2.9) | 8 ( 2.0) |
| Stage IIA | 12 ( 4.5) | 1 ( 0.7) | 13 ( 3.2) |
| Stage IIB | 14 ( 5.2) | 2 ( 1.5) | 16 ( 4.0) |
| Stage IIIA | 13 ( 4.9) | 11 ( 8.0) | 24 ( 5.9) |
| Stage IIIB | 38 ( 14.2) | 25 ( 18.2) | 63 ( 15.6) |
| Stage IV | 162 ( 60.4) | 86 ( 62.8) | 248 ( 61.2) |
| Not Done | 1 ( 0.4) | 0 | 1 ( 0.2) |
| Unknown | 12 ( 4.5) | 5 ( 3.6) | 17 ( 4.2) |
| Current Disease Stage at Enrollment, n(%) | | | |
| Stage IIIB | 35 ( 13.1) | 20 ( 14.6) | 55 ( 13.6) |
| Stage IV | 233 ( 86.9) | 117 ( 85.4) | 350 ( 86.4) |

| | | | |
|---|---|---|---|
| Locations of Metastatic Disease at Enrollment[2], n(%) | | | |
| Adrenal gland | 36 ( 13.4) | 16 ( 11.7) | 52 ( 12.8) |
| Bone | 61 ( 22.8) | 21 ( 15.3) | 82 ( 20.2) |
| Brain | 18 ( 6.7) | 9 ( 6.6) | 27 ( 6.7) |
| Liver | 36 ( 13.4) | 22 ( 16.1) | 58 ( 14.3) |
| Lung | 180 ( 67.2) | 90 ( 65.7) | 270 ( 66.7) |
| Lymph node | 151 ( 56.3) | 80 ( 58.4) | 231 ( 57.0) |
| Mediastinum | 26 ( 9.7) | 9 ( 6.6) | 35 ( 8.6) |
| Pleural cavity | 66 ( 24.6) | 27 ( 19.7) | 93 ( 23.0) |
| Pericardial cavity | 14 ( 5.2) | 6 ( 4.4) | 20 ( 4.9) |
| Skin | 1 ( 0.4) | 1 ( 0.7) | 2 ( 0.5) |
| Chest wall | 6 ( 2.2) | 2 ( 1.5) | 8 ( 2.0) |
| Bronchus | 0 | 1 ( 0.7) | 1 ( 0.2) |
| Trachea | 4 ( 1.5) | 1 ( 0.7) | 5 ( 1.2) |
| Abdominal cavity | 6 ( 2.2) | 4 ( 2.9) | 10 ( 2.5) |
| Abdominal wall | 1 ( 0.4) | 0 | 1 ( 0.2) |
| Other | 23 ( 8.6) | 12 ( 8.8) | 35 ( 8.6) |
| Missing | 32 ( 11.9) | 18 ( 13.1) | 50 ( 12.3) |
| Number of Metastatic Sites at Enrollment | | | |
| n (missing) | 236 (32) | 119 (18) | 355 (50) |
| Mean (SD) | 2.7 (1.3) | 2.5 (1.2) | 2.6 (1.3) |
| Median | 3.0 | 2.0 | 2.0 |
| Min, Max | 1, 8 | 1, 7 | 1, 8 |
| Time from Initial Diagnosis Date to Initial Dose Administered[3] (months) | | | |
| n (missing) | 259 (9) | 134 (3) | 393 (12) |
| Mean (SD) | 8.94 (16.74) | 11.37 (31.23) | 9.77 (22.73) |
| Median | 2.10 | 1.84 | 2.04 |
| Min, Max | 0.5, 118.2 | 0.5, 189.1 | 0.5, 189.1 |

| | Atezolizumab (N=268) | Chemotherapy (N=137) | Total (N=405) |
|---|---|---|---|
| Time from Earliest Date of 1st Diag. of Locally Recurrent Disease or Locally Advanced Unresectable Disease or Metastatic Disease to Initial Dose Administered (months) | | | |
| n (missing) | 257 (11) | 132 (5) | 389 (16) |
| Mean (SD) | 4.34 (11.29) | 3.67 (8.05) | 4.11 (10.30) |
| Median | 1.71 | 1.61 | 1.68 |
| Min, Max | 0.1, 114.1 | 0.1, 76.8 | 0.1, 114.1 |
| EGFR Mutation[4], n(%) | | | |
| EGFR mutations other than L858R or exon 19 deletions | 1 ( 0.4) | 1 ( 0.7) | 2 ( 0.5) |
| No mutation | 239 ( 89.2) | 118 ( 86.1) | 357 ( 88.1) |
| Not Done | 28 ( 10.4) | 18 ( 13.1) | 46 ( 11.4) |
| ALK Rearrangement[4], n(%) | | | |
| No | 236 ( 88.1) | 117 ( 85.4) | 353 ( 87.2) |
| Not evaluable | 3 ( 1.1) | 1 ( 0.7) | 4 ( 1.0) |
| Not Done | 29 ( 10.8) | 19 ( 13.9) | 48 ( 11.9) |
| Baseline Target Tumor Sum Longest Diameter (mm) | | | |
| n (missing) | 268 (0) | 137 (0) | 405 (0) |
| Mean (SD) | 88.67 (47.60) | 85.57 (47.82) | 87.62 (47.64) |
| Median | 80.50 | 80.00 | 80.00 |
| Min, Max | 10.0, 317.0 | 13.0, 290.0 | 10.0, 317.0 |
| Baseline Target Tumor Sum Longest Diameter Category, n(%) | | | |
| <Median | 137 ( 51.1) | 70 ( 51.1) | 207 ( 51.1) |
| >=Median | 131 ( 48.9) | 67 ( 48.9) | 198 ( 48.9) |
| Lactate Dehydrogenase, n(%) | | | |
| High | 95 ( 35.4) | 40 ( 29.2) | 135 ( 33.3) |
| Normal | 157 ( 58.6) | 88 ( 64.2) | 245 ( 60.5) |
| Low | 13 ( 4.9) | 7 ( 5.1) | 20 ( 4.9) |
| Missing | 3 ( 1.1) | 2 ( 1.5) | 5 ( 1.2) |
| Baseline Creatinine Clearance, n(%) | | | |
| <45 mL/min | 37 ( 13.8) | 21 ( 15.3) | 58 ( 14.3) |
| >=45 mL/min | 231 ( 86.2) | 116 ( 84.7) | 347 ( 85.7) |

[1] Based on eCRF data.
[2] A patient can be counted in more than one location (when multiple locations are checked).
[3] Time from <diagnosis> to initial dose administered = (First treatment intake – <diagnosis> date + 1)/30.4375.
[4] EGFR & ALK testing was not mandated for patients with squamous NSCLC.

**Table 16. Baseline PD-L1 Expression Status (SP142, SP263) (ITT Population)**

| | Atezolizumab (N=302) | Chemotherapy (N=151) | Total (N=453) |
|---|---|---|---|
| PD-L1 IHC Status by SP142 Assay, n(%) | | | |
| TC3 or IC3 | 18 ( 6.0) | 10 ( 6.6) | 28 ( 6.2) |
| TC0/1/2 and IC0/1/2 | 269 ( 89.1) | 135 ( 89.4) | 404 ( 89.2) |
| (TC1/2 and IC0/1/2) or (TC0 and IC1/2) | 112 ( 37.1) | 56 ( 37.1) | 168 ( 37.1) |
| TC1/2/3 or IC1/2/3 | 130 ( 43.0) | 66 ( 43.7) | 196 ( 43.3) |
| TC0 and IC0 | 157 ( 52.0) | 79 ( 52.3) | 236 ( 52.1) |
| Unknown | 15 ( 5.0) | 6 ( 4.0) | 21 ( 4.6) |
| PD-L1 IHC Status by SP263 Assay, n(%) | | | |
| TC >= 50% | 50 ( 16.6) | 25 ( 16.6) | 75 ( 16.6) |
| TC < 50% | 228 ( 75.5) | 114 ( 75.5) | 342 ( 75.5) |
| TC 1-49% | 77 ( 25.5) | 53 ( 35.1) | 130 ( 28.7) |
| TC >= 1% | 127 ( 42.1) | 78 ( 51.7) | 205 ( 45.3) |
| TC < 1% | 151 ( 50.0) | 61 ( 40.4) | 212 ( 46.8) |
| Unknown | 24 ( 7.9) | 12 ( 7.9) | 36 ( 7.9) |

**Table 17. Baseline PD-L1 Expression Status (SP142, SP263) (Platinum-ineligible Population)**

| | Atezolizumab (N=268) | Chemotherapy (N=137) | Total (N=405) |
|---|---|---|---|
| PD-L1 IHC Status by SP142 Assay, n(%) | | | |
| TC3 or IC3 | 14 ( 5.2) | 10 ( 7.3) | 24 ( 5.9) |
| TC0/1/2 and IC0/1/2 | 243 ( 90.7) | 121 ( 88.3) | 364 ( 89.9) |
| (TC1/2 and IC0/1/2) or (TC0 and IC1/2) | 102 ( 38.1) | 50 ( 36.5) | 152 ( 37.5) |
| TC1/2/3 or IC1/2/3 | 116 ( 43.3) | 60 ( 43.8) | 176 ( 43.5) |
| TC0 and IC0 | 141 ( 52.6) | 71 ( 51.8) | 212 ( 52.3) |
| Unknown | 11 ( 4.1) | 6 ( 4.4) | 17 ( 4.2) |
| PD-L1 IHC Status by SP263 Assay, n(%) | | | |
| TC >= 50% | 39 ( 14.6) | 22 ( 16.1) | 61 ( 15.1) |
| TC < 50% | 211 ( 78.7) | 103 ( 75.2) | 314 ( 77.5) |
| TC 1-49% | 73 ( 27.2) | 48 ( 35.0) | 121 ( 29.9) |
| TC >= 1% | 112 ( 41.8) | 70 ( 51.1) | 182 ( 44.9) |
| TC < 1% | 138 ( 51.5) | 55 ( 40.1) | 193 ( 47.7) |
| Unknown | 18 ( 6.7) | 12 ( 8.8) | 30 ( 7.4) |

Relevant comorbidities defined as the following HLGTs: Cardiac arrhythmias, Coronary artery disorders, Heart failures, Myocardial disorders, Cardiac valve disorders, Arteriosclerosis, stenosis, vascular insufficiency and necrosis,
Vascular hypertensive disorders, Central nervous system vascular disorders, Mental impairment disorders, Neurological disorders NEC, Peripheral neuropathies, Increased intracranial pressure and hydrocephalus, Encephalopathies,
Deliria (incl confusion), Psychiatric disorders NEC, Dementia and amnestic conditions,
Nephropathies, Renal disorders (excl nephropathies), Electrolyte and fluid balance conditions,
Glucose metabolism disorders (incl diabetes mellitus), Appetite and general nutritional disorders,
Bronchial disorders (excl neoplasms), Lower respiratory tract disorders (excl obstruction and infection), Pulmonary vascular disorders.

## Numbers analysed

**Intent-to-treat (ITT) Population:** all randomised patients irrespective of whether the assigned treatment was actually received. For analyses on ITT, patients will be grouped according to the treatment assigned at randomisation. The ITT population will be the population for the analysis of efficacy parameters. The ITT patient population comprised 453 patients; 302 patients randomised to the atezolizumab arm and 151 patients randomised to the chemotherapy arm.

The **platinum-ineligible population** (see clarification and definition above, at the beginning of baseline characteristics): A total of 405 patients corresponding to 89% of the ITT population, and of these, 268 patients were randomised to the atezolizumab arm and 137 patients were randomised to the chemotherapy arm.

**Safety-Evaluable Population:** all randomised patients who received any amount of study treatment. For analyses on Safety-Evaluable Population, patients will be grouped according to whether any amount

of atezolizumab was received, including the case when atezolizumab was received in error. The Safety-Evaluable Population will be the population for the analysis of safety parameters.

The **safety-evaluable population** included 447 (98.7%) patients who either received at least one dose of atezolizumab (300 patients) or at least one dose of chemotherapy (vinorelbine or gemcitabine) (147 patients).

The study data cut off (CCOD) 30 April 2022.

## Outcomes and estimation

Clarification: Since analyses from the platinum-ineligible population were performed ad hoc, they are presented in the subsequent section (see 'Ancillary analyses').

**Table 18. Overview of Efficacy (ITT Population)**

| | Atezolizumab N = 302 | Chemotherapy N = 151 |
|---|---|---|
| **Primary Efficacy Endpoint** | | |
| **Overall Survival** | | |
| No (%) of events | 249 (82.5%) | 130 (86.1%) |
| Median (95% CI) [a], months | 10.3 (9.4, 11.9) | 9.2 (5.9, 11.2) |
| Stratified HR (95% CI) [b] | 0.78 (0.63, 0.97) | |
| p-value (Stratified Log-rank) | p=0.028 | |
| **Key Secondary Efficacy Endpoints** | | |
| **Landmark Overall Survival Rates, % (95% CI [c])** | | |
| 6 months | 64.0 (58.6, 69.5) | 57.5 (49.4, 65.7) |
| 12 months | 43.7 (37.9, 49.4) | 38.6 (30.5, 46.7) |
| 18 months | 31.4 (26.0, 36.8) | 24.0 (16.8, 31.2) |
| 24 months | 24.3 (19.3, 29.4) | 12.4 (6.7, 18.0) |
| **INV-assessed Progression-Free Survival** | | |
| No (%) of events | 276 (91.4%) | 138 (91.4%) |
| Median (95% CI) [a], months | 4.2 (3.7, 5.5) | 4.0 (2.9, 5.4) |
| Stratified HR (95% CI) [b] | 0.87 (0.70, 1.07) | |
| **Objective Response Rate (confirmed)** | | |
| ORR, n (%) | 51 (16.9%) | 12 (7.9%) |
| Difference in ORR (95% CI) [d] | 8.9% (2.4, 15.5) | |
| **Duration of Response (confirmed)** | | |
| No (%) of events [e] | 40 (78.4%) | 12 (100.0%) |
| Median (95% CI) [a], months | 14.0 (8.1, 20.3) | 7.8 (4.8, 9.7) |

CI = confidence interval; HR = hazard ratio; ORR = objective response rate
a 95% CI computed using the Brookmeyer Crowley method.
b Estimated hazard ratio and 95% CI obtained from Cox model with treatment group as covariate. Stratification factors include histologic subtype, PD-L1 IHC status and brain metastases (Yes/No) (per IxRS data).
c 95% CI computed using linear transformation based on standard errors computed using Greenwood's formula.
d 95% CI of the difference in ORR (atezolizumab – chemotherapy) computed using normal approximation to the binomial distribution.
e Percentages calculated based on number of patients with best overall response of confirmed CR or PR.

**Primary endpoint (OS)**

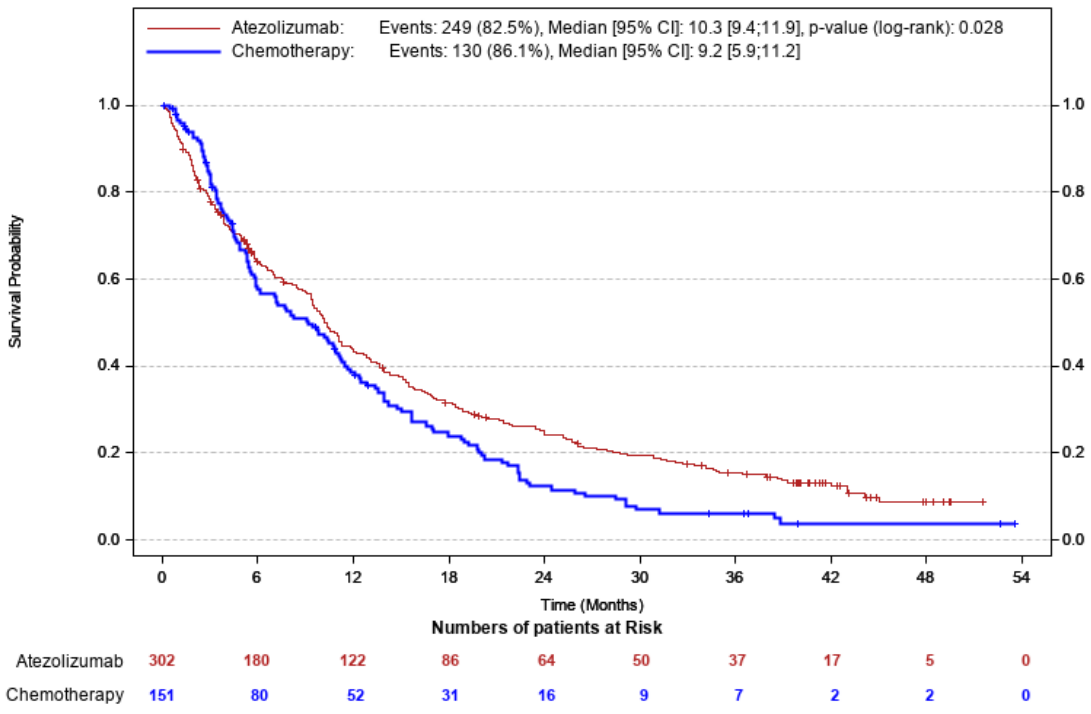
The primary efficacy endpoint of IPSOS was met as the pre-specified final OS analysis alpha boundary (two sided α=0.04295) was crossed in the ITT population.

**Table 19. Overall Survival (ITT Population)**

| | Atezolizumab (N=302) | Chemotherapy (N=151) |
|---|---|---|
| Kaplan-Meier Estimates of Overall Survival (OS) (months) | | |
| Events, n(%) | 249 (82.5%) | 130 (86.1%) |
| Censored, n(%) | 53 (17.5%) | 21 (13.9%) |
| 25th Pctl. (95% CI[1]) | 3.6 (2.8, 5.0) | 3.9 (3.1, 4.9) |
| Median (95% CI[1]) | 10.3 (9.4, 11.9) | 9.2 (5.9, 11.2) |
| 75th Pctl. (95% CI[1]) | 24.0 (18.6, 28.3) | 17.0 (13.9, 21.3) |
| Min, Max | 0.1, 51.5 | 0.1, 53.5 |
| Stratified Analysis | | |
| Hazard ratio (Atezolizumab vs. Chemotherapy)[2] | 0.78 | |
| 95% CI[2] | (0.63, 0.97) | |
| P-value (log-rank) | 0.028 | |
| Unstratified Analysis | | |
| Hazard ratio (Atezolizumab vs. Chemotherapy)[2] | 0.79 | |
| 95% CI[2] | (0.64, 0.97) | |
| P-value (log-rank) | 0.028 | |

1 95% Confidence Interval (CI) computed using the Brookmeyer and Crowley method.
2 Estimated hazard ratio and 95% Confidence Interval (CI) obtained from Cox model with treatment group as covariate.
For the stratified analysis, histologic subtype, PD-L1 IHC status and brain metastases (Yes/No) were added as stratification factors (per IxRS data).

**Table 20. Kaplan-Meier Plot of Overall Survival (ITT Population)**




+ Censored
P-value obtained from a stratified log-rank test. Stratification factors (per IxRS data) are: histologic subtype, PD-L1 IHC status and brain metastases.

## Secondary endpoints

### 1) Landmark Overall Survival Rates at 6, 12, 18 and 24 Months (ITT Population)

**Table 21. Overall Survival Rates at the 6, 12, 18 and 24-Month Timepoints (ITT Population)**

| Timepoint | | | Atezolizumab (N=302) | Chemotherapy (N=151) |
|---|---|---|---|---|
| 6 Months | Number of Patients Still at Risk | n | 180 | 80 |
| | Kaplan-Meier Overall Survival (OS) Rate | (%) | 64.0 | 57.5 |
| | | (95% CI[1]) | (58.6, 69.5) | (49.4, 65.7) |
| | Difference in OS Rates (Atezolizumab - Chemotherapy) | (%) | 6.5 | |
| | | (95% CI[2]) | (-3.3, 16.3) | |
| 12 Months | Number of Patients Still at Risk | n | 122 | 52 |
| | Kaplan-Meier Overall Survival (OS) Rate | (%) | 43.7 | 38.6 |
| | | (95% CI[1]) | (37.9, 49.4) | (30.5, 46.7) |
| | Difference in OS Rates (Atezolizumab - Chemotherapy) | (%) | 5.1 | |
| | | (95% CI[2]) | (-4.9, 15.0) | |
| 18 Months | Number of Patients Still at Risk | n | 86 | 31 |
| | Kaplan-Meier Overall Survival (OS) Rate | (%) | 31.4 | 24.0 |
| | | (95% CI[1]) | (26.0, 36.8) | (16.8, 31.2) |
| | Difference in OS Rates (Atezolizumab - Chemotherapy) | (%) | 7.4 | |
| | | (95% CI[2]) | (-1.6, 16.5) | |
| 24 Months | Number of Patients Still at Risk | n | 64 | 16 |
| | Kaplan-Meier Overall Survival (OS) Rate | (%) | 24.3 | 12.4 |
| | | (95% CI[1]) | (19.3, 29.4) | (6.7, 18.0) |
| | Difference in OS Rates (Atezolizumab - Chemotherapy) | (%) | 11.9 | |
| | | (95% CI[2]) | (4.4, 19.5) | |

[1] 95% confidence interval (CI) computed using linear transformation based on standard errors computed using the Greenwood's formula.
[2] 95% confidence interval (CI) for the difference in OS rates estimated using a normal approximation method.

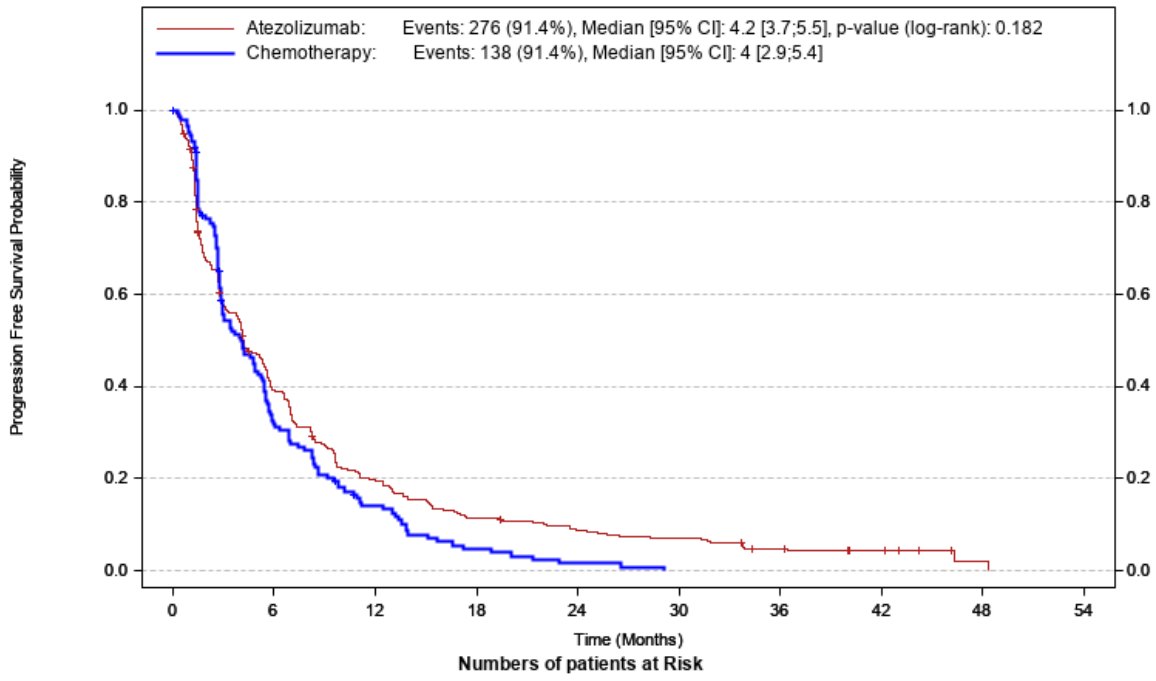
**2) Investigator-Assessed Progression-Free Survival (PFS)**

**Table 22. Investigator-Assessed PFS per RECIST v1.1 (ITT Population)**

| | Atezolizumab (N=302) | Chemotherapy (N=151) |
|---|---|---|
| Kaplan-Meier Estimates of Progression Free Survival (PFS) (months) | | |
| Events, n(%) | 276 (91.4%) | 138 (91.4%) |
| Earliest contributing event | | |
| Death | 89 | 48 |
| Disease Progression | 187 | 90 |
| Censored, n(%) | 26 (8.6%) | 13 (8.6%) |
| 25th Pctl. (95% CI[1]) | 1.4 (1.4, 1.7) | 2.4 (1.5, 2.6) |
| Median (95% CI[1]) | 4.2 (3.7, 5.5) | 4.0 (2.9, 5.4) |
| 75th Pctl. (95% CI[1]) | 9.6 (8.2, 11.1) | 8.3 (5.9, 9.8) |
| Min, Max | 0.0, 48.3 | 0.0, 29.1 |
| Stratified Analysis | | |
| Hazard ratio (Atezolizumab vs. Chemotherapy)[2] | 0.87 | |
| 95% CI[2] | (0.70, 1.07) | |
| P-value (log-rank) | 0.182 | |
| Unstratified Analysis | | |
| Hazard ratio (Atezolizumab vs. Chemotherapy)[2] | 0.83 | |
| 95% CI[2] | (0.67, 1.02) | |
| P-value (log-rank) | 0.080 | |

[1] 95% Confidence Interval (CI) computed using the Brookmeyer and Crowley method.
[2] Estimated hazard ratio and 95% Confidence Interval (CI) obtained from Cox model with treatment group as covariate.
For the stratified analysis, histologic subtype, PD-L1 IHC status and brain metastases (Yes/No) were added as stratification factors (per IxRS data).

**Figure 7. Kaplan-Meier Plot of Investigator-Assessed PFS per RECIST v1.1 (ITT Population)**




+ Censored

P-value obtained from a stratified log-rank test. Stratification factors (per IxRS data) are: histologic subtype, PD-L1 IHC status and brain metastases.

**3) Best Overall response**

**Table 23. Confirmed Best Overall Response per RECIST v1.1 – Investigator (ITT Population)**

| | Atezolizumab (N=302) | Chemotherapy (N=151) |
|---|---|---|
| Best Overall Response (BOR), n(%) | | |
| Complete Response (CR) | 4 (1.3) | 0 (0.0) |
| 95% CI[1] | (0.4, 3.4) | (NE, NE) |
| Partial Response (PR) | 47 (15.6) | 12 (7.9) |
| 95% CI[1] | (11.7, 20.2) | (4.2, 13.5) |
| Stable Disease (SD) | 122 (40.4) | 73 (48.3) |
| 95% CI[1] | (34.8, 46.2) | (40.1, 56.6) |
| Progressive Disease (PD) | 67 (22.2) | 36 (23.8) |
| 95% CI[1] | (17.6, 27.3) | (17.3, 31.4) |
| Non-Evaluable (NE) | 14 (4.6) | 12 (7.9) |
| 95% CI[1] | (2.6, 7.7) | (4.2, 13.5) |
| Missing | 48 (15.9) | 18 (11.9) |
| 95% CI[1] | (12.0, 20.5) | (7.2, 18.2) |
| Objective Response Rate (ORR) | | |
| n(%) | 51 (16.9) | 12 (7.9) |
| 95% CI[1] | (12.8, 21.6) | (4.2, 13.5) |
| Difference in ORR (Atezolizumab - Chemotherapy) | | |
| % | 8.9 | |
| 95% CI[2] | (2.4, 15.5) | |
| P-value[3] | 0.010 | |

[1] 95% confidence interval (CI) computed using the Clopper-Pearson method.
[2] 95% confidence interval (CI) of the difference in ORR (Atezolizumab - Chemotherapy) computed using normal approximation to the binomial distribution.
[3] P-value (two-sided) obtained from Chi-square test.

**4) Duration of response**

**Table 24. Summary of Duration of Response (ITT Patients with Confirmed Response per RECIST v1.1)**

| | Atezolizumab (N=302) | Chemotherapy (N=151) |
|---|---|---|
| Patients with Best Overall Response (BOR) of CR or PR, n(%) | 51 (16.9) | 12 (7.9) |
| Kaplan-Meier Estimates of Duration of Response (months) | | |
| Events, n(%)[1] | 40 (78.4%) | 12 (100.0%) |
| Earliest contributing event | | |
| Death | 8 | 3 |
| Disease Progression | 32 | 9 |
| Censored, n(%)[1] | 11 (21.6%) | 0 (0.0%) |
| 25th Pctl. (95% CI[2]) | 5.5 (4.2, 10.2) | 4.2 (2.9, 8.2) |
| Median (95% CI[1]) | 14.0 (8.1, 20.3) | 7.8 (4.8, 9.7) |
| 75th Pctl. (95% CI[2]) | 33.8 (18.7, 43.3) | 10.6 (7.4, 12.7) |
| Min, Max | 1.4, 44.7 | 2.2, 15.7 |
| Stratified Analysis | | |
| Hazard ratio (Atezolizumab vs. Chemotherapy)[3] | 0.40 | |
| 95% CI[3] | (0.19, 0.85) | |
| P-value (log-rank) | 0.014 | |
| Unstratified Analysis | | |
| Hazard ratio (Atezolizumab vs. Chemotherapy)[3] | 0.36 | |
| 95% CI[3] | (0.18, 0.72) | |
| P-value (log-rank) | 0.003 | |

Note: Duration of response is defined only for patients with a best overall response (BOR) of Complete Response (CR) or Partial Response (PR).
[1] Percentages are calculated based on number of patients with BOR of CR or PR.
[2] 95% Confidence Interval (CI) computed using the Brookmeyer and Crowley method.
[3] Estimated hazard ratio and 95% Confidence Interval (CI) obtained from Cox model with treatment group as covariate.
For the stratified analysis, histologic subtype, PD-L1 IHC status and brain metastases (Yes/No) were added as stratification factors (per IxRS data).

## Ancillary analyses

**Sensitivity Analyses on Overall Survival (ITT Population)**

Sensitivity analyses to confirm the robustness of the primary OS analysis were performed including:

- Unstratified log-rank analysis
- Sensitivity analysis to account for the risk of over-stratification
- Sensitivity analysis to account for potential mis-stratification
- Sensitivity analysis to account for non-proportionality
- Sensitivity analysis to assess the impact of non-protocol anti-cancer immunotherapy (NPT)

**Table 25. Sensitivity Analyses on Overall Survival (ITT Population)**

| | Atezolizumab N=302 | Chemotherapy N=151 |
|---|---|---|
| **Primary analysis** | | |
| Median (95% CI) [a], months | 10.3 (9.4, 11.9) | 9.2 (5.9, 11.2) |
| Stratified HR (95% CI) [b,c] | 0.78 (0.63, 0.97) | |
| **Sensitivity Analyses** | | |
| **Unstratified analysis** | | |
| Median (95% CI) [a], months | 10.3 (9.4, 11.9) | 9.2 (5.9, 11.2) |
| Unstratified HR (95% CI) | 0.79 (0.64, 0.97) | |
| **Over-stratification** | | |
| Median (95% CI) [a], months | 10.3 (9.4, 11.9) | 9.2 (5.9, 11.2) |
| Stratified HR (95% CI) [b,d] | 0.79 (0.63, 0.97) | |
| **Mis-stratification** | | |
| Median (95% CI) [a], months | 10.3 (9.4, 11.9) | 9.2 (5.9, 11.2) |
| Stratified HR (95% CI) [b,e] | 0.79 (0.63, 0.98) | |
| **Impact of Non-Protocol-Specified Anti-Cancer Immunotherapy** | | |
| **Rank Preserving Structural Failure Time (RPSFT) Model** | | |
| Median (95% CI) [a], months | 10.3 (9.4, 11.9) | 9.1 (5.9, 10.8) |
| RPSFT HR [b] (95% CI) [f] | 0.74 (0.57, 0.97) | |
| **Impact of Non-proportionality Assumption** | | |
| **Non-Proportional Hazard - Restricted Mean Survival Time** | | |
| Estimate (95% CI), months | 16.1 (14.2, 17.9) | 12.5 (10.5, 14.4) |
| Difference (95% CI) | 3.6 (0.9, 6.3) | |

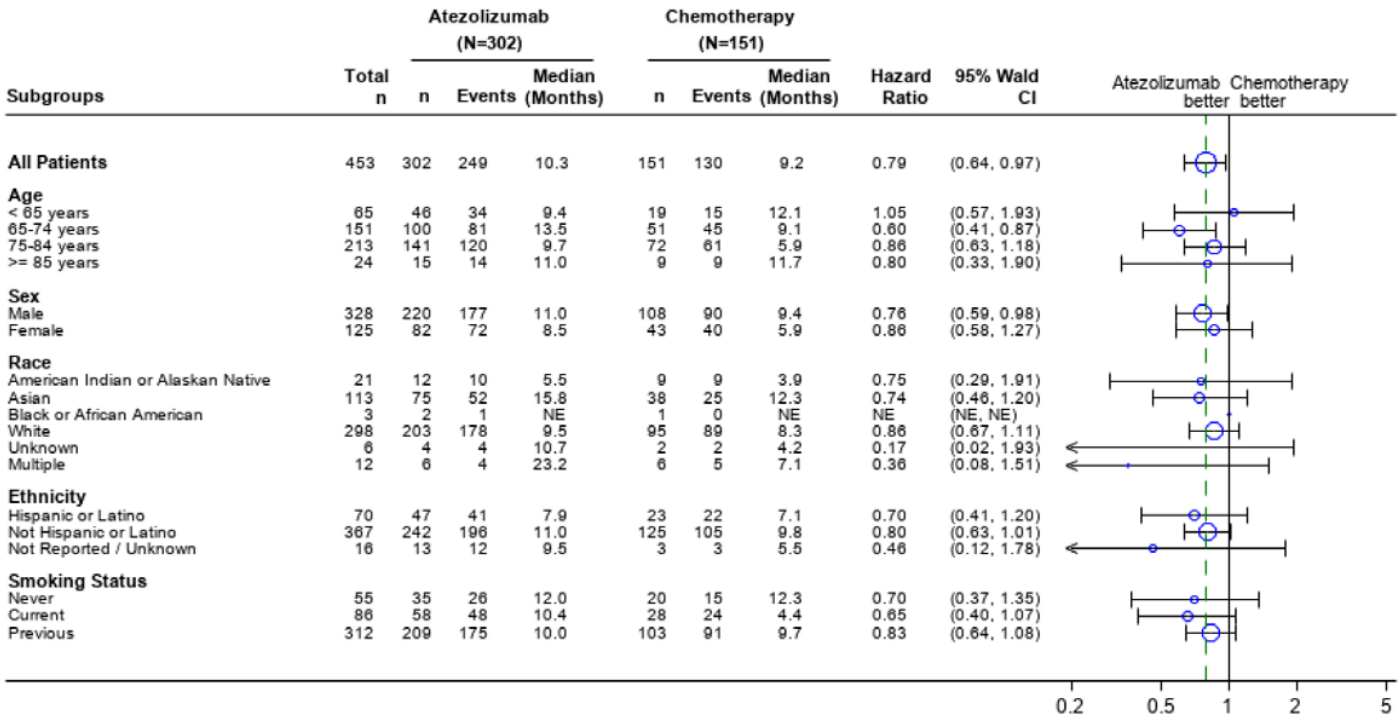
CI = confidence interval; HR = hazard ratio; ITT = intent to treat
a 95% CI computed using the Brookmeyer Crowley method
b Estimated hazard ratio and 95% CI obtained from Cox model with treatment group as covariate.
c Stratification factors included histologic subtype, PD-L1 IHC status and brain metastases (Yes/No) (per IxRS data).
d Histologic subtype was added as stratification factor (per IxRS data).
e Stratification factors included histologic subtype, PD-L1 IHC status and brain metastases (Yes/No) (per eCRF/Lab data)
f 95% CI calculated using inflation of standard error based on ITT test.

**Subgroup analyses OS (ITT Population)**

The consistency of OS results was investigated by estimating the treatment effect in predefined subgroups based on key demographics and baseline prognostic characteristics.

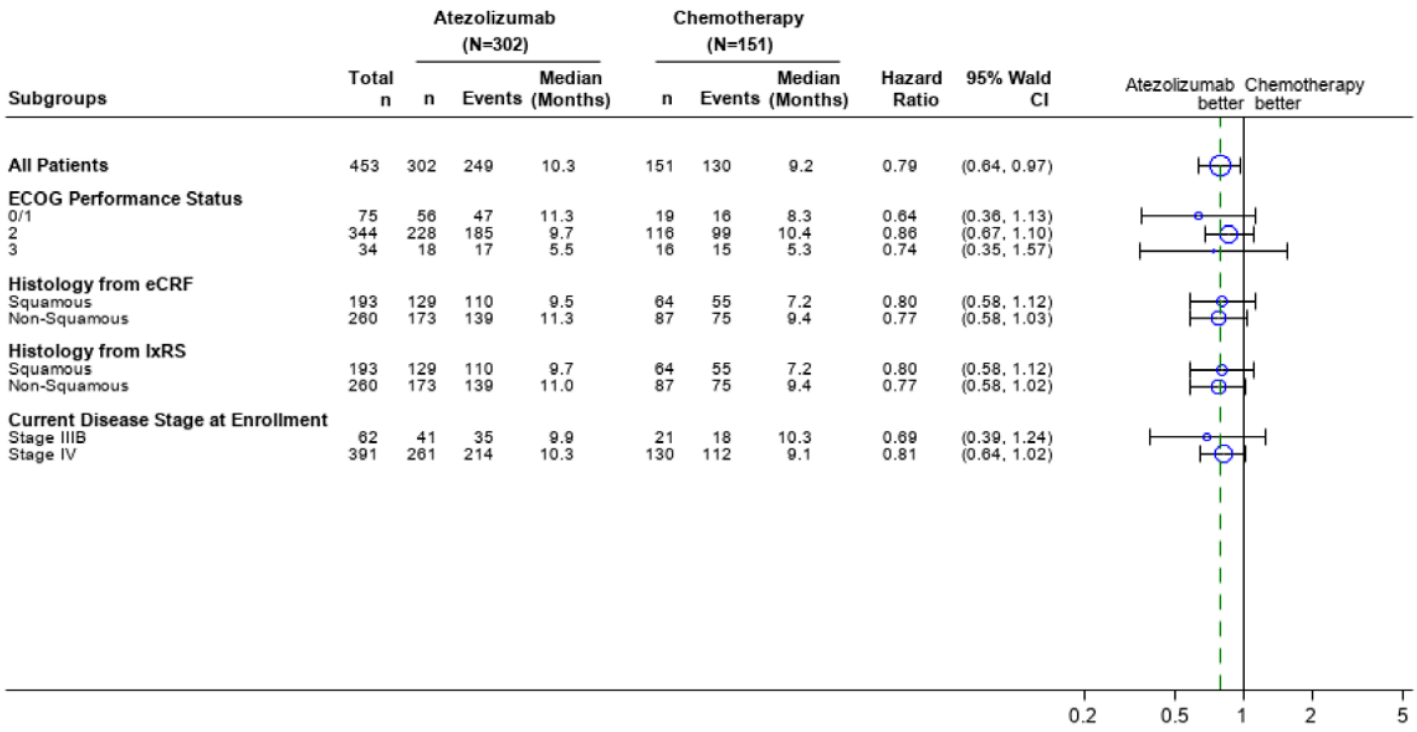
It is important to note that the study was not powered to detect differences in the individual subgroups and that in some subgroups, the small sample size and the wide 95% CIs hampers the ability to draw solid conclusions about the consistency of the treatment effect.

**Figure 8. Forest Plot - Subgroup Analysis of Overall Survival by Baseline Demographic Characteristics (ITT Population)**



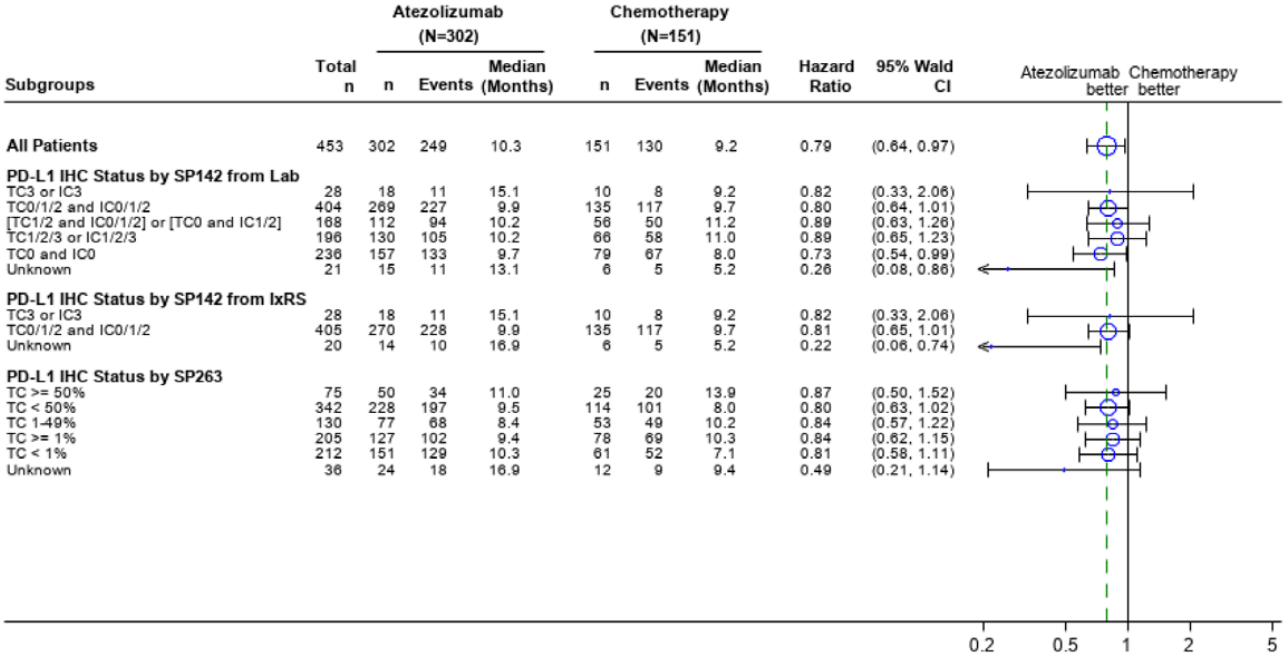

NE = Not estimable; Median Survival was estimated from Kaplan-Meier method. Unstratified hazard ratio relative to Chemotherapy and 95% CI for the hazard ratio were estimated using Cox regression. The vertical dashed line indicates the hazard ratio for all patients. The diameter of the circle is proportional to the square root of the total number of events. Randomized treatments are displayed.

**Figure 9. Forest Plot - Subgroup Analysis of Overall Survival by Baseline Disease Characteristics (ITT Population)**




NE = Not estimable; Median Survival was estimated from Kaplan-Meier method. Unstratified hazard ratio relative to Chemotherapy and 95% CI for the hazard ratio were estimated using Cox regression. The vertical dashed line indicates the hazard ratio for all patients. The diameter of the circle is proportional to the square root of the total number of events. Randomized treatments are displayed.

**Figure 10. Forest Plot - Subgroup Analysis of Overall Survival by PD-L1 Status (ITT Population)**




NE = Not estimable; Median Survival was estimated from Kaplan-Meier method. Unstratified hazard ratio relative to Chemotherapy and 95% CI for the hazard ratio were estimated using Cox regression. The vertical dashed line indicates the hazard ratio for all patients. The diameter of the circle is proportional to the square root of the total number of events. Randomized treatments are displayed.

## Subsequent treatment

**Table 26. Subsequent Non-Protocol Anti-Cancer Therapies (ITT Population)**

| Type of Therapy<br>Medication | Atezolizumab (N=302)<br>n (%) | Chemotherapy (N=151)<br>n (%) | Total (N=453)<br>n (%) |
|---|---|---|---|
| Number of Patients with Any Subsequent Anti-Cancer Therapy | 61 ( 20.2) | 45 ( 29.8) | 106 ( 23.4) |
| Overall Total Number of Medications | 95 | 62 | 157 |
| Chemotherapy | 48 ( 15.9) | 16 ( 10.6) | 64 ( 14.1) |
| CARBOPLATIN | 16 ( 5.3) | 7 ( 4.6) | 23 ( 5.1) |
| PEMETREXED | 15 ( 5.0) | 4 ( 2.6) | 19 ( 4.2) |
| GEMCITABINE | 16 ( 5.3) | 2 ( 1.3) | 18 ( 4.0) |
| DOCETAXEL | 5 ( 1.7) | 3 ( 2.0) | 8 ( 1.8) |
| VINORELBINE | 7 ( 2.3) | 1 ( 0.7) | 8 ( 1.8) |
| PACLITAXEL | 5 ( 1.7) | 2 ( 1.3) | 7 ( 1.5) |
| VINORELBINE TARTRATE | 4 ( 1.3) | 3 ( 2.0) | 7 ( 1.5) |
| CISPLATIN | 3 ( 1.0) | 0 ( 0.0) | 3 ( 0.7) |
| ETOPOSIDE | 2 ( 0.7) | 0 ( 0.0) | 2 ( 0.4) |
| PEMETREXED DISODIUM | 1 ( 0.3) | 1 ( 0.7) | 2 ( 0.4) |
| GEMCITABINE HYDROCHLORIDE | 1 ( 0.3) | 0 ( 0.0) | 1 ( 0.2) |
| LOBAPLATIN | 0 ( 0.0) | 1 ( 0.7) | 1 ( 0.2) |
| Cancer Immunotherapy | 4 ( 1.3) | 28 ( 18.5) | 32 ( 7.1) |
| NIVOLUMAB | 1 ( 0.3) | 13 ( 8.6) | 14 ( 3.1) |
| ATEZOLIZUMAB | 1 ( 0.3) | 9 ( 6.0) | 10 ( 2.2) |
| PEMBROLIZUMAB | 0 ( 0.0) | 5 ( 3.3) | 5 ( 1.1) |
| TO B2450 | 1 ( 0.3) | 1 ( 0.7) | 2 ( 0.4) |

| | | | |
|---|---|---|---|
| CAMRELIZUMAB | 1 ( 0.3) | 0 ( 0.0) | 1 ( 0.2) |
| TKI | 10 ( 3.3) | 5 ( 3.3) | 15 ( 3.3) |
| CATEQUENTINIB | 3 ( 1.0) | 1 ( 0.7) | 4 ( 0.9) |
| ERLOTINIB | 2 ( 0.7) | 1 ( 0.7) | 3 ( 0.7) |
| AFATINIB | 2 ( 0.7) | 0 ( 0.0) | 2 ( 0.4) |
| CATEQUENTINIB HYDROCHLORIDE | 1 ( 0.3) | 1 ( 0.7) | 2 ( 0.4) |
| AL 2846 | 1 ( 0.3) | 0 ( 0.0) | 1 ( 0.2) |
| CRIZOTINIB | 1 ( 0.3) | 0 ( 0.0) | 1 ( 0.2) |
| DABRAFENIB | 0 ( 0.0) | 1 ( 0.7) | 1 ( 0.2) |
| ERLOTINIB HYDROCHLORIDE | 0 ( 0.0) | 1 ( 0.7) | 1 ( 0.2) |
| GEFITINIB | 1 ( 0.3) | 0 ( 0.0) | 1 ( 0.2) |
| TRAMETINIB | 0 ( 0.0) | 1 ( 0.7) | 1 ( 0.2) |
| Other | 3 ( 1.0) | 1 ( 0.7) | 4 ( 0.9) |
| UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE | 1 ( 0.3) | 1 ( 0.7) | 2 ( 0.4) |
| ALL OTHER THERAPEUTIC PRODUCTS | 1 ( 0.3) | 0 ( 0.0) | 1 ( 0.2) |
| PHENTOLAMINE MESILATE | 1 ( 0.3) | 0 ( 0.0) | 1 ( 0.2) |

Note: At each level of summation, patients reporting more than one subsequent therapy are counted only once.
Types of therapy and medications within a type are sorted in descending order of total frequency.
Treatments are coded using the WHODrug Global B3 Format dictionary March 1, 2022.

**Table 27. Improvement of ECOG Performance Status in Patients with Subsequent Platinum Therapy (ITT Population)**

| | Atezolizumab (N=18) | Chemotherapy (N=8) | Total (N=26) |
|---|---|---|---|
| Improvement of ECOG PS at any time post-baseline, n(%) | | | |
| Yes* | 10 (55.6) | 3 (37.5) | 13 (50.0) |
| No | 8 (44.4) | 5 (62.5) | 13 (50.0) |

*One patient in the Atezolizumab arm (Patient 1699) with improvement in ECOG PS post-baseline was erroneously reported as having received platinum as subsequent anti-cancer therapy at the time the data snapshot was taken (15 June 2022); data entries have since been corrected in the eCRF and this patient received best supportive care only.

**Table 28. Overview of Platinum-Containing Regimens in Subsequent Therapy Lines (ITT Population)**

| | Atezolizumab (N=302) n (%) | Chemotherapy (N=151) n (%) | Total (N=453) n (%) |
|---|---|---|---|
| Platinum Monotherapy | 1 ( 0.3) | 0 | 1 ( 0.2) |
| Carboplatin | 1 ( 0.3) | 0 | 1 ( 0.2) |
| Platinum in Doublet | 16 ( 5.3) | 8 ( 5.3) | 24 ( 5.3) |
| Carboplatin + Docetaxel | 0 | 1 ( 0.7) | 1 ( 0.2) |
| Carboplatin + Gemcitabine | 1 ( 0.3) | 1 ( 0.7) | 2 ( 0.4) |
| Carboplatin + Gemcitabine Hydrochloride | 1 ( 0.3) | 0 | 1 ( 0.2) |
| Carboplatin + Paclitaxel | 3 ( 1.0) | 2 ( 1.3) | 5 ( 1.1) |
| Carboplatin + Pemetrexed* | 7 ( 2.3) | 2 ( 1.3) | 9 ( 2.0) |
| Carboplatin + Pemetrexed Disodium | 1 ( 0.3) | 1 ( 0.7) | 2 ( 0.4) |
| Carboplatin + Vinorelbine | 1 ( 0.3) | 0 | 1 ( 0.2) |
| Cisplatin + Gemcitabine | 1 ( 0.3) | 0 | 1 ( 0.2) |
| Cisplatin + Vinorelbine Tartrate | 1 ( 0.3) | 0 | 1 ( 0.2) |
| Lobaplatin + Docetaxel | 0 | 1 ( 0.7) | 1 ( 0.2) |
| Platinum in Triplet | 1 ( 0.3) | 0 | 1 ( 0.2) |
| Carboplatin + Cisplatin + Pemetrexed** | 1 ( 0.3) | 0 | 1 ( 0.2) |

*One patient in the Atezolizumab arm was erroneously reported as having received platinum (carboplatin + pemetrexed) as subsequent anti-cancer therapy at the time the data snapshot was taken (15 June 2022); data entries have since been corrected in the eCRF and this patient received best supportive care only.
**Switch from cisplatin to carboplatin after Cycle 1

**Results from the Platinum-ineligible population (N=405)**

Baseline demographic characteristics and baseline disease characteristics for the platinum-ineligible population (N=405) are shown in Table 13 and Table 14, respectively.

## Table 29. Duration of Survival Follow-Up (Platinum-ineligible Population)

| | Atezolizumab (N=268) | Chemotherapy (N=137) | Total (N=405) |
|---|---|---|---|
| Kaplan-Meier Estimates of Duration of Survival Follow-Up (months) | | | |
| Events, n(%) | 45 (16.8%) | 17 (12.4%) | 62 (15.3%) |
| Censored, n(%) | 223 (83.2%) | 120 (87.6%) | 343 (84.7%) |
| 25th Pctl. (95% CI[1]) | 38.2 (35.5, 40.1) | 36.5 (34.3, 39.9) | 36.8 (34.3, 39.9) |
| Median (95% CI[1]) | 41.3 (40.0, 44.2) | 39.9 (36.5, NE) | 41.0 (39.9, 44.2) |
| 75th Pctl. (95% CI[1]) | 48.0 (43.1, 49.4) | 52.7 (39.9, NE) | 48.0 (43.1, 49.5) |
| Min, Max | 0.1, 51.5 | 0.1, 53.5 | 0.1, 53.5 |

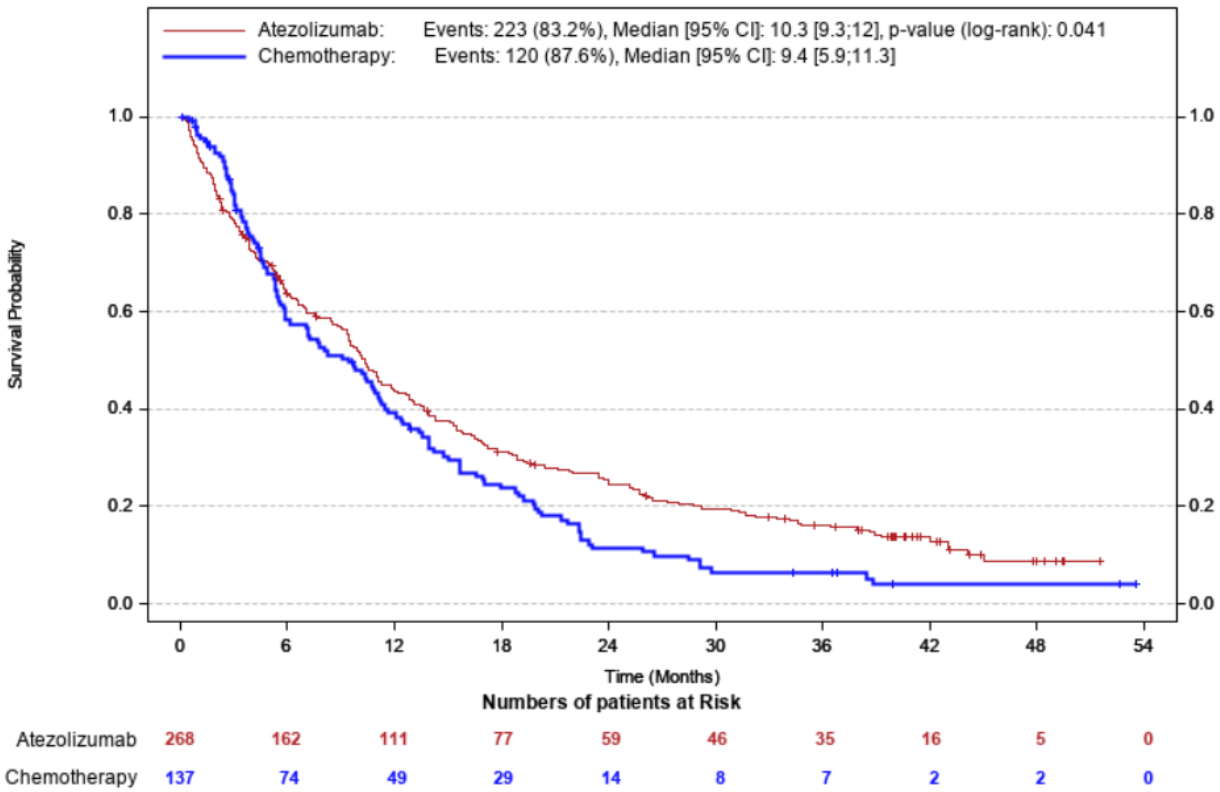
The inverse Kaplan-Meier methodology was used to estimate the duration of survival follow-up.
[1] 95% Confidence Interval (CI) computed using the Brookmeyer and Crowley method.
Relevant comorbidities defined as the following HLGTs: Cardiac arrhythmias, Coronary artery disorders, Heart failures, Myocardial disorders, Cardiac valve disorders, Arteriosclerosis, stenosis, vascular insufficiency and necrosis, Vascular hypertensive disorders, Central nervous system vascular disorders, Mental impairment disorders, Neurological disorders NEC, Peripheral neuropathies, Increased intracranial pressure and hydrocephalus, Encephalopathies, Deliria (incl confusion), Psychiatric disorders NEC, Dementia and amnestic conditions, Nephropathies, Renal disorders (excl nephropathies), Electrolyte and fluid balance conditions, Glucose metabolism disorders (incl diabetes mellitus), Appetite and general nutritional disorders, Bronchial disorders (excl neoplasms), Lower respiratory tract disorders (excl obstruction and infection), Pulmonary vascular disorders.

## Table 30. Overall Survival (Platinum-ineligible Population)

| | Atezolizumab (N=268) | Chemotherapy (N=137) |
|---|---|---|
| Kaplan-Meier Estimates of Overall Survival (OS) (months) | | |
| Events, n(%) | 223 (83.2%) | 120 (87.6%) |
| Censored, n(%) | 45 (16.8%) | 17 (12.4%) |
| 25th Pctl. (95% CI[1]) | 3.7 (2.8, 5.1) | 4.0 (3.1, 5.2) |
| Median (95% CI[1]) | 10.3 (9.3, 12.0) | 9.4 (5.9, 11.3) |
| 75th Pctl. (95% CI[1]) | 24.0 (18.6, 28.7) | 17.0 (13.9, 20.2) |
| Min, Max | 0.1, 51.5 | 0.1, 53.5 |
| Stratified Analysis | | |
| Hazard ratio (Atezolizumab vs. Chemotherapy)[2] | 0.79 | |
| 95% CI[2] | (0.63, 0.99) | |
| P-value (log-rank) | 0.041 | |
| Unstratified Analysis | | |
| Hazard ratio (Atezolizumab vs. Chemotherapy)[2] | 0.78 | |
| 95% CI[2] | (0.63, 0.98) | |
| P-value (log-rank) | 0.034 | |

[1] 95% Confidence Interval (CI) computed using the Brookmeyer and Crowley method.
[2] Estimated hazard ratio and 95% Confidence Interval (CI) obtained from Cox model with treatment group as covariate. For the stratified analysis, histologic subtype, PD-L1 IHC status and brain metastases (Yes/No) were added as stratification factors (per IxRS data).
Relevant comorbidities defined as the following HLGTs: Cardiac arrhythmias, Coronary artery disorders, Heart failures, Myocardial disorders, Cardiac valve disorders, Arteriosclerosis, stenosis, vascular insufficiency and necrosis, Vascular hypertensive disorders, Central nervous system vascular disorders, Mental impairment disorders, Neurological disorders NEC, Peripheral neuropathies, Increased intracranial pressure and hydrocephalus, Encephalopathies, Deliria (incl confusion), Psychiatric disorders NEC, Dementia and amnestic conditions, Nephropathies, Renal disorders (excl nephropathies), Electrolyte and fluid balance conditions, Glucose metabolism disorders (incl diabetes mellitus), Appetite and general nutritional disorders, Bronchial disorders (excl neoplasms), Lower respiratory tract disorders (excl obstruction and infection), Pulmonary vascular disorders.

**Figure 11. Kaplan-Meier Overall Survival (Platinum-ineligible Population)**




+ Censored

P-value obtained from a stratified log-rank test. Stratification factors (per IxRS data) are: histologic subtype, PD-L1 IHC status and brain metastases.

**Table 31. Progression Free Survival as per Investigator – RECIST v1.1 (Platinum-ineligible Population)**

| | Atezolizumab (N=268) | Chemotherapy (N=137) |
|---|---|---|
| Kaplan-Meier Estimates of Progression Free Survival (PFS) (months) | | |
| Events, n(%) | 245 (91.4%) | 125 (91.2%) |
| Earliest contributing event | | |
| Death | 83 | 44 |
| Disease Progression | 162 | 81 |
| Censored, n(%) | 23 (8.6%) | 12 (8.8%) |
| 25th Pctl. (95% CI[1]) | 1.5 (1.4, 2.1) | 2.5 (1.5, 2.8) |
| Median (95% CI[1]) | 4.7 (4.0, 5.6) | 4.2 (3.0, 5.5) |
| 75th Pctl. (95% CI[1]) | 9.7 (8.3, 12.5) | 8.4 (6.3, 10.7) |
| Min, Max | 0.0, 48.3 | 0.0, 29.1 |
| Stratified Analysis | | |
| Hazard ratio (Atezolizumab vs. Chemotherapy)[2] | 0.85 | |
| 95% CI[2] | (0.68, 1.06) | |
| P-value (log-rank) | 0.151 | |
| Unstratified Analysis | | |
| Hazard ratio (Atezolizumab vs. Chemotherapy)[2] | 0.82 | |
| 95% CI[2] | (0.66, 1.02) | |
| P-value (log-rank) | 0.076 | |

[1] 95% Confidence Interval (CI) computed using the Brookmeyer and Crowley method.
[2] Estimated hazard ratio and 95% Confidence Interval (CI) obtained from Cox model with treatment group as covariate. For the stratified analysis, histologic subtype, PD-L1 IHC status and brain metastases (Yes/No) were added as stratification factors (per IxRS data).
Relevant comorbidities defined as the following HLGTs: Cardiac arrhythmias, Coronary artery disorders, Heart failures, Myocardial disorders, Cardiac valve disorders, Arteriosclerosis, stenosis, vascular insufficiency and necrosis, Vascular hypertensive disorders, Central nervous system vascular disorders, Mental impairment disorders, Neurological disorders NEC, Peripheral neuropathies, Increased intracranial pressure and hydrocephalus, Encephalopathies, Deliria (incl confusion), Psychiatric disorders NEC, Dementia and amnestic conditions, Nephropathies, Renal disorders (excl nephropathies), Electrolyte and fluid balance conditions, Glucose metabolism disorders (incl diabetes mellitus), Appetite and general nutritional disorders, Bronchial disorders (excl neoplasms), Lower respiratory tract disorders (excl obstruction and infection), Pulmonary vascular disorders.

**Table 32. Confirmed Best Overall Response per RECIST v1.1 – Investigator (Platinum-ineligible Population)**

| | Atezolizumab (N=268) | Chemotherapy (N=137) |
|---|---|---|
| Best Overall Response (BOR), n(%) | | |
| Complete Response (CR) | 4 (1.5) | 0 (0.0) |
| 95% CI[1] | (0.4, 3.8) | (NE, NE) |
| Partial Response (PR) | 45 (16.8) | 11 (8.0) |
| 95% CI[1] | (12.5, 21.8) | (4.1, 13.9) |
| Stable Disease (SD) | 110 (41.0) | 69 (50.4) |
| 95% CI[1] | (35.1, 47.2) | (41.7, 59.0) |
| Progressive Disease (PD) | 53 (19.8) | 31 (22.6) |
| 95% CI[1] | (15.2, 25.1) | (15.9, 30.6) |
| Non-Evaluable (NE) | 11 (4.1) | 10 (7.3) |
| 95% CI[1] | (2.1, 7.2) | (3.6, 13.0) |
| Missing | 45 (16.8) | 16 (11.7) |
| 95% CI[1] | (12.5, 21.8) | (6.8, 18.3) |
| Objective Response Rate (ORR) | | |
| n(%) | 49 (18.3) | 11 (8.0) |
| 95% CI[1] | (13.8, 23.4) | (4.1, 13.9) |
| Difference in ORR (Atezolizumab – Chemotherapy) | | |
| % | 10.3 | |
| 95% CI[2] | (3.2, 17.3) | |
| P-value[3] | 0.006 | |

[1] 95% confidence interval (CI) computed using the Clopper-Pearson method.
[2] 95% confidence interval (CI) of the difference in ORR (Atezolizumab – Chemotherapy) computed using normal approximation to the binomial distribution.
[3] P-value (two-sided) obtained from Chi-square test.

**Table 33. Duration of Confirmed Response as per Investigator – RECIST v1.1 (Platinum-ineligible Population)**

| | Atezolizumab (N=268) | Chemotherapy (N=137) |
|---|---|---|
| Patients with Best Overall Response (BOR) of CR or PR, n(%) | 49 (18.3) | 11 (8.0) |
| Kaplan-Meier Estimates of Duration of Response (months) | | |
| Events, n(%)[1] | 38 (77.6%) | 11 (100.0%) |
| Earliest contributing event | | |
| Death | 8 | 3 |
| Disease Progression | 30 | 8 |
| Censored, n(%)[1] | 11 (22.4%) | 0 (0.0%) |
| 25th Pctl. (95% CI[2]) | 5.6 (4.2, 10.2) | 4.8 (2.2, 8.2) |
| Median (95% CI[2]) | 14.5 (8.1, 20.3) | 8.2 (4.8, 11.6) |
| 75th Pctl. (95% CI[2]) | 33.8 (18.7, 43.3) | 11.6 (8.2, NE) |
| Min, Max | 1.4, 44.7 | 2.2, 15.7 |
| Stratified Analysis | | |
| Hazard ratio (Atezolizumab vs. Chemotherapy)[3] | 0.42 | |
| 95% CI[3] | (0.19, 0.91) | |
| P-value (log-rank) | 0.024 | |
| Unstratified Analysis | | |
| Hazard ratio (Atezolizumab vs. Chemotherapy)[3] | 0.37 | |
| 95% CI[3] | (0.18, 0.75) | |
| P-value (log-rank) | 0.004 | |

Note: Duration of response is defined only for patients with a best overall response (BOR) of Complete Response (CR) or Partial Response (PR).
[1] Percentages are calculated based on number of patients with BOR of CR or PR.
[2] 95% Confidence Interval (CI) computed using the Brookmeyer and Crowley method.
[3] Estimated hazard ratio and 95% Confidence Interval (CI) obtained from Cox model with treatment group as covariate. For the stratified analysis, histologic subtype, PD-L1 IHC status and brain metastases (Yes/No) were added as stratification factors (per IxRS data).

## *Summary of main study(ies)*

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Summary of Efficacy for trial MO29872 (IPSOS)**

| | | | |
|---|---|---|---|
| **Title:** A Phase III, open-label, multicenter, randomised study to investigate the efficacy and safety of atezolizumab compared with chemotherapy in patients with treatment naive advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) non-small cell lung cancer who are deemed ineligible for platinum-containing therapy. | | | |
| Study identifier | IPSOS<br>Protocol number: MO29872<br>EudraCT number: 2015-004105-16<br>NCT number: NCT03191786 | | |
| Design | IPSOS is a Phase III, global, multicenter, open-label, randomised, controlled study | | |
| | Duration of main phase: | | Patients received atezolizumab until disease progression per RECIST v1.1, unacceptable toxicity, patient or physician decision to discontinue, or death.<br>Patients received vinorelbine or gemcitabine until disease progression per RECIST v1.1, unacceptable toxicity, patient or physician decision to discontinue, or death. |
| | Duration of Run-in phase: | | not applicable |
| | Duration of Extension phase: | | not applicable |
| Hypothesis | Superiority | | |
| Treatments groups | Atezolizumab | | 1200 mg by IV infusion on Day 1 of every 21-day cycle<br>N= 302 |
| | Chemotherapy | | Vinorelbine: IV infusion at 25-30 mg/m2 on Days 1 and 8 of each 21-day cycle or on Days 1, 8 and 15 of each 28-day cycle.<br>Vinorelbine: oral administration at 60-80 mg/m2 on Days 1 and 8 of each 21-day cycle or on Days 1, 8 and 15 of each 28-day cycle, with weekly dosing recommended in some labels.<br>Gemcitabine: IV infusion at 1000-1250 mg/m2 on Days 1 and 8 of each 21-day cycle or on Days 1, 8 and 15 of each 28-day cycle.<br>N=151 |
| Endpoints and definitions | Primary endpoint | overall survival (OS) | defined as the time from randomisation to death from any cause |
| | Secondary endpoint | landmark OS Rates | OS rates at 6, 12, 18 and 24 months |
| | | investigator-assessed objective response rate (ORR) | defined as partial response plus complete response (confirmation being required) as determined by the investigator per RECIST v1.1 |

| | | | |
|---|---|---|---|
| | | investigator-assessed progression-free survival (INV-assessed PFS) | defined as time from randomisation to the first occurrence of disease progression, as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurs first |
| | | investigator-assessed duration of response (DOR) | defined as the time from the first occurrence of a documented objective response to the time of disease progression, as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurs first. |
| | | OS and PFS defined by the Ventana SP263 IHC assay | OS and investigator-assessed PFS according to RECIST v1.1 defined by the Ventana SP263 IHC<br>Assay |
| Database lock | CCOD: 30 April 2022 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis of OS (ITT Population)** | | |
| Analysis population and time point description | Of the 453 enrolled patients, 302 patients were randomised to the atezolizumab monotherapy arm and 151 patients were randomised to the chemotherapy (gemcitabine or vinorelbine) arm. | | |
| Descriptive statistics and estimate variability | Treatment group | Atezolizumab | Chemotherapy |
| | Number of subjects | 302 | 151 |
| | OS (median, months) | 10.3 | 9.2 |
| | 95% CI | 9.4, 11.9 | 5.9, 11.2 |
| Effect estimate per comparison | Primary endpoint:<br>OS | Comparison groups | Atezolizumab vs. Chemotherapy |
| | | Stratified HR | 0.78 |
| | | 95% CI | 0.63, 0.97 |
| | | p-value (Stratified Log-rank) | 0.028 |
| Notes | Not applicable | | |
| **Analysis description** | **Key Secondary analysis (ITT Population)** | | |
| Descriptive statistics and estimate variability | Treatment group | Atezolizumab | Chemotherapy |
| | Number of subject | 302 | 151 |
| | Landmark OS rates (%)<br>6 months<br>12 months<br>18 months<br>24 months | <br>64.0<br>43.7<br>31.4<br>24.3 | <br>57.5<br>38.6<br>24.0<br>12.4 |

| | | | |
|---|---|---|---|
| | 95% CI<br>6 months<br>12 months<br>18 months<br>24 months | <br>58.6, 69.5<br>37.9, 49.4<br>26.0, 36.8<br>19.3, 29.4 | <br>49.4, 65.7<br>30.5, 46.7<br>16.8, 31.2<br>6.7, 18.0 |
| | INV-assessed PFS (median, months) | 4.2 | 4.0 |
| | 95% CI | 3.7, 5.5 | 2.9, 5.4 |
| | Difference in ORR | 8.9 % | |
| | 95% CI | 2.4, 15.5 | |
| | DoR (median, months) | 14.0 | 7.8 |
| | 95% CI | 8.1, 20.3 | 4.8, 9.7 |
| Notes | Not applicable | | |

### *Analysis performed across trials (pooled analyses and meta-analysis)*

Not applicable.

### *Clinical studies in special populations*

No dedicated studies were conducted in special populations.

The number of patients by age category (<65, 65-74, 75-84, >=85) enrolled in IPSOS are shown in Table 12. OS results by age groups are shown in Figure 8.

### *Supportive study(ies)*

Not applicable.

## 2.4.3. Discussion on clinical efficacy

## Design and conduct of clinical studies

Based on data from the pivotal trial **IPSOS** (MO29872): A Phase III, open-label, multicentre, randomised study to investigate the efficacy and safety of atezolizumab compared with chemotherapy in patients with treatment-naive advanced or recurrent or metastatic non-small cell lung cancer who are deemed ineligible for platinum-containing therapy, the MAH for Tecentriq had initially applied for the following extension of indication:

> *Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with NSCLC who are ineligible for platinum-based chemotherapy and who do not have EGFR-mutant or ALK-positive NSCLC, who have:*
>
> - *locally advanced, unresectable NSCLC not amenable for definitive chemoradiotherapy, or*

- *metastatic NSCLC (see section 5.1)*

The MAH did not receive CHMP scientific advice before the conduct of this pivotal trial.

The overall study design of study IPSOS (MO29872) and assessment of results by the Independent data monitoring committee are endorsed. Despite patients in the atezolizumab arm were allowed (per protocol) to continue treatment beyond progression, there is insufficient efficacy/safety evidence to make this a general recommendation. Therefore, all labelling claims for post-PD treatment were removed from the SmPC.

Per-protocol platinum-ineligibility held a seemingly lax and ambiguous definition at inclusion criteria: instead of specific requirements, it was left to individual investigator judgement to decide whether a patient was unfit for a platinum-doublet. This issue constituted a major objection along the procedure, as it was uncertain whether results from the studied population could be representative of patients defined in the proposed therapeutic indication.

From a clinical perspective, platinum-eligibility serves to dichotomize patients into "fit enough for cisplatin or carboplatin" or not, but this definition is better defined in other malignancies, the classical paradigm being metastatic urothelial cancer (Gupta et al. Defining "platinum-ineligible" patients with metastatic urothelial cancer. J Clin Oncol 2019;37:451), while a set of criteria that define platinum-ineligibility in NSCLC is not yet defined, standardised nor internationally applied. Based on the uncertainties from the ambiguous per-protocol definition from IPSOS, and the need to anchor the indication to specific criteria defining platinum-ineligibility, the MAH assessed that ~89% of the IPSOS ITT population met 'directly evaluable' criteria for platinum ineligibility based on criteria defined in the literature (De Marinis et al., 2015 and Camerini et al., 2022), i.e., age >80 years, Eastern Cooperative Oncology Group (ECOG) PS ≥3, ECOG PS 2 in combination with relevant comorbidities, or age ≥70 years in combination with relevant comorbidities. Results from this ad hoc analysis are considered supportive of the finally agreed indication.

Control arm: The selection of vinorelbine and gemcitabine as the sole comparators in the chemotherapy arm was also questioned during the procedure, since other relevant treatments (particularly docetaxel and pemetrexed) were not considered. The MAH provided the following arguments: Firstly, historical data presented from 4 clinical trials (see Table 6) showed that OS for patients who had docetaxel or pemetrexed was not superior to those who had vinorelbine or gemcitabine, which were options in the control arm. It should be noted that the included patients in these trials were treated in the first-line setting of NSCLC and they were defined as unsuitable, ineligible, or unfit for platinum based chemotherapy by the judgement of the treating physician. Second, it is acknowledged that pemetrexed was added to the ESMO treatment guidelines in October 2018 (Planchard et al. 2018), while the IPSOS study was ongoing, so this option was not added to the control arm to avoid a major amendment during study conduct. Thirdly, RWE from MOON-OSS and data from the CRISP database in Germany support the use of vinorelbine and gemcitabine in the proposed setting (data not shown). In conclusion, for the targeted frail population, who are platinum-ineligible, the options of single-agent chemotherapy with either gemcitabine or vinorelbine are acceptable options, while the reason for not including pemetrexed in the control arm is acknowledged.

Statistical methods: Sample size calculation is sufficiently justified. The choice of endpoints is appropriate to evaluate efficacy in the targeted population and the statistical methods in the analysis are overall adequate.

## Efficacy data and additional analyses

A total of 843 patients were screened for entry into the study, 390 patients failed screening, in most cases due to not meeting eligibility criteria, investigator or patient decision, or insufficient tissue for analysis. Patients were recruited from 85 centres across 23 countries covering Europe and the Middle East, Asia Pacific, Central and South America and North America. The first patient was recruited in September 2017.

Of the 453 enrolled patients (ITT population), 302 patients were randomised to the atezolizumab monotherapy arm and 151 patients were randomised to the chemotherapy (gemcitabine or vinorelbine) arm. Of these 453 patients, 405 (i.e., 89%) met the above-mentioned ad hoc selection criteria for platinum-ineligibility (referred as 'Platinum-ineligible population'). As of the CCOD (30 April 2022), 95% of patients in the atezolizumab arm vs. 100% of patients in the chemotherapy arm had discontinued the study and treatment, the majority discontinued treatment due to progressive disease; 50.3% and 51% respectively.

The treatment arms were generally well balanced with respect to demographic and baseline characteristics. The ITT population predominantly comprised White (66%) and male (72%) patients. The median age of patients was 75 years and 73% of patients were aged 70 years or older. The proportion of patients with ECOG PS of 0, 1, 2 and 3 was 1.5%, 15%, 76%, and 7.5%, respectively. Overall, 14% of patients had stage IIIB disease not amenable to multimodality treatment and 86% had stage IV disease. The percentage of patients who had tumours with PD-L1 expression TC< 1%, 1-49% and ≥ 50% as measured by the VENTANA PD-L1 (SP263) assay was 47%, 29% and 16%, respectively, while 8% of patients had an unknown PD-L1 expression status. The distribution between squamous and non-squamous NSCLC was ~40/60% and slightly different from the ~30/70% distribution that is otherwise observed in the NSCLC population, but this fact is not considered influential on the outcome. The overall baseline and disease characteristics were comparable between the ITT and the ad hoc platinum-ineligible population.

Efficacy data are considered overall mature, with an OS event rate of 82.5% and 86.1% in the atezolizumab and the chemotherapy arm, respectively. Median OS in the overall population was 10.3 (95%CI: 9.4-11.9) months in the atezolizumab arm and 9.2 (95%CI: 5.9-11.2) in the chemotherapy arm, stratified HR 0.78 (95%CI: 0.63-0.97). As seen in similar clinical scenarios when anti-PD-1/PD-L1 monotherapy is compared to chemotherapy in the first-line of NSCLC (and some other cancers), an early crossing of the OS KM curves is observed. Investigator-assessed PFS in the overall population was similar for both arms, 4.2 (95%CI: 3.7-5.5) vs 4.0 (95%CI: 2.9-5.4) months in the atezolizumab and chemotherapy arms, respectively, HR 0.87 (95%CI: 0.7-1.07). The overall response rate (ORR) was 16.9% vs 7.9%, respectively, while the duration of response (DoR) was 14.0 (95%CI: 8.1, 20.3) vs 7.8 (95%CI: 4.8, 9.7), respectively.

Ad hoc platinum-ineligible population (n=405, 268 in the atezo arm and 137 in the chemo arm): An exploratory analysis of OS in this population shows a median OS of 10.3 months with atezolizumab monotherapy versus a median of 9.4 months in the chemotherapy arm (unstratified HR=0.78, 95%CI: 0.63, 0.98). Despite the caveats of such post-hoc analyses, this result is consistent with results from the primary analysis and overall considered reassuring and supportive of the proposed extension of indication. From a clinical perspective, the difference of 1 month in OS is considered clinically relevant as it is recognized that the targeted population is by definition frail, and thus an overwhelming improvement of survival was not expected.

For the platinum-ineligible population, data on PFS, ORR and DoR showed comparable results to the primary analysis of the ITT. Hence, for the Atezo vs the chemotherapy group, the median PFS was 4.7

months vs 4.2 months, while the ORR was 18.3% vs 8%, with a median DoR of 14.5 months vs 8.2 months.

The MAH has convincingly argued that the ad hoc platinum-ineligible population (89% of the ITT) of the pivotal IPSOS study is defined by specific criteria, and is supportive of the requested extension of indication. Efficacy and safety are comparable for the subgroup and the overall population, and the comparators used are found to be acceptable.

The efficacy is considered established in the finally agreed indication, supported by the ad hoc platinum-ineligible population:

> *Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with advanced NSCLC who are ineligible for platinum-based therapy (see section 5.1 for selection criteria).*

The further revised indication is relevant for a targeted patient population, with locally advanced, unresectable NSCLC not amenable for definitive chemoradiotherapy, or metastatic NSCLC, in whom the recommended 1st line choice of treatment would otherwise (had they not been considered unsuitable for platinum-based chemotherapy) have been platinum-based chemotherapy.

Based on the positive outcome from the Tecentriq X-76 variation (CHMP positive opinion 09 Nov 2023, EC decision 11 Jan 2024), in which the extrapolation of the SC formulation for atezolizumab was found acceptable for all current and future approved indications for atezolizumab IV, the MAH requested to extend the currently pursued indication (platinum-ineligible patients with advanced NSCLC) to its SC formulation. This was considered acceptable.

### 2.4.4. Conclusions on the clinical efficacy

The MAH has applied for an extension of indication for atezolizumab as a 1st line treatment in adult patients with locally advanced, unresectable or metastatic NSCLC, who are considered ineligible for platinum-based chemotherapy, defining a more frail patient population. For the defined platinum-ineligible subpopulation, efficacy has been demonstrated in comparison to single-agent chemotherapy with either vinorelbine or gemcitabine in the proposed setting.

## *2.5. Clinical safety*

### *Introduction*

The clinical safety data are based on the data snapshot of the final overall survival analysis (clinical cutoff date [CCOD]: 30 April 2022) from Study MO29872 ("IPSOS").

In addition, an overview of the two atezolizumab monotherapy pools, consisting of safety-evaluable patients (all patients who received any amount of atezolizumab) in monotherapy studies are provided as a reference:

- Single-agent atezolizumab regardless of tumor type (n=3178); hereinafter referred to as the **Atezo Mono 1** population. The Atezo Mono 1 pool comprises safety data which informs the core data sheet (CDS).
- Single-agent atezolizumab regardless of tumor type (n=4739); hereinafter referred to as the **Atezo Mono 2** population. The Atezo Mono 2 pool comprises safety data previously reviewed by European Medicines Agency (EMA) that informs the updated draft EU Summary of Product Characteristics (SmPC).

Safety data from the atezolizumab arm and chemotherapy arm of IPSOS are summarised and displayed side-by-side with the two pooled atezolizumab monotherapy populations described above. These pooled data are not intended for a head-to-head comparison to IPSOS data due to the variation in sample sizes, disease stages, line of therapies, treatment durations, and different indications. However, the pooled populations allow for a comprehensive characterisation of the safety profile of atezolizumab when given as monotherapy.

A list of all twelve studies (including IPSOS) contributing to the safety evaluation is provided in Table 34 below and details on the number of patients in each study contributing to the various monotherapy pooled populations are provided in the Table 35 below.

**Table 34. Summary of Studies and Pooled Populations Contributing to Safety Evaluation**

| Study No. | Study Design | Population | No. of Patients Evaluable for Safety | Dose, Route, and Regimen | Data Cutoff Date |
|---|---|---|---|---|---|
| **Pivotal Study** | | | | | |
| IPSOS (MO29872) | Phase III, global, multicenter, open-label, randomized, controlled | Patients with treatment-naïve locally advanced or metastatic NSCLC not harboring an EGFR mutation or ALK translocation who were deemed unsuitable for any platinum doublet chemotherapy due to their poor performance status (ECOG PS of 2-3) or due to their advanced age (≥70 years) in combination with substantial comorbidities or other contraindications for platinum-doublet chemotherapy in the investigator's opinion, regardless of PD-L1 expression status | Atezo = 300<br>Chemo = 147 | Atezolizumab 1200 mg IV q3w | Primary analysis: 30 April 2022 |
| **Atezolizumab Monotherapy Studies** | | | | | |
| OAK (GO28915) | Phase III, global, open-label, multicenter, randomized study | Patients with locally advanced, metastatic, or recurrent non-squamous or squamous NSCLC who have failed a prior platinum-containing regimen (2L and 3L). Patients were stratified by PD-L1 status (IC0 vs. IC1 vs. IC2 vs. IC3), number of prior chemotherapy regimens (1 versus 2), histology (non-squamous versus squamous). | 609 patients treated with atezolizumab monotherapy | Atezolizumab 1200 mg IV q3w | Primary analysis: 7 July 2016 |

| Study No. | Study Design | Population | No. of Patients Evaluable for Safety | Dose, Route, and Regimen | Data Cutoff Date |
|---|---|---|---|---|---|
| POPLAR (GO28753) | Phase II, global, multicenter, open-label, randomized, controlled trial | Patients with locally advanced, metastatic, or recurrent non-squamous or squamous NSCLC who have failed a prior platinum-containing regimen (2L and 3L). Patients were stratified by PD-L1 status (IC0 vs. IC1 vs. IC2 vs. IC3), number of prior chemotherapy regimens (1 versus 2), histology (non-squamous versus squamous). | 142 patients treated with atezolizumab monotherapy | Atezolizumab 1200 mg IV q3w | Updated analysis: 1 December 2015 |
| BIRCH (GO28754) | Phase II, global, multicenter, three-cohort, single-arm trial | Patients with locally advanced or metastatic NSCLC who were treatment-naive in the metastatic setting (1L), or had progressed during or following treatment with one platinum-based regimen (2L), or had progressed during or following at least 2 regimens (3L+ ), one of which had to have been a platinum-containing regimen for advanced disease. Patients were PD-L1 selected (TC2/3 or IC2/3). | 659 patients treated with atezolizumab monotherapy:<br>Cohort 1 (1L) = 139<br>Cohort 2 (2L) = 268<br>Cohort 3 (3L+ ) = 252 | Atezolizumab 1200 mg IV q3w | Updated analysis: 1 December 2015 |
| FIR (GO28625) | Phase II, global, multicenter, three-cohort, single-arm trial | Patients with locally advanced or metastatic NSCLC who were treatment-naive in metastatic setting (1L, Cohort 1) or progressed during or following a prior platinum-based chemotherapy regimen without restriction to the maximum number of prior therapies (i.e., 2L+; Cohort 2), or 2L+ patients with previously treated brain metastases (Cohort 3). Patients were PD-L1 selected (TC2/3 or IC2/3). | 137 patients treated with atezolizumab monotherapy:<br>Cohort 1 (1L) = 31<br>Cohort 2 (2L+) = 93<br>Cohort 3 (2L+ with brain metastases) = 13 | Atezolizumab 1200 mg IV q3w | Primary analysis: 7 January 2015 |

| Study No. | Study Design | Population | No. of Patients Evaluable for Safety | Dose, Route, and Regimen | Data Cutoff Date |
|---|---|---|---|---|---|
| IMvigor211 (GO29294) | Phase III, global, open-label, multicenter, randomized study | Patients with locally advanced or metastatic UC who have progressed during or following a platinum-containing regimen (2L/3L). Patients were stratified by chemotherapy (vinflunine vs. taxane), PD-L1 status (IC0/1 vs. IC2/3), number of risk factors, and presence of liver metastases. | 459 patients treated with atezolizumab monotherapy | Atezolizumab 1200 mg IV q3w | Primary analysis: 13 March 2017 |
| IMvigor210 (GO29293) | Phase II, global, multicenter, two-cohort, single-arm trial | Patients with locally advanced or 1L metastatic UC (no prior chemotherapy in the metastatic setting and ineligible for cisplatin-based chemotherapy) or 2L + patients with locally advanced or metastatic UC (patients who failed a prior platinum-based therapy or progressed within 12 months of a platinum-containing treatment administered in the neoadjuvant or adjuvant setting). Approximately 30% of the patient population was planned to be PD-L1 selected (IC2/3). | 429 patients treated with atezolizumab monotherapy:<br>Cohort 1 (1L) = 119<br>Cohort 2 (2L+) = 310 | Atezolizumab 1200 mg IV q3w | Updated analysis: 4 July 2016 |
| IMmotion150 (WO29074) | Phase II, multicenter, randomized, open-label study | Patients with histologically confirmed, inoperable, locally advanced or metastatic renal cell carcinoma who have not received prior systemic therapy either in the adjuvant or metastatic setting. | 103 patients treated with atezolizumab monotherapy | Atezolizumab 1200 mg IV q3w | Primary analysis: 17 October 2016 |
| PCD4989g (GO27831) | Phase I, open-label, dose-escalation and dose-expansion stages | Patients with locally advanced or metastatic solid tumors (including UC and NSCLC) and hematologic malignancies. | 640 patients treated with atezolizumab monotherapy:<br>UC=95, NSCLC=89, Non-UC + Non NSCLC=456 | Atezolizumab ≤1, 3, 10, 15, 20 mg/kg and 1200 mg q3w | Interim analysis: 31 March 2016 |
| IMpower110 (GO29431) | Phase III, global, randomized, multicenter, open-label study | PD-L1-selected, chemotherapy-naïve patients with Stage IV non-squamous or squamous NSCLC. | 286 patients treated with atezolizumab monotherapy | Atezolizumab 1200 mg IV q3w | Updated analysis: 4 February 2020 |
| IMpower010 (GO29527) | Phase III, global, randomized, multicenter, open-label study | Patients with Stage IB (tumors ≥4 cm)-Stage IIIA NSCLC following complete resection and adjuvant cisplatin-based chemotherapy. | Atezo=495<br>BSC=495 | Atezolizumab 1200 mg IV q3w | Primary analysis: 21 January 2021 |
| IMvigor010 (WO29636) | Phase III, open-label, randomized study | Patients with muscle invasive urothelial carcinoma, who are at high risk for recurrence following resection | 390 patients treated with atezolizumab monotherapy | Atezolizumab 1200 mg IV q3w | Primary analysis: 30 November 2019 |
| IMmotion010 (WO39210) | Phase III, multicenter, randomized, placebo-controlled, double-blind study | Patients with renal cell carcinoma at high risk of developing metastasis following nephrectomy. | 390 patients treated with atezolizumab monotherapy | Atezolizumab 1200 mg IV q3w | Final analysis: 03 May 2022 |

1L=first-line; 2L=second-line; 2L+=second-line and beyond; 3L=third-line; 3L+=third-line and beyond; atezo=atezolizumab; AUC=area under the concentration-time curve; BSC=best supportive care; CE=carboplatin+etoposide; CIT=cancer immunotherapy; ECOG=Eastern Cooperative Oncology Group; IC=tumor-infiltrating immune cell; IHC= immunohistochemistry; IV=intravenous; NSCLC=non–small cell lung cancer; OS=overall survival; qw=weekly; q3w=every 3 weeks; PD-L1=programmed death-ligand 1; SC=subcutaneous; SCLC=small cell lung cancer; TC=tumor cell; UC=urothelial carcinoma

**Table 35. Overview of Pooling Strategy**

| Study | No. of Safety-Evaluable Patients | Atezo Mono 1 n=3178 | Atezo Mono 2 n=4739 |
|---|---|---|---|
| OAK | 609 | X | X |
| BIRCH | 659 | X | X |
| POPLAR | 142 | X | X |
| FIR | 137 | X | X |
| PCD4989g | 640 | X | X |
| IMvigor210 | 429 | X | X |
| IMvigor211 | 459 | X | X |
| IMmotion150 | 103 | X | X |
| IMpower110 | 286 | - | X |
| IMpower010 | 495 | - | X |
| IMvigor010 | 390 | - | X |
| IMmotion010 | 390 | - | X |

## *Patient exposure*

**Table 36. Exposure to Atezolizumab at a Dose of 1200 mg Every Three Weeks (Safety-Evaluable Population)**

| | IPSOS | | |
|---|---|---|---|
| | Atezolizumab (N=300) | Atezo Mono[1] (N=3178) | Atezo Mono[2] (N=4739) |
| Number of doses | | | |
| n | 300 | 3178 | 4739 |
| Mean (SD) | 12.4 (15.9) | 9.9 (9.8) | 10.9 (9.5) |
| Median | 6.0 | 6.0 | 8.0 |
| Min - Max | 1 - 73 | 1 - 64 | 1 - 73 |
| Treatment duration (M) | | | |
| n | 300 | 3178 | 4739 |
| Mean (SD) | 8.4 (11.5) | 6.6 (7.5) | 7.3 (7.2) |
| Median | 3.5 | 3.5 | 4.9 |
| Min - Max | 0 - 51 | 0 - 53 | 0 - 53 |
| Treatment duration (M) | | | |
| n | 300 | 3178 | 4739 |
| <= 3 | 140 (46.7%) | 1469 (46.2%) | 1787 (37.7%) |
| >3-6 | 43 (14.3%) | 545 (17.1%) | 755 (15.9%) |
| >6-12 | 52 (17.3%) | 513 (16.1%) | 1427 (30.1%) |
| >12-18 | 20 ( 6.7%) | 341 (10.7%) | 391 ( 8.3%) |
| >18-24 | 12 ( 4.0%) | 222 ( 7.0%) | 239 ( 5.0%) |
| >24 | 33 (11.0%) | 88 ( 2.8%) | 140 ( 3.0%) |

Atezo = Atezolizumab. Atezo Mono[1]: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + WO29074(IMMOTION150 Arm B prior to crossover); Atezo Mono [2]: Atezo Mono [1] + GO29431(IMPOWER110) + GO29527(IMPOWER010) + WO29636(IMVIGOR010) + WO39210(IMMOTION010 Arm A).
M=Months; NE = Not estimable.
Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, WO29074:17OCT2016, WO29636:30NOV2019, WO39210:03MAY2022, MO29872:30APR2022.

***Exposure to Gemcitabine or Vinorelbine***

**Table 37. Exposure to Study Treatment (Safety-Evaluable Population)**

| | Atezolizumab N=300 | Chemotherapy N=147 | Gemcitabine N=63 | Vinorelbine N=84 |
|---|---|---|---|---|
| Treatment duration (months) | | | | |
| Mean (SD) | 8.4 (11.5) | 3.2 (3.7) | 2.8 (2.4) | 3.5 (4.4) |
| Median | 3.5 | 2.3 | 2.3 | 1.8 |
| Min – Max | 0 - 51 | 0 - 21 | 0 - 13 | 0 - 21 |
| Treatment duration (n, %) | | | | |
| 0 to≤3 months | 140 (46.7%) | 101 (68.7%) | 45 (71.4%) | 56 (66.7%) |
| >3 to≤6 months | 43 (14.3%) | 31 (21.1%) | 14 (22.2%) | 17 (20.2%) |
| >6 to≤12 months | 52 (17.3%) | 6 (4.1%) | 3 (4.8%) | 3 (3.6%) |
| >12 months | 65 (21.7%) | 9 (6.1%) | 1 (1.6%) | 8 (9.5%) |
| Dose intensity (%) | | | | |
| Median | 99.0 | - | 95.5 | 99.7 |
| Min – Max | 51 – 105 | - | 67 – 102 | 57 – 103 |
| Number of cycles initiated | | | | |
| Median | 6.0 | - | 4.0 | 3.0 |
| Min – Max | 1 – 73 | - | 1 – 19 | 1 – 31 |

## *Adverse events*

***Demographics and Baseline Characteristics***

**Table 38. Summary of Key Demographic and Baseline Characteristics (Safety-Evaluable Population)**

| | IPSOS | | | |
|---|---|---|---|---|
| | Chemotherapy (N=147) | Atezolizumab (N=300) | Atezo Mono[1] (N=3178) | Atezo Mono[2] (N=4739) |
| Age (years) | | | | |
| n | 147 | 300 | 3178 | 4739 |
| Mean (SD) | 73.8 (8.5) | 73.6 (9.1) | 63.3 (10.8) | 63.0 (10.5) |
| Median | 75.0 | 75.0 | 64.0 | 64.0 |
| Min - Max | 37 - 89 | 33 - 94 | 20 - 92 | 20 - 92 |
| Age Group (years) | | | | |
| n | 147 | 300 | 3178 | 4739 |
| <65 | 18 (12.2%) | 46 (15.3%) | 1595 (50.2%) | 2472 (52.2%) |
| >=65 | 129 (87.8%) | 254 (84.7%) | 1583 (49.8%) | 2267 (47.8%) |
| Age Group (years) | | | | |
| n | 147 | 300 | 3178 | 4739 |
| < 65 | 18 (12.2%) | 46 (15.3%) | 1595 (50.2%) | 2472 (52.2%) |
| 65 - 74 | 50 (34.0%) | 100 (33.3%) | 1105 (34.8%) | 1645 (34.7%) |
| 75 - 84 | 70 (47.6%) | 139 (46.3%) | 458 (14.4%) | 600 (12.7%) |
| >=85 | 9 ( 6.1%) | 15 ( 5.0%) | 20 ( 0.6%) | 22 ( 0.5%) |

| | | | | |
|---|---|---|---|---|
| Sex | | | | |
| n | 147 | 300 | 3178 | 4739 |
| Female | 42 (28.6%) | 81 (27.0%) | 1146 (36.1%) | 1582 (33.4%) |
| Male | 105 (71.4%) | 219 (73.0%) | 2032 (63.9%) | 3157 (66.6%) |
| Race | | | | |
| n | 147 | 300 | 3178 | 4739 |
| American Indian or Alaska Native | 9 ( 6.1%) | 12 ( 4.0%) | 4 ( 0.1%) | 6 ( 0.1%) |
| Asian | 34 (23.1%) | 74 (24.7%) | 320 (10.1%) | 598 (12.6%) |
| Black or African American | 1 ( 0.7%) | 2 ( 0.7%) | 73 ( 2.3%) | 91 ( 1.9%) |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 7 ( 0.2%) | 8 ( 0.2%) |
| White | 95 (64.6%) | 202 (67.3%) | 2533 (79.7%) | 3752 (79.2%) |
| Other | 0 | 0 | 121 ( 3.8%) | 127 ( 2.7%) |
| Multiple | 6 ( 4.1%) | 6 ( 2.0%) | 6 ( 0.2%) | 7 ( 0.1%) |
| Unknown | 2 ( 1.4%) | 4 ( 1.3%) | 114 ( 3.6%) | 150 ( 3.2%) |
| Pooled Race Group | | | | |
| n | 147 | 300 | 3178 | 4739 |
| Asian | 34 (23.1%) | 74 (24.7%) | 320 (10.1%) | 598 (12.6%) |
| Black or African American | 1 ( 0.7%) | 2 ( 0.7%) | 73 ( 2.3%) | 91 ( 1.9%) |
| White | 95 (64.6%) | 202 (67.3%) | 2533 (79.7%) | 3752 (79.2%) |
| Other | 17 (11.6%) | 22 ( 7.3%) | 252 ( 7.9%) | 298 ( 6.3%) |
| Ethnicity | | | | |
| n | 147 | 300 | 3178 | 4739 |
| Hispanic or Latino | 22 (15.0%) | 47 (15.7%) | 117 ( 3.7%) | 200 ( 4.2%) |
| Not Hispanic or Latino | 122 (83.0%) | 240 (80.0%) | 2774 (87.3%) | 4197 (88.6%) |
| Not reported | 3 ( 2.0%) | 9 ( 3.0%) | 200 ( 6.3%) | 240 ( 5.1%) |
| Unknown | 0 | 4 ( 1.3%) | 87 ( 2.7%) | 102 ( 2.2%) |
| Region | | | | |
| n | 147 | 300 | 3178 | 4739 |
| Asia-Pacific | 33 (22.4%) | 70 (23.3%) | 240 ( 7.6%) | 503 (10.6%) |
| Australia | 0 | 0 | 42 ( 1.3%) | 51 ( 1.1%) |
| Central and South America | 23 (15.6%) | 38 (12.7%) | 14 ( 0.4%) | 52 ( 1.1%) |
| Europe and Middle East | 86 (58.5%) | 178 (59.3%) | 1367 (43.0%) | 2291 (48.3%) |
| North America | 5 ( 3.4%) | 14 ( 4.7%) | 1515 (47.7%) | 1842 (38.9%) |
| Baseline Weight (kg) | | | | |
| n | 147 | 300 | 3125 | 4685 |
| Mean (SD) | 66.41 (15.69) | 65.74 (15.34) | 75.62 (18.08) | 76.03 (18.11) |
| Median | 65.00 | 65.00 | 74.00 | 74.20 |
| Min - Max | 35.0 - 128.5 | 31.0 - 130.7 | 34.3 - 175.8 | 34.3 - 175.8 |
| Baseline ECOG Performance Score | | | | |
| n | 147 | 300 | 3069 | 4630 |
| 0 | 0 | 7 ( 2.3%) | 1201 (39.1%) | 2120 (45.8%) |
| 1 | 19 (12.9%) | 49 (16.3%) | 1832 (59.7%) | 2457 (53.1%) |
| 2 | 113 (76.9%) | 226 (75.3%) | 36 ( 1.2%) | 53 ( 1.1%) |
| 3 | 15 (10.2%) | 18 ( 6.0%) | 0 | 0 |
| Tobacco Use History | | | | |
| n | 147 | 300 | 3072 | 4633 |
| Never | 19 (12.9%) | 35 (11.7%) | 842 (27.4%) | 1299 (28.0%) |
| Current | 26 (17.7%) | 57 (19.0%) | 344 (11.2%) | 588 (12.7%) |
| Previous | 102 (69.4%) | 208 (69.3%) | 1886 (61.4%) | 2746 (59.3%) |

Atezo = Atezolizumab. Atezo Mono[1]: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + WO29074(IMMOTION150 Arm B prior to crossover); Atezo Mono [2]: Atezo Mono [1] + GO29431(IMPOWER110) + GO29527(IMPOWER010) + WO29636(IMVIGOR010) + WO39210(IMMOTION010 Arm A).
Actual treatment arms are presented.
Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, WO29074:17OCT2016, WO29636:30NOV2019, WO39210:03MAY2022, MO29872:30APR2022.

***Overview of Safety Profile***

**Table 39. Overview of Safety (Safety-Evaluable Population)**

| | IPSOS | | | |
|---|---|---|---|---|
| | Chemotherapy (N=147) | Atezolizumab (N=300) | Atezo Mono[1] (N=3178) | Atezo Mono[2] (N=4739) |
| Total number of patients with at least one AE | 143 (97.3%) | 275 (91.7%) | 3051 (96.0%) | 4514 (95.3%) |
| Total number of events | 1086 | 2352 | 33377 | 44720 |
| Total number of patients with at least one | | | | |
| Treatment-related AE | 118 (80.3%) | 171 (57.0%) | 2168 (68.2%) | 3272 (69.0%) |
| Grade 3-4 AE | 71 (48.3%) | 136 (45.3%) | 1482 (46.6%) | 1938 (40.9%) |
| Treatment-related Grade 3-4 AE | 49 (33.3%) | 49 (16.3%) | 496 (15.6%) | 711 (15.0%) |
| Grade 5 AE | 13 ( 8.8%) | 35 (11.7%) | 119 ( 3.7%) | 147 ( 3.1%) |
| Treatment-related Grade 5 AE | 4 ( 2.7%) | 3 ( 1.0%) | 11 ( 0.3%) | 16 ( 0.3%) |
| Serious AE | 53 (36.1%) | 146 (48.7%) | 1309 (41.2%) | 1678 (35.4%) |
| Treatment-related serious AE | 23 (15.6%) | 35 (11.7%) | 353 (11.1%) | 494 (10.4%) |
| AE leading to any Study Treatment discontinuation | 20 (13.6%) | 39 (13.0%) | 226 ( 7.1%) | 443 ( 9.3%) |
| AE leading to any Dose modification or Study Treatment interruption | 71 (48.3%) | 96 (32.0%) | 882 (27.8%) | 1331 (28.1%) |
| Total number of patients with at least one AE of Special Interest | 27 (18.4%) | 103 (34.3%) | 1132 (35.6%) | 1912 (40.3%) |
| Total number of events | 37 | 207 | 2250 | 3809 |
| Total number of patients with at least one | | | | |
| Treatment-related AE of Special Interest | 19 (12.9%) | 87 (29.0%) | 805 (25.3%) | 1456 (30.7%) |
| Grade 3-4 AE of Special Interest | 3 ( 2.0%) | 20 ( 6.7%) | 268 ( 8.4%) | 400 ( 8.4%) |
| Treatment-related Grade 3-4 AE of Special Interest | 2 ( 1.4%) | 17 ( 5.7%) | 181 ( 5.7%) | 293 ( 6.2%) |
| Grade 5 AE of Special Interest | 0 | 3 ( 1.0%) | 7 ( 0.2%) | 9 ( 0.2%) |
| Treatment-related Grade 5 AE of Special Interest | 0 | 2 ( 0.7%) | 3 (<0.1%) | 5 ( 0.1%) |
| Serious AE of Special Interest | 2 ( 1.4%) | 20 ( 6.7%) | 175 ( 5.5%) | 254 ( 5.4%) |
| Treatment-related Serious AE of Special Interest | 1 ( 0.7%) | 17 ( 5.7%) | 137 ( 4.3%) | 209 ( 4.4%) |
| AE of Special Interest leading to any Study Treatment discontinuation | 3 ( 2.0%) | 17 ( 5.7%) | 62 ( 2.0%) | 173 ( 3.7%) |
| AE of Special Interest leading to any Dose modification or Study Treatment interruption | 5 ( 3.4%) | 21 ( 7.0%) | 221 ( 7.0%) | 389 ( 8.2%) |
| AE of Special Interest Requiring the Use of Systemic Corticosteroids | 7 ( 4.8%) | 34 (11.3%) | 251 ( 7.9%) | 399 ( 8.4%) |

Atezo = Atezolizumab. Atezo Mono[1]: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + WO29074(IMMOTION150 Arm B prior to crossover); Atezo Mono [2]: Atezo Mono [1] + GO29431(IMPOWER110) + GO29527(IMPOWER010) + WO29636(IMVIGOR010) + WO39210(IMMOTION010 Arm A).
Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v25.1. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. All treatment emergent AEs are included. For the counts in the rows by grade, the patients are counted once at the highest grade.

Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, WO29074:17OCT2016, WO29636:30NOV2019, WO39210:03MAY2022, MO29872:30APR2022.

***Common AEs***

The most common (≥20% of patients in either arm) SOC in which AEs were reported were (atezolizumab arm and chemotherapy arm, respectively):

- General disorders and administration site conditions (49.7% vs. 49.7%)
- Gastrointestinal disorders (42.3% vs. 53.7%)
- Respiratory, thoracic and mediastinal disorders (49.0% vs. 35.4%)
- Infections and infestations (46.7% vs. 36.1%)
- Metabolism and nutrition disorders (43.3% vs. 31.3%)
- Blood and lymphatic disorders (21.3% vs. 46.3%)
- Investigations (29.3% vs. 29.9%)
- Musculoskeletal and connective tissue disorders (26.0% vs. 27.2%)
- Nervous system disorders (20.7% vs. 18.4%)

The most common (≥10% in either arm) AEs by SOC and PT are shown in Table 40.

**Table 40. Common Adverse Events Reported in ≥10% of Patients in Any Treatment Group (Safety-Evaluable Population)**

| | IPSOS | | | |
|---|---|---|---|---|
| MedDRA Preferred Term | Chemotherapy (N=147) | Atezolizumab (N=300) | Atezo Mono[1] (N=3178) | Atezo Mono[2] (N=4739) |
| Fatigue | 34 (23.1%) | 57 (19.0%) | 1142 (35.9%) | 1417 (29.9%) |
| Decreased appetite | 32 (21.8%) | 66 (22.0%) | 810 (25.5%) | 947 (20.0%) |
| Nausea | 35 (23.8%) | 32 (10.7%) | 747 (23.5%) | 917 (19.4%) |
| Cough | 13 ( 8.8%) | 59 (19.7%) | 660 (20.8%) | 859 (18.1%) |
| Diarrhoea | 24 (16.3%) | 40 (13.3%) | 624 (19.6%) | 866 (18.3%) |
| Pyrexia | 10 ( 6.8%) | 31 (10.3%) | 639 (20.1%) | 869 (18.3%) |
| Constipation | 29 (19.7%) | 47 (15.7%) | 652 (20.5%) | 794 (16.8%) |
| Dyspnoea | 16 (10.9%) | 60 (20.0%) | 651 (20.5%) | 777 (16.4%) |
| Arthralgia | 12 ( 8.2%) | 27 ( 9.0%) | 573 (18.0%) | 787 (16.6%) |
| Anaemia | 49 (33.3%) | 49 (16.3%) | 505 (15.9%) | 660 (13.9%) |
| Asthenia | 19 (12.9%) | 43 (14.3%) | 461 (14.5%) | 612 (12.9%) |
| Back pain | 13 ( 8.8%) | 25 ( 8.3%) | 480 (15.1%) | 592 (12.5%) |
| Vomiting | 23 (15.6%) | 25 ( 8.3%) | 477 (15.0%) | 565 (11.9%) |
| Pruritus | 3 ( 2.0%) | 23 ( 7.7%) | 406 (12.8%) | 647 (13.7%) |
| Rash | 5 ( 3.4%) | 30 (10.0%) | 358 (11.3%) | 515 (10.9%) |
| Headache | 7 ( 4.8%) | 15 ( 5.0%) | 352 (11.1%) | 498 (10.5%) |
| Urinary tract infection | 12 ( 8.2%) | 29 ( 9.7%) | 338 (10.6%) | 467 ( 9.9%) |
| Oedema peripheral | 6 ( 4.1%) | 25 ( 8.3%) | 332 (10.4%) | 414 ( 8.7%) |
| Pneumonia | 16 (10.9%) | 45 (15.0%) | 206 ( 6.5%) | 264 ( 5.6%) |
| Neutropenia | 19 (12.9%) | 2 ( 0.7%) | 36 ( 1.1%) | 73 ( 1.5%) |
| Neutrophil count decreased | 17 (11.6%) | 1 ( 0.3%) | 5 ( 0.2%) | 20 ( 0.4%) |

Atezo = Atezolizumab. Atezo Mono[1]: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + WO29074(IMMOTION150 Arm B prior to crossover); Atezo Mono [2]: Atezo Mono [1] + GO29431(IMPOWER110) + GO29527(IMPOWER010) + WO29636(IMVIGOR010) + WO39210(IMMOTION010 Arm A).
Investigator text for AEs encoded using MedDRA v25.1. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once at the highest NCI CTCAE grade. All treatment emergent AEs are included.

Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, WO29074:17OCT2016, WO29636:30NOV2019, WO39210:03MAY2022, MO29872:30APR2022.

**Table 41. Adverse Events by Preferred Term, with a Difference of at Least 5% between IPSOS Atezolizumab Arm and Chemotherapy Arm (Safety-Evaluable Population)**

| | IPSOS | | | |
|---|---|---|---|---|
| MedDRA Preferred Term | Chemotherapy (N=147) | Atezolizumab (N=300) | Atezo Mono[1] (N=3178) | Atezo Mono[2] (N=4739) |
| Nausea | 35 (23.8%) | 32 (10.7%) | 747 (23.5%) | 917 (19.4%) |
| Cough | 13 ( 8.8%) | 59 (19.7%) | 660 (20.8%) | 859 (18.1%) |
| Dyspnoea | 16 (10.9%) | 60 (20.0%) | 651 (20.5%) | 777 (16.4%) |
| Anaemia | 49 (33.3%) | 49 (16.3%) | 505 (15.9%) | 660 (13.9%) |
| Vomiting | 23 (15.6%) | 25 ( 8.3%) | 477 (15.0%) | 565 (11.9%) |
| Pruritus | 3 ( 2.0%) | 23 ( 7.7%) | 406 (12.8%) | 647 (13.7%) |
| Rash | 5 ( 3.4%) | 30 (10.0%) | 358 (11.3%) | 515 (10.9%) |
| Hypothyroidism | 0 | 19 ( 6.3%) | 137 ( 4.3%) | 309 ( 6.5%) |
| Neutropenia | 19 (12.9%) | 2 ( 0.7%) | 36 ( 1.1%) | 73 ( 1.5%) |
| White blood cell count decreased | 14 ( 9.5%) | 2 ( 0.7%) | 25 ( 0.8%) | 41 ( 0.9%) |
| Leukopenia | 11 ( 7.5%) | 4 ( 1.3%) | 9 ( 0.3%) | 24 ( 0.5%) |
| Neutrophil count decreased | 17 (11.6%) | 1 ( 0.3%) | 5 ( 0.2%) | 20 ( 0.4%) |

Atezo = Atezolizumab. Atezo Mono[1]: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + WO29074(IMMOTION150 Arm B prior to crossover); Atezo Mono [2]: Atezo Mono [1] + GO29431(IMPOWER110) + GO29527(IMPOWER010) + WO29636(IMVIGOR010) + WO39210(IMMOTION010 Arm A).
Investigator text for AEs encoded using MedDRA v25.1. All treatment emergent AEs are included. All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest NCI CTCAE grade.
Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, WO29074:17OCT2016, WO29636:30NOV2019, WO39210:03MAY2022, MO29872:30APR2022.

***Grade 3-4 AEs***

**Table 42. Summary of Grade 3-4 Adverse Events with a Difference of at Least 2% between IPSOS Atezolizumab Arm and Chemotherapy Arm by Preferred Term (Safety-Evaluable Population)**

| | IPSOS | | | |
|---|---|---|---|---|
| MedDRA Preferred Term | Chemotherapy (N=147) | Atezolizumab (N=300) | Atezo Mono[1] (N=3178) | Atezo Mono[2] (N=4739) |
| Anaemia | 7 (4.8%) | 8 (2.7%) | 160 ( 5.0%) | 178 ( 3.8%) |
| Pulmonary embolism | 5 (3.4%) | 4 (1.3%) | 59 ( 1.9%) | 74 ( 1.6%) |
| Hypertension | 2 (1.4%) | 14 (4.7%) | 42 ( 1.3%) | 61 ( 1.3%) |
| Pleural effusion | 2 (1.4%) | 11 (3.7%) | 37 ( 1.2%) | 38 ( 0.8%) |
| Neutropenia | 14 (9.5%) | 2 (0.7%) | 11 ( 0.3%) | 20 ( 0.4%) |
| Lymphopenia | 5 (3.4%) | 4 (1.3%) | 8 ( 0.3%) | 9 ( 0.2%) |
| White blood cell count decreased | 7 (4.8%) | 0 | 5 ( 0.2%) | 6 ( 0.1%) |
| Neutrophil count decreased | 11 (7.5%) | 0 | 2 (<0.1%) | 3 (<0.1%) |
| Leukopenia | 4 (2.7%) | 0 | 0 | 4 (<0.1%) |

Atezo = Atezolizumab. Atezo Mono[1]: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + WO29074(IMMOTION150 Arm B prior to crossover); Atezo Mono [2]: Atezo Mono [1] + GO29431(IMPOWER110) + GO29527(IMPOWER010) + WO29636(IMVIGOR010) + WO39210(IMMOTION010 Arm A).
Investigator text for AEs encoded using MedDRA v25.1. All treatment emergent AEs are included. All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest NCI CTCAE grade.
Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, WO29074:17OCT2016, WO29636:30NOV2019, WO39210:03MAY2022, MO29872:30APR2022.

**Table 43. Summary of Grade 3-4 Adverse Events with an Incidence Rate of at Least 5% in Any Treatment Group by System Organ Class and Preferred Term (Safety-Evaluable Population)**

| MedDRA System Organ Class<br>MedDRA Preferred Term | IPSOS<br>Chemotherapy<br>(N=147) | IPSOS<br>Atezolizumab<br>(N=300) | Atezo Mono[1]<br>(N=3178) | Atezo Mono[2]<br>(N=4739) |
|---|---|---|---|---|
| Blood and lymphatic system disorders | | | | |
| Anaemia | 7 (4.8%) | 8 (2.7%) | 160 ( 5.0%) | 178 ( 3.8%) |
| Neutropenia | 14 (9.5%) | 2 (0.7%) | 11 ( 0.3%) | 20 ( 0.4%) |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Dyspnoea | 7 (4.8%) | 15 (5.0%) | 117 ( 3.7%) | 122 ( 2.6%) |
| Infections and infestations | | | | |
| Pneumonia | 10 (6.8%) | 23 (7.7%) | 95 ( 3.0%) | 117 ( 2.5%) |
| Metabolism and nutrition disorders | | | | |
| Hyponatraemia | 5 (3.4%) | 16 (5.3%) | 98 ( 3.1%) | 111 ( 2.3%) |
| Investigations | | | | |
| Neutrophil count decreased | 11 (7.5%) | 0 | 2 (<0.1%) | 3 (<0.1%) |

Atezo = Atezolizumab. Atezo Mono[1]: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + WO29074(IMMOTION150 Arm B prior to crossover); Atezo Mono [2]: Atezo Mono [1] + GO29431(IMPOWER110) + GO29527(IMPOWER010) + WO29636(IMVIGOR010) + WO39210(IMMOTION010 Arm A).
Investigator text for AEs encoded using MedDRA v25.1. All treatment emergent AEs are included. All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest NCI CTCAE grade.
Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, WO29074:17OCT2016, WO29636:30NOV2019, WO39210:03MAY2022, MO29872:30APR2022.

***Adverse events of special interest (AESI)***

Three Grade 5 AESIs were reported in the atezolizumab arm (hepatitis, pneumonitis, and myasthenia gravis).

**Table 44. Summary of AESIs of Atezolizumab (Safety-Evaluable Population)**

| | IPSOS | | | |
|---|---|---|---|---|
| | Chemotherapy (N=147) | Atezolizumab (N=300) | Atezo Mono[1] (N=3178) | Atezo Mono[2] (N=4739) |
| Total number of patients with at least one AE of Special Interest | 27 (18.4%) | 103 (34.3%) | 1132 (35.6%) | 1912 (40.3%) |
| Total number of events | 37 | 207 | 2250 | 3809 |
| Total number of patients with at least one | | | | |
| Treatment-related AE of Special Interest | 19 (12.9%) | 87 (29.0%) | 805 (25.3%) | 1456 (30.7%) |
| Grade 3-4 AE of Special Interest | 3 ( 2.0%) | 20 ( 6.7%) | 268 ( 8.4%) | 400 ( 8.4%) |
| Treatment-related Grade 3-4 AE of Special Interest | 2 ( 1.4%) | 17 ( 5.7%) | 181 ( 5.7%) | 293 ( 6.2%) |
| Grade 5 AE of Special Interest | 0 | 3 ( 1.0%) | 7 ( 0.2%) | 9 ( 0.2%) |
| Treatment-related Grade 5 AE of Special Interest | 0 | 2 ( 0.7%) | 3 (<0.1%) | 5 ( 0.1%) |
| Serious AE of Special Interest | 2 ( 1.4%) | 20 ( 6.7%) | 175 ( 5.5%) | 254 ( 5.4%) |
| Treatment-related Serious AE of Special Interest | 1 ( 0.7%) | 17 ( 5.7%) | 137 ( 4.3%) | 209 ( 4.4%) |
| AE of Special Interest leading to any Study Treatment discontinuation | 3 ( 2.0%) | 17 ( 5.7%) | 62 ( 2.0%) | 173 ( 3.7%) |
| AE of Special Interest leading to any Dose modification or Study Treatment interruption | 5 ( 3.4%) | 21 ( 7.0%) | 221 ( 7.0%) | 389 ( 8.2%) |
| AE of Special Interest Requiring the Use of Systemic Corticosteroids | 7 ( 4.8%) | 34 (11.3%) | 251 ( 7.9%) | 399 ( 8.4%) |
| Identified Risks: patients with at least one | | | | |
| Immune-Mediated Rash | 11 ( 7.5%) | 45 (15.0%) | 613 (19.3%) | 949 (20.0%) |
| Immune-Mediated Hepatitis (Diagnosis and Lab Abnormalities) | 9 ( 6.1%) | 32 (10.7%) | 343 (10.8%) | 564 (11.9%) |

| | | | | |
|---|---|---|---|---|
| **Identified Risks: patients with at least one** | | | | |
| Immune-Mediated Hepatitis (Lab Abnormalities) | 8 ( 5.4%) | 27 ( 9.0%) | 315 ( 9.9%) | 523 (11.0%) |
| Immune-Mediated Hypothyroidism | 1 ( 0.7%) | 27 ( 9.0%) | 164 ( 5.2%) | 400 ( 8.4%) |
| Immune-Mediated Pneumonitis | 3 ( 2.0%) | 13 ( 4.3%) | 91 ( 2.9%) | 138 ( 2.9%) |
| Immune-Mediated Hyperthyroidism | 3 ( 2.0%) | 7 ( 2.3%) | 30 ( 0.9%) | 114 ( 2.4%) |
| Immune-Mediated Hepatitis (Diagnosis) | 1 ( 0.7%) | 7 ( 2.3%) | 62 ( 2.0%) | 81 ( 1.7%) |
| Infusion-Related Reactions | 0 | 2 ( 0.7%) | 32 ( 1.0%) | 82 ( 1.7%) |
| Immune-Mediated Colitis | 0 | 3 ( 1.0%) | 34 ( 1.1%) | 59 ( 1.2%) |
| Immune-Mediated Pericardial Disorders | 0 | 1 ( 0.3%) | 45 ( 1.4%) | 48 ( 1.0%) |
| Immune-Mediated Pancreatitis | 0 | 3 ( 1.0%) | 18 ( 0.6%) | 37 ( 0.8%) |
| Immune-Mediated Severe Cutaneous Reactions | 0 | 0 | 22 ( 0.7%) | 30 ( 0.6%) |
| Immune-Mediated Myositis (Myositis+Rhabdomyolysis) | 0 | 0 | 13 ( 0.4%) | 32 ( 0.7%) |
| Immune-Mediated Diabetes Mellitus | 0 | 4 ( 1.3%) | 10 ( 0.3%) | 26 ( 0.5%) |
| Immune-Mediated Adrenal Insufficiency | 0 | 1 ( 0.3%) | 12 ( 0.4%) | 24 ( 0.5%) |
| Immune-Mediated Meningoencephalitis | 0 | 0 | 14 ( 0.4%) | 22 ( 0.5%) |
| Immune-Mediated Myositis | 0 | 0 | 8 ( 0.3%) | 25 ( 0.5%) |
| Immune-Mediated Meningitis | 0 | 0 | 12 ( 0.4%) | 18 ( 0.4%) |
| Immune-Mediated Nephritis | 1 ( 0.7%) | 0 | 3 (<0.1%) | 11 ( 0.2%) |
| Rhabdomyolysis | 0 | 0 | 5 ( 0.2%) | 7 ( 0.1%) |
| Immune-Mediated Guillain-Barre Syndrome | 0 | 0 | 5 ( 0.2%) | 6 ( 0.1%) |
| Immune-Mediated Hypophysitis | 0 | 0 | 2 (<0.1%) | 5 ( 0.1%) |
| Immune-Mediated Encephalitis | 0 | 0 | 2 (<0.1%) | 4 (<0.1%) |
| Immune-Mediated Myocarditis | 0 | 1 ( 0.3%) | 0 | 4 (<0.1%) |
| Immune-Mediated Myasthenia Gravis | 0 | 1 ( 0.3%) | 1 (<0.1%) | 1 (<0.1%) |
| **Identified Risks: patients with at least one** | | | | |
| Haemophagocytic Lymphohistiocytosis | 0 | 0 | 1 (<0.1%) | 2 (<0.1%) |
| Immune-Mediated Myelitis | 0 | 0 | 1 (<0.1%) | 1 (<0.1%) |
| Immune-Mediated Facial Paresis | 0 | 0 | 1 (<0.1%) | 1 (<0.1%) |
| **Potential Risks: patients with at least one** | | | | |
| Immune-Mediated Ocular Inflammatory Toxicity | 0 | 0 | 16 ( 0.5%) | 22 ( 0.5%) |
| Immune-Mediated Vasculitis | 0 | 0 | 7 ( 0.2%) | 14 ( 0.3%) |
| Autoimmune Hemolytic Anemia | 0 | 0 | 4 ( 0.1%) | 6 ( 0.1%) |

Atezo = Atezolizumab. Atezo Mono[1]: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + WO29074(IMMOTION150 Arm B prior to crossover); Atezo Mono [2]: Atezo Mono [1] + GO29431(IMPOWER110) + GO29527(IMPOWER010) + WO29636(IMVIGOR010) + WO39210(IMMOTION010 Arm A).
Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v25.1. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. All treatment emergent AEs are included. For the counts in the rows by grade, the patients are counted once at the highest grade.

Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, WO29074:17OCT2016, WO29636:30NOV2019, WO39210:03MAY2022, MO29872:30APR2022.

**Table 45. Adverse Events of Special Interest for Atezolizumab by Medical Concept (Atezo Mono Pooled) (N=5039)**

| Medical concept | Atezo Mono Pooled (N=5039) |
|---|---|
| Immune-Mediated Rash | 994 (19.7%) |
| Immune-Mediated Hepatitis (Diagnosis and Lab Abnormalities) | 596 (11.8%) |
| Immune-Mediated Hepatitis (Lab Abnormalities) | 550 (10.9%) |
| Immune-Mediated Hypothyroidism | 427 ( 8.5%) |
| Immune-Mediated Pneumonitis | 151 ( 3.0%) |
| Immune-Mediated Hyperthyroidism | 121 ( 2.4%) |
| Immune-Mediated Hepatitis (Diagnosis) | 88 ( 1.7%) |
| Infusion-Related Reactions | 84 ( 1.7%) |
| Immune-Mediated Colitis | 62 ( 1.2%) |
| Immune-Mediated Pericardial Disorders | 49 ( 1.0%) |
| Immune-Mediated Pancreatitis | 40 ( 0.8%) |
| Immune-Mediated Myositis (Myositis+Rhabdomyolysis) | 32 ( 0.6%) |
| Immune-Mediated Diabetes Mellitus | 30 ( 0.6%) |
| Immune-Mediated Severe Cutaneous Reactions | 30 ( 0.6%) |
| Immune-Mediated Adrenal Insufficiency | 25 ( 0.5%) |
| Immune-Mediated Myositis | 25 ( 0.5%) |
| Immune-Mediated Meningoencephalitis | 22 ( 0.4%) |
| Immune-Mediated Ocular Inflammatory Toxicity | 22 ( 0.4%) |
| Immune-Mediated Meningitis | 18 ( 0.4%) |
| Immune-Mediated Vasculitis | 14 ( 0.3%) |
| Immune-Mediated Nephritis | 11 ( 0.2%) |
| Rhabdomyolysis | 7 ( 0.1%) |
| Autoimmune Hemolytic Anemia | 6 ( 0.1%) |
| Immune-Mediated Guillain-Barre Syndrome | 6 ( 0.1%) |
| Immune-Mediated Hypophysitis | 5 (<0.1%) |
| Immune-Mediated Myocarditis | 5 (<0.1%) |
| Immune-Mediated Encephalitis | 4 (<0.1%) |
| Haemophagocytic Lymphohistiocytosis | 2 (<0.1%) |
| Immune-Mediated Myasthenia Gravis | 2 (<0.1%) |
| Immune-Mediated Facial Paresis | 1 (<0.1%) |
| Immune-Mediated Myelitis | 1 (<0.1%) |

Atezo = Atezolizumab. Atezo Mono Pooled: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS) + WO29074(IMMOTION150 Arm B prior to crossover) + WO29636(IMVIGOR010) + WO39210(IMMOTION010 Arm A).
Investigator text for AEs encoded using MedDRA v25.1. Percentages are based on N in the column headings. For frequency counts by medical concept, multiple occurrences of the same medical concept in an individual are counted only once. All treatment emergent AEs are included.
Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022, WO29074:17OCT2016, WO29636:30NOV2019, WO39210:03MAY2022.

## *Serious adverse event/deaths/other significant events*

### *Serious adverse events*

**Table 46. Serious Adverse Events with an Incidence Rate of at Least 2% in Any Treatment Arm by System Organ Class and Preferred Term (Safety-Evaluable Population)**

| MedDRA System Organ Class<br>MedDRA Preferred Term | IPSOS<br>Chemotherapy (N=147) | IPSOS<br>Atezolizumab (N=300) | Atezo Mono[1] (N=3178) | Atezo Mono[2] (N=4739) |
|---|---|---|---|---|
| Infections and infestations | | | | |
| Pneumonia | 11 (7.5%) | 33 (11.0%) | 112 (3.5%) | 141 (3.0%) |
| Urinary tract infection | 0 | 1 ( 0.3%) | 61 (1.9%) | 98 (2.1%) |
| Sepsis | 4 (2.7%) | 0 | 41 (1.3%) | 50 (1.1%) |
| Lower respiratory tract infection | 4 (2.7%) | 5 ( 1.7%) | 15 (0.5%) | 18 (0.4%) |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Dyspnoea | 2 (1.4%) | 6 ( 2.0%) | 89 (2.8%) | 91 (1.9%) |
| Pulmonary embolism | 3 (2.0%) | 3 ( 1.0%) | 42 (1.3%) | 52 (1.1%) |
| Pleural effusion | 2 (1.4%) | 9 ( 3.0%) | 40 (1.3%) | 42 (0.9%) |
| Pneumonitis | 2 (1.4%) | 8 ( 2.7%) | 35 (1.1%) | 48 (1.0%) |
| Chronic obstructive pulmonary disease | 2 (1.4%) | 7 ( 2.3%) | 10 (0.3%) | 19 (0.4%) |
| General disorders and administration site conditions | | | | |
| Pyrexia | 1 (0.7%) | 3 ( 1.0%) | 79 (2.5%) | 103 (2.2%) |
| Death | 2 (1.4%) | 7 ( 2.3%) | 19 (0.6%) | 24 (0.5%) |
| Blood and lymphatic system disorders | | | | |
| Febrile neutropenia | 3 (2.0%) | 0 | 7 (0.2%) | 7 (0.1%) |

Atezo = Atezolizumab. Atezo Mono[1]: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + WO29074(IMMOTION150 Arm B prior to crossover); Atezo Mono [2]: Atezo Mono [1] + GO29431(IMPOWER110) + GO29527(IMPOWER010) + WO29636(IMVIGOR010) + WO39210(IMMOTION010 Arm A).
Investigator text for AEs encoded using MedDRA v25.1. All treatment emergent AEs are included. All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest NCI CTCAE grade.
Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, WO29074:17OCT2016, WO29636:30NOV2019, WO39210:03MAY2022, MO29872:30APR2022.

### *Deaths*

**Table 47. Summary of Deaths and Primary Cause of Death**

| | IPSOS<br>Chemotherapy (N=147) | IPSOS<br>Atezolizumab (N=300) | Atezo Mono[1] (N=3178) | Atezo Mono[2] (N=4739) |
|---|---|---|---|---|
| Primary cause of death | | | | |
| n | 129 (87.8%) | 248 (82.7%) | 1898 (59.7%) | 2345 (49.5%) |
| ADVERSE EVENT | 13 ( 8.8%) | 35 (11.7%) | 120 ( 3.8%) | 148 ( 3.1%) |
| PROGRESSIVE DISEASE | 103 (70.1%) | 179 (59.7%) | 1476 (46.4%) | 1729 (36.5%) |
| RECURRENCE OF DISEASE | 0 | 0 | 0 | 88 ( 1.9%) |
| OTHER | 13 ( 8.8%) | 34 (11.3%) | 302 ( 9.5%) | 380 ( 8.0%) |

Atezo = Atezolizumab. Atezo Mono[1]: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + WO29074(IMMOTION150 Arm B prior to crossover); Atezo Mono [2]: Atezo Mono [1] + GO29431(IMPOWER110) + GO29527(IMPOWER010) + WO29636(IMVIGOR010) + WO39210(IMMOTION010 Arm A).
Other cause of death is displayed verbatim. Death from public record is classified as Other in MO29872(IPSOS). Grade 5 Adverse Events of Disease Progression Coded as DISEASE RECURRENCE/PROGRESSIVE. A patient in GO29293 had missing data for Other cause of death.

Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, WO29074:17OCT2016, WO29636:30NOV2019, WO39210:03MAY2022, MO29872:30APR2022.

**Table 48. Summary of Grade 5 Adverse Events (Safety-Evaluable Population)**

| MedDRA System Organ Class<br>MedDRA Preferred Term | Atezolizumab (N=300)<br>n (%) | Chemotherapy (N=147)<br>n (%) |
|---|---|---|
| Any Adverse Events | 35 ( 11.7) | 13 ( 8.8) |
| Infections and infestations | | |
| - Overall - | 14 ( 4.7) | 8 ( 5.4) |
| Pneumonia | 8 ( 2.7) | 2 ( 1.4) |
| Sepsis | 0 | 4 ( 2.7) |
| Lower respiratory tract infection | 1 ( 0.3) | 2 ( 1.4) |
| Septic shock | 2 ( 0.7) | 0 |
| Covid-19 | 1 ( 0.3) | 0 |
| Infective exacerbation of chronic obstructive airways disease | 1 ( 0.3) | 0 |
| Pneumonia aspiration | 1 ( 0.3) | 0 |
| General disorders and administration site conditions | | |
| - Overall - | 10 ( 3.3) | 2 ( 1.4) |
| Death | 7 ( 2.3) | 2 ( 1.4) |
| Sudden cardiac death | 2 ( 0.7) | 0 |
| General physical health deterioration | 1 ( 0.3) | 0 |
| Respiratory, thoracic and mediastinal disorders | | |
| - Overall - | 5 ( 1.7) | 1 ( 0.7) |
| Chronic obstructive pulmonary disease | 1 ( 0.3) | 0 |
| Hypoxia | 0 | 1 ( 0.7) |
| Pneumonitis | 1 ( 0.3) | 0 |
| Pneumothorax | 1 ( 0.3) | 0 |
| Respiratory arrest | 1 ( 0.3) | 0 |
| Respiratory failure | 1 ( 0.3) | 0 |
| Cardiac disorders | | |
| - Overall - | 4 ( 1.3) | 0 |
| Acute left ventricular failure | 1 ( 0.3) | 0 |
| Acute myocardial infarction | 1 ( 0.3) | 0 |
| Cardiac arrest | 1 ( 0.3) | 0 |
| Cardiac disorder | 1 ( 0.3) | 0 |
| Nervous system disorders | | |
| - Overall - | 1 ( 0.3) | 1 ( 0.7) |
| Cerebrovascular accident | 0 | 1 ( 0.7) |
| Myasthenia gravis | 1 ( 0.3) | 0 |
| Blood and lymphatic system disorders | | |
| - Overall - | 0 | 1 ( 0.7) |
| Febrile neutropenia | 0 | 1 ( 0.7) |
| Hepatobiliary disorders | | |
| - Overall - | 1 ( 0.3) | 0 |
| Immune-mediated hepatitis | 1 ( 0.3) | 0 |

Investigator text for AEs encoded using MedDRA version 25.0. All counts represent patients. Multiple occurrences of the same AE in one individual are counted once.
AEs started on or after first dose of study drug are included.

***Deaths from Other Causes***

Deaths due to causes other than progressive disease (PD) or which occurred after the AE reporting period and were not considered related to previous study treatment were reported as "Deaths due to other causes".

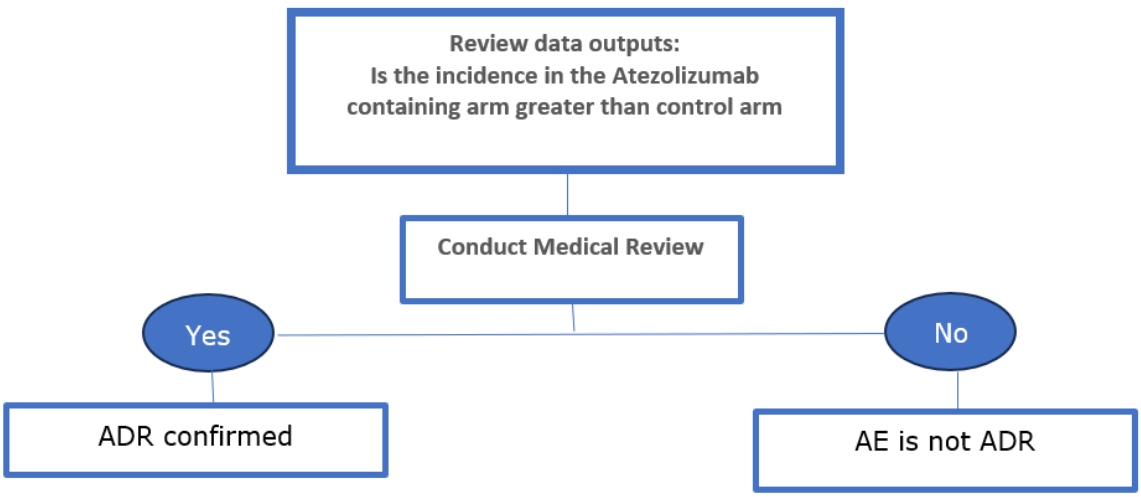
Thirty-four deaths in the Atezolizumab arm and 13 deaths in the Chemotherapy arm were reported under the category of 'other'. The 'other' causes of death were: a) deaths that occurred after the end of the AE reporting period and were assessed by the investigator as unrelated to study treatment and not due to disease progression (Atezolizumab 21, 8.5% vs. Chemotherapy: 11, 8.5%), and b) post-study reporting of death, i.e., reports of death identified through public records for patients who were discontinued from the study prematurely prior to their death and where the cause of death was not collected (Atezolizumab 13, 5.2% vs. Chemotherapy: 2, 1.6%). For the former, investigators provided the condition that resulted in the patient's death, if known, as free text in the database. The majority of these conditions reported by investigators were single-event occurrences and did not indicate a clinically meaningful pattern. The most common ($n \geq 2$) causes of death that occurred after the AE reporting period were 'unknown' (Atezolizumab arm: $n=8$ vs. Chemotherapy arm: $n=5$), 'unexplained death' (Atezolizumab arm: $n=2$), heart failure (Atezolizumab arm: $n=2$), septic shock (Chemotherapy: $n=2$) and Covid/ Covid-19 (Chemotherapy arm: $n=2$).

## *Adverse drug reactions*

At the time of the primary analysis of OS (CCOD 30 April 2022) for IPSOS, no new adverse drug reactions (ADRs) with atezolizumab monotherapy treatment were identified.

The methodology used to identify any new ADRs in IPSOS is outlined in Figure 12. The exposure-adjusted analysis for certain AE preferred terms (PTs) is also described below.

**Figure 12. Methodology to Identify ADRs to Atezolizumab in IPSOS**




The pooled atezolizumab monotherapy population in the Tecentriq SmPC has been updated with IPSOS data, corresponding to a pool of 5039 patients (Atezo Mono 2 + IPSOS). The previously identified

ADRs (including the ADR table) associated with atezolizumab monotherapy were updated if they met any of the following parameters:

- For all events, if the frequency category for the ADR escalated (e.g., from common to very common), or de-escalated (e.g., from very common to common). No ADRs met this criterion of a frequency categorisation change.
- Other factors considered: Time to onset, duration, and severity were also reviewed for inclusion of the events even if the category remained unchanged (i.e., the criteria from the bullet above was not met) and the information was updated accordingly when considered representative of new safety information requiring communication to health care providers and patients. The SmPC section, *Description of Selected Adverse Reactions,* was updated accordingly.

**Table 49. Adverse Drug Reactions by Medical Concept (Atezo Mono Pooled) (N=5039)**

| **Medical concept** | **Atezo Mono Pooled (N=5039)** |
|---|---|
| Fatigue | 1474 (29.3%) |
| Decreased Appetite | 1013 (20.1%) |
| Rash | 994 (19.7%) |
| Nausea | 949 (18.8%) |
| Cough | 918 (18.2%) |
| Diarrhoea | 910 (18.1%) |
| Pyrexia | 900 (17.9%) |
| Dyspnoea | 837 (16.6%) |
| Arthralgia | 814 (16.2%) |
| Pruritus | 670 (13.3%) |
| Asthenia | 655 (13.0%) |
| Back Pain | 617 (12.2%) |
| Vomiting | 590 (11.7%) |
| Urinary Tract Infection | 555 (11.0%) |
| Headache | 513 (10.2%) |
| Musculoskeletal Pain | 448 ( 8.9%) |
| Nasopharyngitis | 442 ( 8.8%) |
| Hypothyroidism | 427 ( 8.5%) |
| Abdominal Pain | 357 ( 7.1%) |
| AST increased | 314 ( 6.2%) |
| ALT increased | 313 ( 6.2%) |
| Blood creatinine increased | 296 ( 5.9%) |
| Chills | 266 ( 5.3%) |
| Dry Skin | 263 ( 5.2%) |
| Influenza Like Illness | 257 ( 5.1%) |
| Dry Mouth | 228 ( 4.5%) |
| Hyponatraemia | 228 ( 4.5%) |
| Hypokalaemia | 191 ( 3.8%) |
| Oropharyngeal Pain | 188 ( 3.7%) |
| Hyperglycaemia | 177 ( 3.5%) |
| Thrombocytopenia | 172 ( 3.4%) |
| Pneumonitis | 151 ( 3.0%) |

| | |
|---|---|
| Nasal Congestion | 135 ( 2.7%) |
| Hypotension | 129 ( 2.6%) |
| Hyperthyroidism | 121 ( 2.4%) |
| Infusion Related Reaction (includes Hypersensitivity+Anaphylatic Reactions) | 109 ( 2.2%) |
| Dysphagia | 102 ( 2.0%) |
| Hepatitis (Diagnosis) | 88 ( 1.7%) |
| Hypoxia | 85 ( 1.7%) |
| Colitis | 62 ( 1.2%) |
| Pericardial Disorders | 49 ( 1.0%) |
| Pancreatitis | 40 ( 0.8%) |
| Psoriasis | 35 ( 0.7%) |
| Myositis | 32 ( 0.6%) |
| Diabetes Mellitus | 30 ( 0.6%) |
| Severe Cutaneous Reactions | 30 ( 0.6%) |
| Adrenal Insufficiency | 25 ( 0.5%) |
| Meningoencephalitis | 22 ( 0.4%) |
| Nephritis | 11 ( 0.2%) |
| Guillain-Barre Syndrome | 6 ( 0.1%) |
| Hypophysitis | 5 (<0.1%) |
| Myocarditis | 5 (<0.1%) |
| Uveitis | 3 (<0.1%) |
| Haemophagocytic Lymphohistiocytosis | 2 (<0.1%) |
| Myasthenic Syndrome | 2 (<0.1%) |
| Facial Paresis | 1 (<0.1%) |
| Myelitis | 1 (<0.1%) |
| Pemphigoid | 1 (<0.1%) |

Atezo = Atezolizumab. Atezo Mono Pooled: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS) + WO29074(IMMOTION150 Arm B prior to crossover) + WO29636(IMVIGOR010) + WO39210(IMMOTION010 Arm A).
Investigator text for AEs encoded using MedDRA v25.1. Percentages are based on N in the column headings. For frequency counts by medical concept, multiple occurrences of the same medical concept in an individual are counted only once. All treatment emergent AEs are included.
Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022, WO29074:17OCT2016, WO29636:30NOV2019, WO39210:03MAY2022.

## *Laboratory findings*

### *All laboratory safety parameters*

The frequency of clinically relevant shifts in hematology parameter abnormalities was: low neutrophils (0.9% atezolizumab vs. 19.8% chemotherapy), low white blood cells (1.1% vs. 14.1%) and low lymphocytes (11.1% vs. 18.5%) in the chemotherapy and in the atezolizumab arm, respectively.

Among biochemistry laboratory parameter abnormalities, the frequency of clinically relevant shifts was similar between the arms except for a higher (≥2%) incidence of low sodium levels (13.5% vs. 5.3%) and high potassium levels (2.6% vs. 0%) in the atezolizumab arm compared with the chemotherapy arm (data not shown).

### *Thyroid function*

Blood samples for thyroid function assessment were collected routinely (every 4 cycles).

Overall, the majority of patients with baseline and non-missing post-baseline thyroid stimulating hormone (TSH) measurements maintained normal TSH levels during the study. Treatment-emergent TSH laboratory abnormalities (defined as normal at baseline and abnormal at post-baseline) were reported in a similar percentage of patients in both treatment arms (TSH low: 7.3% atezolizumab vs. 4.1% chemotherapy, TSH high: 7.0% vs. 6.1%.

***Hy's Law***

Two patients in the atezolizumab arm fulfilled the laboratory criteria suggestive for Hy's law with an elevated ALT or AST>3×baseline value in combination with an elevated total bilirubin [ >2×ULN]). The first patient experienced elevated liver function tests at the onset of immune-mediated hepatitis with positive hepatitis B core antibody detection, which resulted in death. The second patient experienced elevated liver function tests at the onset of biliary cholangitis. The patient's symptoms were resolved, and liver function tests parameters returned to normal following treatment. This patient also experienced hyperbilirubinaemia approximately 15 months later; this event did not qualify for instances of elevation in transaminase with simultaneous elevation in bilirubin and therefore did not meet the definition of Hy's law per protocol.

***Electrocardiography***

At baseline, 8 patients (2.7%) in the atezolizumab arm and 7 patients (4.8%) in the chemotherapy arm had a clinically significant electrocardiogram (ECG) abnormality.

Post-baseline, 28 patients (9.3%) on atezolizumab and 5 patients (3.4%) on chemotherapy had clinically significant ECG abnormalities. Of the 28 patients in the atezolizumab arm, 15 patients experienced cardiac AEs associated with the clinically significant ECG abnormalities. One of the 15 patients experienced a Grade 5 cardiac AE (acute left ventricular failure), which was assessed as related to study treatment.

Of the remaining 14 patients, 11 experienced Grade 1 or Grade 2 cardiac AEs; in 4 patients the cardiac AEs were considered related to study treatment (Grade 1 events of cardiac failure, ventricular extrasystoles, atrioventricular block first degree, and conduction disorder). Three patients experienced a Grade 3 cardiac AE, all of which were events of atrial fibrillation and were considered unrelated to study treatment by the investigator.

At the time of the CCOD, the cardiac events were resolved in 7/14 patients.

## *Safety in special populations*

### *Age*

### Table 50. Overview of Safety by Age (Safety-Evaluable Population)

Overall Summary of Adverse Events, by Age Group for Chemotherapy
Safety-Evaluable Population

| | Chemotherapy (N=147) | | | | |
|---|---|---|---|---|---|
| | < 65 (N=18) | >= 65 (N=129) | 65-74 (N=50) | 75-84 (N=70) | >= 85 (N=9) |
| Total number of patients with at least one AE | 15 ( 83.3) | 128 ( 99.2) | 50 (100.0) | 69 ( 98.6) | 9 (100.0) |
| Total number of events | 166 | 920 | 392 | 489 | 39 |
| Total number of patients with at least one | | | | | |
| Treatment-related AE | 11 ( 61.1) | 107 ( 82.9) | 42 ( 84.0) | 57 ( 81.4) | 8 ( 88.9) |
| Grade 3-4 AE | 7 ( 38.9) | 64 ( 49.6) | 28 ( 56.0) | 33 ( 47.1) | 3 ( 33.3) |
| Treatment-related Grade 3-4 AE | 6 ( 33.3) | 43 ( 33.3) | 21 ( 42.0) | 20 ( 28.6) | 2 ( 22.2) |
| Grade 5 AE | 1 ( 5.6) | 12 ( 9.3) | 6 ( 12.0) | 5 ( 7.1) | 1 ( 11.1) |
| Treatment-related Grade 5 AE | 0 | 4 ( 3.1) | 2 ( 4.0) | 2 ( 2.9) | 0 |
| Serious AE | 2 ( 11.1) | 51 ( 39.5) | 21 ( 42.0) | 28 ( 40.0) | 2 ( 22.2) |
| Treatment-related serious AE | 1 ( 5.6) | 22 ( 17.1) | 12 ( 24.0) | 9 ( 12.9) | 1 ( 11.1) |
| AE leading to any Study Treatment discontinuation | 2 ( 11.1) | 18 ( 14.0) | 4 ( 8.0) | 12 ( 17.1) | 2 ( 22.2) |
| AE leading to any Dose modification or Study Treatment interruption | 9 ( 50.0) | 62 ( 48.1) | 31 ( 62.0) | 28 ( 40.0) | 3 ( 33.3) |

Overall Summary of Adverse Events, by Age Group for Atezolizumab
Safety-Evaluable Population

| | Atezolizumab (N=300) | | | | |
|---|---|---|---|---|---|
| | < 65 (N=46) | >= 65 (N=254) | 65-74 (N=100) | 75-84 (N=139) | >= 85 (N=15) |
| Total number of patients with at least one AE | 39 ( 84.8) | 236 ( 92.9) | 93 ( 93.0) | 128 ( 92.1) | 15 (100.0) |
| Total number of events | 229 | 2123 | 793 | 1189 | 141 |
| Total number of patients with at least one | | | | | |
| Treatment-related AE | 18 ( 39.1) | 153 ( 60.2) | 61 ( 61.0) | 84 ( 60.4) | 8 ( 53.3) |
| Grade 3-4 AE | 18 ( 39.1) | 118 ( 46.5) | 45 ( 45.0) | 65 ( 46.8) | 8 ( 53.3) |
| Treatment-related Grade 3-4 AE | 9 ( 19.6) | 40 ( 15.7) | 17 ( 17.0) | 21 ( 15.1) | 2 ( 13.3) |
| Grade 5 AE | 4 ( 8.7) | 31 ( 12.2) | 13 ( 13.0) | 17 ( 12.2) | 1 ( 6.7) |
| Treatment-related Grade 5 AE | 0 | 3 ( 1.2) | 1 ( 1.0) | 2 ( 1.4) | 0 |
| Serious AE | 16 ( 34.8) | 130 ( 51.2) | 54 ( 54.0) | 69 ( 49.6) | 7 ( 46.7) |
| Treatment-related serious AE | 8 ( 17.4) | 27 ( 10.6) | 12 ( 12.0) | 13 ( 9.4) | 2 ( 13.3) |
| AE leading to any Study Treatment discontinuation | 6 ( 13.0) | 33 ( 13.0) | 8 ( 8.0) | 22 ( 15.8) | 3 ( 20.0) |
| AE leading to any Dose modification or Study Treatment interruption | 11 ( 23.9) | 85 ( 33.5) | 28 ( 28.0) | 52 ( 37.4) | 5 ( 33.3) |

AEs started on or after first dose of study drug are included.

***Gender***

**Table 51. Overview of Safety by Gender (Safety-Evaluable Population)**

Overall Summary of Adverse Events, by Sex
Safety-Evaluable Population

| | Chemotherapy (N=147) | | Atezolizumab (N=300) | |
|---|---|---|---|---|
| | Male (N=105) | Female (N=42) | Male (N=219) | Female (N=81) |
| Total number of patients with at least one AE | 103 ( 98.1) | 40 ( 95.2) | 198 ( 90.4) | 77 ( 95.1) |
| Total number of events | 725 | 361 | 1701 | 651 |
| Total number of patients with at least one | | | | |
| Treatment-related AE | 86 ( 81.9) | 32 ( 76.2) | 128 ( 58.4) | 43 ( 53.1) |
| Grade 3-4 AE | 47 ( 44.8) | 24 ( 57.1) | 93 ( 42.5) | 43 ( 53.1) |
| Treatment-related Grade 3-4 AE | 36 ( 34.3) | 13 ( 31.0) | 38 ( 17.4) | 11 ( 13.6) |
| Grade 5 AE | 9 ( 8.6) | 4 ( 9.5) | 25 ( 11.4) | 10 ( 12.3) |
| Treatment-related Grade 5 AE | 2 ( 1.9) | 2 ( 4.8) | 2 ( 0.9) | 1 ( 1.2) |
| Serious AE | 38 ( 36.2) | 15 ( 35.7) | 101 ( 46.1) | 45 ( 55.6) |
| Treatment-related serious AE | 17 ( 16.2) | 6 ( 14.3) | 27 ( 12.3) | 8 ( 9.9) |
| AE leading to any Study Treatment discontinuation | 15 ( 14.3) | 5 ( 11.9) | 24 ( 11.0) | 15 ( 18.5) |
| AE leading to any Dose modification or Study Treatment interruption | 50 ( 47.6) | 21 ( 50.0) | 65 ( 29.7) | 31 ( 38.3) |

AEs started on or after first dose of study drug are included.

***Race***

**Table 52. Overview of Safety by Race (Safety-Evaluable Population)**

Overall Summary of Adverse Events, by Race for Chemotherapy
Safety-Evaluable Population

| | Chemotherapy (N=147) | | | | | |
|---|---|---|---|---|---|---|
| | American Indian or Alaska Native (N=9) | Asian (N=34) | Black or African American (N=1) | White (N=95) | Multiple (N=6) | Unknown (N=2) |
| Total number of patients with at least one AE | 8 ( 88.9) | 34 (100.0) | 1 (100.0) | 92 ( 96.8) | 6 (100.0) | 2 (100.0) |
| Total number of events | 101 | 258 | 14 | 586 | 110 | 17 |
| Total number of patients with at least one | | | | | | |
| Treatment-related AE | 8 ( 88.9) | 28 ( 82.4) | 1 (100.0) | 75 ( 78.9) | 4 ( 66.7) | 2 (100.0) |
| Grade 3-4 AE | 4 ( 44.4) | 15 ( 44.1) | 1 (100.0) | 48 ( 50.5) | 2 ( 33.3) | 1 ( 50.0) |
| Treatment-related Grade 3-4 AE | 4 ( 44.4) | 15 ( 44.1) | 1 (100.0) | 28 ( 29.5) | 1 ( 16.7) | 0 |
| Grade 5 AE | 0 | 4 ( 11.8) | 0 | 7 ( 7.4) | 1 ( 16.7) | 1 ( 50.0) |
| Treatment-related Grade 5 AE | 0 | 0 | 0 | 3 ( 3.2) | 1 ( 16.7) | 0 |
| Serious AE | 0 | 13 ( 38.2) | 0 | 35 ( 36.8) | 3 ( 50.0) | 2 (100.0) |
| Treatment-related serious AE | 0 | 9 ( 26.5) | 0 | 12 ( 12.6) | 2 ( 33.3) | 0 |
| AE leading to any Study Treatment discontinuation | 0 | 5 ( 14.7) | 0 | 15 ( 15.8) | 0 | 0 |
| AE leading to any Dose modification or Study Treatment interruption | 2 ( 22.2) | 19 ( 55.9) | 0 | 45 ( 47.4) | 4 ( 66.7) | 1 ( 50.0) |

AEs started on or after first dose of study drug are included.

Overall Summary of Adverse Events, by Race for Atezolizumab
Safety-Evaluable Population

| | Atezolizumab (N=300) | | | | | |
|---|---|---|---|---|---|---|
| | American Indian or Alaska Native (N=12) | Asian (N=74) | Black or African American (N=2) | White (N=202) | Multiple (N=6) | Unknown (N=4) |
| Total number of patients with at least one AE | 6 ( 50.0) | 71 ( 95.9) | 2 (100.0) | 186 ( 92.1) | 6 (100.0) | 4 (100.0) |
| Total number of events | 63 | 572 | 37 | 1536 | 105 | 39 |
| Total number of patients with at least one | | | | | | |
| Treatment-related AE | 5 ( 41.7) | 44 ( 59.5) | 1 ( 50.0) | 113 ( 55.9) | 4 ( 66.7) | 4 (100.0) |
| Grade 3-4 AE | 2 ( 16.7) | 37 ( 50.0) | 2 (100.0) | 90 ( 44.6) | 3 ( 50.0) | 2 ( 50.0) |
| Treatment-related Grade 3-4 AE | 0 | 16 ( 21.6) | 0 | 29 ( 14.4) | 1 ( 16.7) | 3 ( 75.0) |
| Grade 5 AE | 0 | 5 ( 6.8) | 0 | 27 ( 13.4) | 2 ( 33.3) | 1 ( 25.0) |
| Treatment-related Grade 5 AE | 0 | 1 ( 1.4) | 0 | 2 ( 1.0) | 0 | 0 |
| Serious AE | 2 ( 16.7) | 36 ( 48.6) | 1 ( 50.0) | 101 ( 50.0) | 3 ( 50.0) | 3 ( 75.0) |
| Treatment-related serious AE | 1 ( 8.3) | 17 ( 23.0) | 0 | 15 ( 7.4) | 1 ( 16.7) | 1 ( 25.0) |
| AE leading to any Study Treatment discontinuation | 0 | 8 ( 10.8) | 1 ( 50.0) | 27 ( 13.4) | 0 | 3 ( 75.0) |
| AE leading to any Dose modification or Study Treatment interruption | 3 ( 25.0) | 19 ( 25.7) | 0 | 70 ( 34.7) | 1 ( 16.7) | 3 ( 75.0) |

AEs started on or after first dose of study drug are included.

### *Hepatic Impairment*

Hepatic impairment was defined using National Cancer Institute Organ Dysfunction Working Group criteria.

**Table 53. Overview of Safety by Hepatic Impairment (Safety-Evaluable Population)**

Overall Summary of Adverse Events, by Hepatic Impairment
Safety-Evaluable Population

| | Chemotherapy (N=147) | | | Atezolizumab (N=300) | | |
|---|---|---|---|---|---|---|
| | Normal (N=132) | Mild (N=13) | Moderate (N=2) | Normal (N=273) | Mild (N=24) | Moderate (N=2) |
| Total number of patients with at least one AE | 129 ( 97.7) | 12 ( 92.3) | 2 (100.0) | 251 ( 91.9) | 21 ( 87.5) | 2 (100.0) |
| Total number of events | 984 | 86 | 16 | 2180 | 150 | 11 |
| Total number of patients with at least one | | | | | | |
| Treatment-related AE | 108 ( 81.8) | 8 ( 61.5) | 2 (100.0) | 158 ( 57.9) | 10 ( 41.7) | 2 (100.0) |
| Grade 3-4 AE | 66 ( 50.0) | 5 ( 38.5) | 0 | 123 ( 45.1) | 11 ( 45.8) | 1 ( 50.0) |
| Treatment-related Grade 3-4 AE | 46 ( 34.8) | 3 ( 23.1) | 0 | 43 ( 15.8) | 4 ( 16.7) | 1 ( 50.0) |
| Grade 5 AE | 13 ( 9.8) | 0 | 0 | 32 ( 11.7) | 3 ( 12.5) | 0 |
| Treatment-related Grade 5 AE | 4 ( 3.0) | 0 | 0 | 2 ( 0.7) | 1 ( 4.2) | 0 |
| Serious AE | 49 ( 37.1) | 3 ( 23.1) | 1 ( 50.0) | 135 ( 49.5) | 9 ( 37.5) | 1 ( 50.0) |
| Treatment-related serious AE | 22 ( 16.7) | 1 ( 7.7) | 0 | 31 ( 11.4) | 2 ( 8.3) | 1 ( 50.0) |
| AE leading to any Study Treatment discontinuation | 19 ( 14.4) | 0 | 1 ( 50.0) | 36 ( 13.2) | 3 ( 12.5) | 0 |
| AE leading to any Dose modification or Study Treatment interruption | 65 ( 49.2) | 5 ( 38.5) | 1 ( 50.0) | 87 ( 31.9) | 8 ( 33.3) | 0 |

AEs started on or after first dose of study drug are included.
One patient with missing AST value and normal bilirubin value at baseline could not be assigned to any category of hepatic impairment.

### *Renal Impairment*

For renal impairment, the following estimated glomerular filtration rate (eGFR) values were used to define each group: Normal = eGFR ≥90 mL/min/1.73 m2, Mild = eGFR ≥60 and <90 mL/min/1.73 m2, Moderate = eGFR ≥30 and <60 mL/min/1.73 m2, and Severe = eGFR <30 mL/min/1.73 m2.

## Table 54. Overview of Safety by Renal Impairment (Safety-Evaluable Population)

Overall Summary of Adverse Events, by Renal Impairment
Safety-Evaluable Population

| | Chemotherapy (N=147) | | | Atezolizumab (N=300) | | | |
|---|---|---|---|---|---|---|---|
| | Normal (N=48) | Mild (N=72) | Moderate (N=27) | Normal (N=92) | Mild (N=154) | Moderate (N=53) | Severe (N=1) |
| Total number of patients with at least one AE | 44 ( 91.7) | 72 (100.0) | 27 (100.0) | 81 ( 88.0) | 143 ( 92.9) | 50 ( 94.3) | 1 (100.0) |
| Total number of events | 370 | 519 | 197 | 615 | 1266 | 463 | 8 |
| Total number of patients with at least one | | | | | | | |
| Treatment-related AE | 35 ( 72.9) | 61 ( 84.7) | 22 ( 81.5) | 45 ( 48.9) | 91 ( 59.1) | 34 ( 64.2) | 1 (100.0) |
| Grade 3-4 AE | 23 ( 47.9) | 38 ( 52.8) | 10 ( 37.0) | 41 ( 44.6) | 64 ( 41.6) | 30 ( 56.6) | 1 (100.0) |
| Treatment-related Grade 3-4 AE | 19 ( 39.6) | 24 ( 33.3) | 6 ( 22.2) | 18 ( 19.6) | 22 ( 14.3) | 9 ( 17.0) | 0 |
| Grade 5 AE | 5 ( 10.4) | 5 ( 6.9) | 3 ( 11.1) | 11 ( 12.0) | 21 ( 13.6) | 3 ( 5.7) | 0 |
| Treatment-related Grade 5 AE | 2 ( 4.2) | 1 ( 1.4) | 1 ( 3.7) | 1 ( 1.1) | 2 ( 1.3) | 0 | 0 |
| Serious AE | 15 ( 31.3) | 26 ( 36.1) | 12 ( 44.4) | 44 ( 47.8) | 72 ( 46.8) | 30 ( 56.6) | 0 |
| Treatment-related serious AE | 10 ( 20.8) | 9 ( 12.5) | 4 ( 14.8) | 13 ( 14.1) | 19 ( 12.3) | 3 ( 5.7) | 0 |
| AE leading to any Study Treatment discontinuation | 6 ( 12.5) | 8 ( 11.1) | 6 ( 22.2) | 12 ( 13.0) | 21 ( 13.6) | 6 ( 11.3) | 0 |
| AE leading to any Dose modification or Study Treatment interruption | 25 ( 52.1) | 33 ( 45.8) | 13 ( 48.1) | 21 ( 22.8) | 53 ( 34.4) | 22 ( 41.5) | 0 |

AEs started on or after first dose of study drug are included.

### *Tobacco Use History*

## Table 55. Overview of Safety by Tobacco Use History (Safety-Evaluable Population)

Overall Summary of Adverse Events, by Tobacco Use History
Safety-Evaluable Population

| | Chemotherapy (N=147) | | | Atezolizumab (N=300) | | |
|---|---|---|---|---|---|---|
| | Never (N=19) | Current (N=26) | Previous (N=102) | Never (N=35) | Current (N=57) | Previous (N=208) |
| Total number of patients with at least one AE | 19 (100.0) | 25 ( 96.2) | 99 ( 97.1) | 31 ( 88.6) | 50 ( 87.7) | 194 ( 93.3) |
| Total number of events | 120 | 208 | 758 | 275 | 401 | 1676 |
| Total number of patients with at least one | | | | | | |
| Treatment-related AE | 15 ( 78.9) | 19 ( 73.1) | 84 ( 82.4) | 17 ( 48.6) | 37 ( 64.9) | 117 ( 56.3) |
| Grade 3-4 AE | 6 ( 31.6) | 13 ( 50.0) | 52 ( 51.0) | 17 ( 48.6) | 26 ( 45.6) | 93 ( 44.7) |
| Treatment-related Grade 3-4 AE | 6 ( 31.6) | 6 ( 23.1) | 37 ( 36.3) | 4 ( 11.4) | 14 ( 24.6) | 31 ( 14.9) |
| Grade 5 AE | 3 ( 15.8) | 3 ( 11.5) | 7 ( 6.9) | 4 ( 11.4) | 9 ( 15.8) | 22 ( 10.6) |
| Treatment-related Grade 5 AE | 0 | 2 ( 7.7) | 2 ( 2.0) | 0 | 1 ( 1.8) | 2 ( 1.0) |
| Serious AE | 7 ( 36.8) | 13 ( 50.0) | 33 ( 32.4) | 17 ( 48.6) | 27 ( 47.4) | 102 ( 49.0) |
| Treatment-related serious AE | 3 ( 15.8) | 5 ( 19.2) | 15 ( 14.7) | 3 ( 8.6) | 8 ( 14.0) | 24 ( 11.5) |
| AE leading to any Study Treatment discontinuation | 2 ( 10.5) | 5 ( 19.2) | 13 ( 12.7) | 4 ( 11.4) | 8 ( 14.0) | 27 ( 13.0) |
| AE leading to any Dose modification or Study Treatment interruption | 9 ( 47.4) | 14 ( 53.8) | 48 ( 47.1) | 14 ( 40.0) | 18 ( 31.6) | 64 ( 30.8) |

AEs started on or after first dose of study drug are included.

***ECOG PS***

**Table 56. Overview of Safety by ECOG (Safety-Evaluable Population)**

Overall Summary of Adverse Events, By Baseline ECOG PS
Safety-Evaluable Population

| | Chemotherapy (N=147) | | | Atezolizumab (N=300) | | | |
|---|---|---|---|---|---|---|---|
| | ECOG PS 1 (N=19) | ECOG PS 2 (N=113) | ECOG PS 3 (N=15) | ECOG PS 0 (N=7) | ECOG PS 1 (N=49) | ECOG PS 2 (N=226) | ECOG PS 3 (N=18) |
| Total number of patients with at least one AE | 19 (100.0) | 110 ( 97.3) | 14 ( 93.3) | 7 (100.0) | 44 ( 89.8) | 208 ( 92.0) | 16 ( 88.9) |
| Total number of events | 186 | 816 | 84 | 87 | 446 | 1667 | 152 |
| Total number of patients with at least one | | | | | | | |
| Treatment-related AE | 18 ( 94.7) | 89 ( 78.8) | 11 ( 73.3) | 6 ( 85.7) | 31 ( 63.3) | 124 ( 54.9) | 10 ( 55.6) |
| Grade 3-4 AE | 9 ( 47.4) | 54 ( 47.8) | 8 ( 53.3) | 5 ( 71.4) | 16 ( 32.7) | 109 ( 48.2) | 6 ( 33.3) |
| Treatment-related Grade 3-4 AE | 4 ( 21.1) | 40 ( 35.4) | 5 ( 33.3) | 0 | 8 ( 16.3) | 36 ( 15.9) | 5 ( 27.8) |
| Grade 5 AE | 2 ( 10.5) | 10 ( 8.8) | 1 ( 6.7) | 0 | 2 ( 4.1) | 29 ( 12.8) | 4 ( 22.2) |
| Treatment-related Grade 5 AE | 0 | 4 ( 3.5) | 0 | 0 | 1 ( 2.0) | 2 ( 0.9) | 0 |
| Serious AE | 8 ( 42.1) | 41 ( 36.3) | 4 ( 26.7) | 3 ( 42.9) | 18 ( 36.7) | 117 ( 51.8) | 8 ( 44.4) |
| Treatment-related serious AE | 0 | 21 ( 18.6) | 2 ( 13.3) | 0 | 5 ( 10.2) | 27 ( 11.9) | 3 ( 16.7) |
| AE leading to any Study Treatment discontinuation | 4 ( 21.1) | 15 ( 13.3) | 1 ( 6.7) | 0 | 10 ( 20.4) | 27 ( 11.9) | 2 ( 11.1) |
| AE leading to any Dose modification or Study Treatment interruption | 9 ( 47.4) | 54 ( 47.8) | 8 ( 53.3) | 2 ( 28.6) | 19 ( 38.8) | 68 ( 30.1) | 7 ( 38.9) |

AEs started on or after first dose of study drug are included.

***Use in pregnancy and lactation***

There were no pregnancies in IPSOS.

There are no clinical studies of atezolizumab in pregnant women. Atezolizumab is not recommended during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

No reproductive or teratogenicity studies in animals have been conducted with atezolizumab. The programmed death-ligand 1/programmed death-1 (PD-L1/PD-1) signaling pathway is well established as essential in maternal / fetal tolerance and embryo-fetal survival during gestation. Administration of atezolizumab is expected to have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo lethality.

It is not known whether atezolizumab is excreted in human breast milk. No studies have been conducted to assess the impact of atezolizumab on milk production or its presence in breast milk.

***Overdose***

In the atezolizumab Phase Ia dose-escalation Study PCD4989g, the highest dose per unit weight to which patients have been exposed was 20 mg/kg IV q3w. There is no information on overdose with atezolizumab in IPSOS.

***Drug abuse***

No information is available. However, on the basis of its pharmacological properties, the risk of abuse or misuse of atezolizumab is considered to be low.

***Withdrawal and rebound***

No information is available. However, based on the mechanism of action, atezolizumab does not affect pathways that are associated with withdrawal or rebound effects.

***Effects on ability to drive or operate machinery or impairment of mental ability***

No studies of the effects on the ability to drive and to use machines have been performed for atezolizumab. Atezolizumab may have a minor influence on the ability to drive and use machines.

## *Safety related to drug-drug interactions and other interactions*

No formal pharmacokinetic drug-drug interaction studies have been conducted with atezolizumab.

## *Discontinuation due to adverse events*

### *Treatment discontinuations*

At the CCOD, in the safety-evaluable population of IPSOS, the proportion of patients who had discontinued from treatment was 95.0% for the atezolizumab arm vs. 100.0% for the chemotherapy arm, with the main reasons being progressive disease (50.3% vs. 51.0%) and death (20.0% vs. 12.2%).

Comparison between IPSOS and Atezo Mono Pooled Populations

**Table 57. Patient Status: Overview of Frequency and Reasons for Treatment Discontinuation from Atezolizumab (Safety-Evaluable Population)**

| | Atezolizumab (N=300) | Atezo Mono[1] (N=3178) | Atezo Mono[2] (N=4739) |
|---|---|---|---|
| Patients Discontinued from Atezo | | | |
| All Reasons | 285 (95.0%) | 2627 (82.7%) | 3364 (71.0%) |
| Adverse event | 38 (12.7%) | 213 ( 6.7%) | 431 ( 9.1%) |
| Death | 60 (20.0%) | 15 ( 0.5%) | 52 ( 1.1%) |
| Progressive disease | 151 (50.3%) | 1862 (58.6%) | 1862 (39.3%) |
| Progression of disease | 0 | 371 (11.7%) | 505 (10.7%) |
| Lost to follow-up | 1 ( 0.3%) | 2 (<0.1%) | 3 (<0.1%) |
| Other | 1 ( 0.3%) | 10 ( 0.3%) | 28 ( 0.6%) |
| Physician decision | 3 ( 1.0%) | 34 ( 1.1%) | 55 ( 1.2%) |
| Protocol violation | 0 | 14 ( 0.4%) | 14 ( 0.3%) |
| Protocol Deviation | 0 | 0 | 2 (<0.1%) |
| Withdrawal by subject | 27 ( 9.0%) | 94 ( 3.0%) | 161 ( 3.4%) |
| Non-compliance | 3 ( 1.0%) | 8 ( 0.3%) | 9 ( 0.2%) |
| Symptomatic Deterioration | 0 | 4 ( 0.1%) | 23 ( 0.5%) |
| Disease relapse | 0 | 0 | 219 ( 4.6%) |
| Study terminated by sponsor | 1 ( 0.3%) | 0 | 0 |

Atezo = Atezolizumab. Atezo Mono[1]: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + WO29074(IMMOTION150 Arm B prior to crossover); Atezo Mono [2]: Atezo Mono [1] + GO29431(IMPOWER110) + GO29527(IMPOWER010) + WO29636(IMVIGOR010) + WO39210(IMMOTION010 Arm A).
Actual treatment arms are presented.
Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, WO29074:17OCT2016, WO29636:30NOV2019, WO39210:03MAY2022, MO29872:30APR2022.

***Study discontinuations***

Comparison between IPSOS and Atezo Mono Pooled Populations

**Table 58. Patient Status: Overview of Frequency and Reasons for Withdrawal from Study (Safety-Evaluable Population)**

| | Chemotherapy (N=147) | Atezolizumab (N=300) | Atezo Mono[1] (N=3178) | Atezo Mono[2] (N=4739) |
|---|---|---|---|---|
| Study Status | | | | |
| n | 147 ( 100%) | 300 ( 100%) | 3178 ( 100%) | 4739 ( 100%) |
| Ongoing | 0 | 15 ( 5.0%) | 1108 (34.9%) | 2134 (45.0%) |
| Discontinued study | 147 ( 100%) | 285 (95.0%) | 2070 (65.1%) | 2605 (55.0%) |
| Reason for Study Discontinuation | | | | |
| All Reasons | 147 ( 100%) | 285 (95.0%) | 2070 (65.1%) | 2605 (55.0%) |
| Death | 127 (86.4%) | 235 (78.3%) | 1887 (59.4%) | 2317 (48.9%) |
| Progressive disease | 0 | 0 | 3 (<0.1%) | 3 (<0.1%) |
| Lost to follow-up | 3 ( 2.0%) | 9 ( 3.0%) | 70 ( 2.2%) | 84 ( 1.8%) |
| Other | 0 | 0 | 1 (<0.1%) | 4 (<0.1%) |
| Physician decision | 0 | 1 ( 0.3%) | 1 (<0.1%) | 1 (<0.1%) |
| Protocol violation | 0 | 0 | 11 ( 0.3%) | 11 ( 0.2%) |
| Protocol Deviation | 0 | 0 | 0 | 1 (<0.1%) |
| Withdrawal by subject | 12 ( 8.2%) | 25 ( 8.3%) | 97 ( 3.1%) | 182 ( 3.8%) |
| Disease relapse | 0 | 0 | 0 | 2 (<0.1%) |
| Study terminated by sponsor | 5 ( 3.4%) | 15 ( 5.0%) | 0 | 0 |

Atezo = Atezolizumab. Atezo Mono[1]: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + WO29074(IMMOTION150 Arm B prior to crossover); Atezo Mono [2]: Atezo Mono [1] + GO29431(IMPOWER110) + GO29527(IMPOWER010) + WO29636(IMVIGOR010) + WO39210(IMMOTION010 Arm A).
Actual treatment arms are presented.
Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, WO29074:17OCT2016, WO29636:30NOV2019, WO39210:03MAY2022, MO29872:30APR2022.

***Adverse Events that Led to Withdrawal of Study Treatment***

The proportion of patients experiencing AEs leading to discontinuation of study treatment was similar in the atezolizumab arm (13.0%) and chemotherapy arm (13.6%).

The most frequent AEs (≥1% of patients) leading to withdrawal of atezolizumab were pneumonitis (3.0% atezolizumab vs. 1.4% chemotherapy) and pneumonia (1.0% vs. 0.7%). All other AEs leading to atezolizumab treatment discontinuation were single occurrences.

The most frequent AEs (≥1% of patients) leading to withdrawal of chemotherapy were fatigue (0% atezolizumab vs. 2.7% chemotherapy), pneumonitis (3.0% vs. 1.4%), diarrhea (0% vs. 1.4%) and vomiting (0% vs. 1.4%). Other AEs leading to discontinuation of chemotherapy were single occurrences.

The proportion of patients with AEs leading to discontinuation of study treatment was higher in the atezolizumab arm of IPSOS (13.0%) than the Atezo Mono pooled populations (7.1%-9.3%).

Across all populations, the only AEs leading to withdrawal that were reported in ≥1% of patients were pneumonitis (IPSOS atezolizumab arm: 3.0% vs. Atezo Mono pools: 0.3%-0.5%) and pneumonia (1.0% vs. 0.3%-0.4%).

***Adverse Events that Led to Dose Modification/Interruption***

Dose modifications of atezolizumab were not permitted per protocol but interruptions or delays of the administration were allowed.

The proportion of patients experiencing AEs leading to dose modification/interruption was lower in the atezolizumab arm (32.0%) compared with the chemotherapy arm (48.3%).

The most frequently reported AEs (≥2%) leading to atezolizumab dose modification/interruption were pneumonia (3.0% atezolizumab vs. 7.5% chemotherapy) and dyspnea (2.3% vs 2.7%).

In the chemotherapy arm, the most frequently reported AEs (≥2%) leading to dose modification/interruption were hematologic toxicities including neutropenia (0.7% atezolizumab vs. 10.9% chemotherapy), neutrophil count decreased (0% vs. 6.1%), white blood cell count decreased (0% vs. 6.1%), anemia (0.3% vs. 4.8%), and leukopenia (0% vs. 4.1%), as well as the events of pneumonia (3.0% vs. 7.5%), dyspnea (2.3% vs. 2.7%), fatigue (1.0% vs. 2.7%), decreased appetite (0.7% vs. 2.7%), bronchitis (0.3% vs. 2.0%), constipation (0% vs. 2.0%), and weight decreased (0% vs. 2.0%).

The proportions of patients with AEs leading to atezolizumab dose interruption were comparable between the atezolizumab arm of IPSOS (32.0%) and the Atezo Mono pooled populations (27.8%-28.1%).

### *Post marketing experience*

Since the International Birth Date (18 May 2016) through 17 May 2023, an estimated cumulative total of 433,872 patients have received TECENTRIQ (atezolizumab) from marketing experience (149,664 patients in the United States, 129,404 patients in the European Economic Area, 50,233 patients in Japan, and 104,572 patients in Rest of the World). Among these, 36,459 (8%) patients received atezolizumab for the treatment of 1L NSCLC (11,827 patients in the European Economic Area; 5,772 patients in the United States, 10,927 patients in Japan, and 7,934 patients in Rest of the World). A further 112,262 (26%) patients received atezolizumab for the treatment of 2L+ NSCLC (50,995 patients in the European Economic Area; 19,060 patients in the United States, 6,796 patients in Japan, and 35,411 patients in Rest of the World).

Safety signals were identified during the latest PBRER reporting interval. The new important identified risks that include immune-mediated pericardial disorders, immune-mediated myelitis and facial paresis, and haemophagocytic lymphohistiocytosis were based on comprehensive review of clinical trial data, literature and post-marketing exposure. Review of the safety results from all completed and ongoing clinical studies during the reporting period suggest that the atezolizumab risk profile remains consistent with the current reference safety information, and the new information did not alter the overall benefit-risk profile of atezolizumab (Periodic Benefit Risk Evaluation Report).

## 2.5.1. Discussion on clinical safety

The randomised safety-evaluable population for IPSOS includes all treated patients i.e., all randomised patients who received at least one dose of atezolizumab (n=300) and all randomised patients who received at least one dose in the control arm (single-agent vinorelbine or gemcitabine per investigator's choice, n=147).

During the randomisation phase, patients randomised to the atezolizumab arm received 1200 mg atezolizumab by IV infusion on Day 1 of every 21-day cycle.

Single-agent atezolizumab regardless of tumour type has been evaluated in a total of 4739 patients, referred to as the pooled population (Atezo mono 2). When adding the 300 patients that were treated with atezolizumab in the IPSOS study this amounts to 5039 patients which is the reference pooled safety population reflected in the section 4.8 of the SmPC.

The median duration of survival follow-up in the IPSOS study was 41.0 months. The median number of doses of atezolizumab treatment in IPSOS was 6.

**Comparison between IPSOS and Atezo Mono Pooled Populations** - The patient demographics and baseline characteristics in the atezolizumab arm of IPSOS were generally comparable with the Atezo Mono pooled populations, except for the following: there were more men enrolled in IPSOS compared with the Atezo Mono populations; more Asian and Hispanic/Latino patients, as well as patients from Asia-Pacific and Central/South America in IPSOS; fewer patients from North America in IPSOS; more patients with ECOG PS 2 and 3; and fewer patients with ECOG PS 0 and 1 in IPSOS; IPSOS enrolled older patients (median age: 75 years) compared to the Atezo Mono pooled populations (median age: 64 years). There were more patients 75-84 years of age and ≥85 years of age in IPSOS; IPSOS included more patients with a history of tobacco use.

These differences are due to the countries IPSOS was open in and the fact that IPSOS included patients who were deemed unsuitable for platinum-doublet chemotherapy either due to their poor performance status (ECOG PS of 2 or 3) or, for patients with an ECOG PS of 0 or 1, due to older age (≥70 years) in combination with substantial comorbidities or other contraindication(s) for platinum-doublet chemotherapy, whereas other studies have typically excluded patients with ECOG PS ≥2. The discussion of the comparison between IPSOS and atezo mono pooled populations is generally supported.

In the atezolizumab arm of IPSOS (n=300), common AEs were reported for ≥10% of patients including decreased appetite (22.0%), dyspnoea (20.0%), cough (19.7%), fatigue (19.0%), anaemia (16.3%), constipation (15.7%), pneumonia (15.0%), asthenia (14.3%), diarrhoea (13.3%), nausea (10.7%), pyrexia (10.3%) and rash (10.0%). In the pooled population (Atezo mono 2, n=4739) the most common AEs were fatigue, decreased appetite, nausea, cough, diarrhoea, pyrexia, constipation, arthralgia and dyspnoea (all >15%) which is expected in a patient population with primarily advanced cancer disease. Typical chemotherapy-related AEs (nausea, vomiting, anaemia, neutropenia) were, as expected, more common in the chemotherapy arm. Cough, dyspnoea, pruritus, rash and hypothyroidism were more common in the atezolizumab arm. This is consistent with the known AE profile of these respective treatments.

In IPSOS, the proportion of patients with **Grade 3-4 AEs** in the atezolizumab arm (45.3%) was similar to that in the chemotherapy arm (48.3%). The most common Grade 3-4 AEs by PT (≥5% of patients in either arm) were (atezolizumab vs. chemotherapy, respectively): pneumonia (7.7% vs. 6.8%), dyspnoea (5.0% vs. 4.8%), hyponatremia (5.3% vs. 3.4%), neutropenia (0.7% vs. 9.5%), anaemia (2.7% vs. 4.8%), and neutrophil count decreased (0% vs. 7.5%).

A similar proportion of patients (45.3%) in the atezolizumab arm of IPSOS experienced Grade 3-4 AEs compared with the Atezo Mono pooled populations (40.9%-46.6%). The most common Grade 3-4 AEs by PT (≥5% of patients in either arm) were (atezolizumab vs. Atezo Mono pooled populations, respectively): pneumonia (7.7% vs. 2.5-3.0%), dyspnea (5.0% vs. 2.6-3.7%), hyponatremia (5.3% vs. 2.3-3.1%), anaemia (2.7% vs. 3.8-5.0%), and neutrophil count decreased (0% vs. < 0.1% each).

Adverse events of special interest (**AESI**) for atezo were selected based on its mechanism of action. Overall, the proportion of patients who experienced AESIs was 34.3% in the atezolizumab arm and 18.4% in the chemotherapy arm. The majority of AESIs were of Grade 1-2 severity. Among the atezo arm of IPSOS (n=300) the most frequent (>2%) AESIs were immune-mediated rash (15.0%), immune-mediated hepatitis (lab abnormalities) (9.0%), immune-mediated hypothyroidism (9.0%), immune-mediated pneumonitis (4.3%), immune-mediated hyperthyroidism (2.3%) and immune-mediated hepatitis (diagnosis) (2.3%). **Grade 3-4 AESIs** were reported in 6.7% (20 patients) of patients in the atezolizumab arm and 2.0% (3 patients) in the chemotherapy arm. Three Grade 5 AESIs were reported

in the atezolizumab arm (hepatitis, pneumonitis, and myasthenia gravis). The proportion of patients in the atezolizumab arm who experienced AESIs leading to treatment discontinuation and dose interruption was 5.7% and 7.0%, respectively. The proportion of patients who experienced AESIs that required systemic corticosteroid treatment was 11.3% (34 patients) in the atezolizumab arm and 4.8% (7 patients) in the chemotherapy arm.

Overall, the proportion of patients who experienced AESIs in the IPSOS atezolizumab arm (34.3%) was lower compared to the Atezo Mono 2 pooled population (40.3%).

The proportion of patients with at least one **SAE** was higher in the atezolizumab arm (48.7%) than in the chemotherapy arm (36.1%). The only SAE with a ≥2% higher incidence in the atezolizumab arm compared with the chemotherapy arm was pneumonia (11.0% vs. 7.5%). The proportions of patients with SAEs was also higher compared to the Atezo Mono 2 pooled population (41.2%). This could potentially be related to the fact that the population targeted in IPSOS was more frail and thus prone to SAEs.

The proportion of patients in the safety-evaluable population who died in the atezolizumab arm (82.7% [248/300 patients]) was lower than that in the chemotherapy arm (87.8% [129/147 patients]). The causes of **death** were progressive disease (atezolizumab: 59.7% vs. chemotherapy: 70.1%), adverse event (11.7% vs. 8.8%), and 'other' causes (11.3% vs. 8.8%). The frequency of deaths due to AE was higher in the atezo arm of IPSOS than compared with the atezo mono 2 pooled population (11.7% vs. 3.1%). The frequency of deaths was higher in the atezolizumab arm of IPSOS (82.7%) compared to the Atezo Mono 2 pooled population (49.5%), with the leading cause of death being disease progression in all populations. This is likely due to the longer observation period in IPSOS and the overall health status (PS ≥2) of the elderly patient population in IPSOS compared to the Mono pools.

Pneumonia was the most common adverse event that led to death in the atezolizumab arm (2.7%) with overall infections and infestations being the cause in 4.7% of cases. Respiratory, thoracic and mediastinal disorders was the cause in 1.7% of cases. Cardiac disorder (overall) was the cause of death in 1.3% of cases. Sudden cardiac death is listed as cause of death in 0.6% of cases. Myasthenia gravis and immune-mediated hepatitis was each cause of death in one case respectively (0.3% and 0.3%).

It is acknowledged that the patient population in IPSOS was older and more frail in comparison with most other atezolizumab monotherapy trials. This is regarded as the most likely explanation behind the higher occurrence of AE related deaths in the IPSOS trial. Regarding causality, the pattern of respiratory/thoracic/mediastinal disorders with or without underlying infection as death cause, follows what is expected in this disease setting.

In comparison to the Atezo Mono 2 pool (n=4739), the updated Atezo monotherapy pool (n=5039) for ADRs includes patients from the safety population from IPSOS treated with atezolizumab (n=300). At the time of the primary analysis of OS (CCOD 30 April 2022) for IPSOS, no new **adverse drug reactions** (ADRs) with atezolizumab monotherapy treatment were identified. The proportions of ADRs in the updated pool are justified and appropriately reflected in section 4.8 of the SmPC.

**Laboratory findings:** Overall, the percentage of patients in the atezolizumab arm who experienced clinically relevant shifts from baseline (defined as shifts from Grade 0, 1, or 2 at baseline to Grade 3 or 4 post baseline) in any laboratory safety test parameter during study treatment was low. The frequency of clinically relevant shifts in hematology parameter abnormalities including low neutrophils (0.9% atezolizumab vs. 19.8% chemotherapy), low white blood cells (1.1% vs. 14.1%) and low lymphocytes (11.1% vs. 18.5%) was higher in the chemotherapy arm than in the atezolizumab arm. Among biochemistry laboratory parameter abnormalities, the frequency of clinically relevant shifts was similar between the arms except for a higher (≥2%) incidence of low sodium levels (13.5% vs. 5.3%) and high potassium levels (2.6% vs. 0%) in the atezolizumab arm compared with the chemotherapy arm.

Treatment-emergent TSH laboratory abnormalities (defined as normal at baseline and abnormal at post-baseline) were reported in patients in both treatment arms (TSH low: 7.3% atezolizumab vs. 4.1% chemotherapy. TSH high: 7.0% vs. 6.1%).

Since the majority of patients were over 65 years old, subgroup analyses by **age** were only meaningful for the 65–74, and 75–84 year old subgroups. Between arms, there was no noteworthy difference in the safety profile for these two subgroups. Within each arm, there was no noteworthy difference in the safety profile between the subgroups with the exception of AEs leading to any study treatment discontinuation (atezolizumab arm: 65-74: 8.0% vs. 75-84: 15.8%; chemotherapy arm: 65-74: 8.0% vs. 75-84: 17.1%) and AEs leading to any dose modification or study treatment interruption (atezolizumab arm: 65-74: 28.0% vs. 75-84: 37.4%; chemotherapy arm: 65-74: 62.0% vs. 75-84: 40.0%) which were more common in the 75-84 year subgroup, although the relatively small sample size precludes any meaningful clinical interpretations. This information has been added to the section 4.8 of the SmPC.

Between arms, there was no clinically relevant difference in the safety profile by **gender**.

Due to low numbers of patients in subgroups other than White and Asian, subgroup analyses by **race** are not considered meaningful.

The majority of patients (approximately 90%) in both treatment arms had "normal" hepatic function at baseline. No meaningful conclusions can be drawn comparing the safety data for the relatively small subgroup of patients with mild (N=24) or moderate (N=2) hepatic impairment versus normal (N=273) in the atezolizumab arm.

No meaningful conclusions can be drawn comparing the safety data for the small subgroup of patients with severe **renal impairment** (n=1) versus the other subgroups in the atezolizumab arm. Although higher rates of Grade 3-4 AEs and SAEs were noted in the subgroups of moderate vs. mild renal impairment within the atezolizumab arm, the relatively small sample size of the moderate renal impairment subgroup precludes any meaningful clinical interpretation. Similarly, higher rates of treatment interruptions due to AEs were noted for the subgroup with moderate renal impairment compared to that with normal renal function in the atezolizumab arm; however the sample size of each of these subgroups were too small to draw any clinically relevant conclusions.

Between arms, the safety profile was generally balanced for previous **smokers.** Since the majority of patients were previous smokers, subgroup analyses by tobacco use history within each arm are not considered meaningful.

The overall safety profile of atezolizumab was generally similar irrespective of baseline **ECOG PS status**.

At the CCOD, in the safety-evaluable population, the proportion of patients who had **discontinued** from treatment was comparable between the two treatment arms (95.0% atezolizumab vs. 100.0% chemotherapy), with the main reasons being progressive disease (50.3% vs. 51.0%) and death (20.0% vs. 12.2%). The proportion of patients treated with atezolizumab in IPSOS that discontinued atezolizumab (95.0%) was higher compared to the Atezo Mono pooled populations (71.0%-82.7%). Progressive disease was the leading cause of treatment discontinuation across all populations. Discontinuations due to death were higher in IPSOS (20.0%) than the Atezo Mono pooled populations (0.5-1.1%).

As of the CCOD, in the safety-evaluable population, the proportion of patients that had discontinued from the study was comparable between the treatment arms (Atezo: 95.0% vs. Chemo: 100%; Table 6). The reasons for study discontinuation were generally balanced between the treatment arms, except for 'death' where a lower percentage of patients in the atezolizumab arm discontinued the study due to death (78.3%) compared with the chemotherapy arm (86.4%). The proportion of patients that

discontinued from study in IPSOS (95.0%) was higher compared to the Atezo Mono pooled populations (55-65.1%), with "death" being the leading cause across all populations.

The proportion of patients experiencing **AEs leading to discontinuation** of study treatment was 13.0% in the atezolizumab arm. The most frequent AEs (≥1% of patients) leading to withdrawal of atezolizumab were pneumonitis (3.0%) and pneumonia (1.0%). All other AEs leading to atezolizumab treatment discontinuation were single occurrences. The proportion of patients with AEs leading to discontinuation of study treatment was higher in the atezolizumab arm of IPSOS (13.0%) than the Atezo Mono pooled populations (7.1%-9.3%).

### 2.5.2. Conclusions on clinical safety

The safety data of atezolizumab in the IPSOS study were generally consistent with the established safety profile of anti-PD/PD-L1 agents and no new ADRs were observed. Common AEs, SAEs and AESIs were observed at rates consistent with previous studies. Rates of death due to AE and AEs leading to discontinuation was higher in the IPSOS trial compared to the atezo mono pooled populations. However, the target population of the IPSOS study was older and more frail than the atezo mono pooled populations.

In conclusion, for the targeted population, the safety profile of atezolizumab monotherapy is considered acceptable and no new safety issues have been raised during the safety assessment.

### 2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.6. Risk management plan*

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 29.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 29.1 with the following content:

### *Safety concerns*

| **Summary of safety concerns** | |
|---|---|
| **Important identified risks** | Immune-related adverse reactions<br>Infusion-related reactions |
| **Important potential risks** | Attenuated efficacy or reduced tolerability in patients with anti-drug antibodies<br>Embryo-foetal toxicity |
| **Missing information** | None |

## *Pharmacovigilance plan*

| Study Status | Summary of Objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 1** – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization | | | | |
| There are no Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization | | | | |
| **Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances | | | | |
| There are no Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances | | | | |
| **Category 3** – Required additional pharmacovigilance activities | | | | |
| There are no Required additional pharmacovigilance activities | | | | |

## *Risk minimisation measures*

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| Immune-mediated adverse reactions | **Routine risk minimization measures:**<br><br>Proposed measures are described in the E.U. SmPC under the following sections:<br><br>Section 4.2 Posology and method of administration<br><br>Section 4.4 Special Warnings and Precautions for Use<br><br>Section 4.8 Undesirable effects Relevant information for patient in PIL<br><br>**Additional risk minimization measures:**<br><br>Patient cards (all immune-mediated adverse reactions excluding SCARs)<br><br>SCARs: A one-off DHPC was disseminated in March 2021 to | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br><br>None<br><br>**Additional pharmacovigilance activities:**<br><br>SCARs: Metrics on the distribution and receipt of the DHPC were taken to assess the effectiveness of this risk minimization activity. |

| | | |
|---|---|---|
| | inform healthcare professionals that immune-mediated SCARs, which were previously known to be potentially associated with use of Tecentriq (atezolizumab), are now considered to be an identified risk. | |
| Infusion-Related Reactions | **Routine risk minimization measures:**<br>Proposed measures are described in the E.U. SmPC under the following sections:<br>Section 4.2 Posology and method of administration<br>Section 4.4 Special Warnings and Precautions for Use<br>Section 4.8 Undesirable effects<br>Relevant information for patient in PIL<br>**Additional risk minimization measures:**<br>Patient cards | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None<br>**Additional pharmacovigilance activities:**<br>None |
| Attenuated efficacy or reduced tolerability in patients with anti-drug antibodies | **Routine risk minimization measures:**<br>Proposed measures are described in the E.U. SmPC under the following sections:<br>Section 4.8 Undesirable effects<br>**No additional risk minimization measures** | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None<br>**Additional pharmacovigilance activities:**<br>None |
| Embryo-fetal toxicity | **Routine risk minimization measures:**<br>Proposed measures are described in the E.U. SmPC under the following sections:<br>Section 4.6 Fertility, pregnancy and lactation | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None<br>**Additional pharmacovigilance activities:** |

| | | |
|---|---|---|
| | Section 5.3 Preclinical safety data<br><br>Relevant information for patient in PIL<br><br>**No additional risk minimization measures** | None |

## *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC have been updated.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

● For the proposed extension, no changes to the package leaflet were made that affected key safety messages.

● The posology proposed in this application is the same as for the currently approved indications.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

The finally agreed wording for Tecentriq's new extension of indication is:

*Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with advanced NSCLC who are ineligible for platinum-based therapy (see section 5.1 for selection criteria).*

### 3.1.2. Available therapies and unmet medical need

Lung cancer remains the leading cause of cancer deaths worldwide; it is the most common cancer in men (together with prostate cancer) and the third most common cancer in women (after breast and colorectal cancer). It accounted for approximately 11% of all new cancers in 2020 with an estimated 2.2 million new cancer cases and 1.8 million deaths (Sung et al. 2021).

Half of all newly diagnosed NSCLC patients present with advanced disease (Stage IIIb or IV) (SEER 2023). In addition to advanced disease at diagnosis, patients could present with poor performance status (PS), advanced age and a history of unintentional weight loss (Bailey et al. 2023).

Platinum-based chemotherapy regimens are an efficacious standard of care, but in some patients with substantial comorbidities or specific contraindications, they may not be tolerated and are therefore not an available treatment option (Quoix et al. 2011). For this reason, treatment tolerability is an important factor in treatment decisions for patients.

### 3.1.3. Main clinical studies

This application is based on the results from the single pivotal trial **IPSOS** (MO29872): *A Phase III, open-label, multicenter, randomised 2:1 study to investigate the efficacy and safety of atezolizumab compared with chemotherapy (vinorelbine or gemcitabine) in patients with treatment-naïve advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) non-small cell lung cancer who are deemed ineligible for platinum-containing therapy.*

Patients were randomised at a 2:1 ratio to receive either atezolizumab 1200 mg IV q3w or single-agent vinorelbine oral or IV (dosing per local principal investigator) or gemcitabine IV (dosing per local principal investigator). No crossover was allowed between treatment arms. Eligible patients were stratified by: histologic subtype (non-squamous vs. squamous), presence/absence of brain metastases, PD-L1 IHC status by VENTANA PD-L1 (SP142) assay (IC3 or TC3 vs. IC0/1/2 and TC0/1/2 vs. unknown). The primary endpoint was overall survival. Patients were recruited globally. Overall, 453 patients were enrolled, and of these a total of 405 patients met the platinum-ineligibility criteria (ad hoc platinum ineligible population), corresponding to 89% of the ITT population. Efficacy data in this subgroup population is comparable to the one of the overall population, and is therefore supportive of the requested extension of indication.

## *3.2. Favourable effects*

As of the CCOD (30 April 2022) and with a median follow-up of 41.0 months in the overall population, efficacy data are considered overall mature.

- Median OS was 10.3 months with atezolizumab monotherapy versus a median of 9.2 months in the chemotherapy arm (stratified HR=0.78, 95% CI 0.63, 0.97).
- The median PFS was 4.2 months vs 4.0 months in the patients treated with atezolizumab vs chemotherapy, respectively, while the ORR was 16.9% vs 7.9%, with a median DoR of 14.0 months vs 7.8 months.

## *3.3. Uncertainties and limitations about favourable effects*

There are some uncertainties and limitations to be considered when interpreting the results of the pivotal IPSOS study and the relevant platinum-ineligible subgroup reflecting the applied indication:

- The definition of platinum-ineligibility is not based on validated criteria from international guidelines, as they do not exist for the targeted disease of advanced NSCLC. The wording of the indication has been revised to make reference to section 5.1 of the SmPC, where specific platinum-ineligible criteria have been defined, i.e. patients >80 years of age, or with an ECOG PS of 3, or patients with an ECOG PS 2 in combination with relevant comorbidities, or of older age (≥70 years) in combination with relevant comorbidities. Efficacy results from the ad hoc platinum ineligible population were considered supportive of the agreed indication.
- The control arm included two options of single-agent chemotherapy (vinorelbine or gemcitabine) and current standard of care options include more options, so it remains uncertain whether

inclusion of pemetrexed or docetaxel as additional possibilities in the control arm would have led to different study results. The applicant provided arguments for not having included docetaxel and pemetrexed as treatment options (see 'Discussion on clinical efficacy'), and therefore this uncertainty was not further pursued.

## *3.4. Unfavourable effects*

- In the atezolizumab arm of IPSOS (n=300), common AEs were reported for ≥10% of patients including decreased appetite (22.0%), dyspnoea (20.0%), cough (19.7%), fatigue (19.0%), anaemia (16.3%), constipation (15.7%), pneumonia (15.0%), asthenia (14.3%), diarrhoea (13.3%), nausea (10.7%), pyrexia (10.3%) and rash (10.0%).
- The most common Grade 3-4 AEs by PT (≥5% of patients in either arm) were (atezolizumab vs. chemotherapy, respectively): pneumonia (7.7% vs. 6.8%), dyspnoea (5.0% vs. 4.8%), hyponatremia (5.3% vs. 3.4%), neutropenia (0.7% vs. 9.5%) and neutrophil count decreased (0% vs. 7.5%).
- The proportion of patients who experienced AESIs was 34.3% in the atezolizumab arm and 18.4% in the chemotherapy arm. The majority of AESIs were of Grade 1-2 severity. Among the atezo arm of IPSOS (n=300) the most frequent (>2%) AESIs were immune-mediated rash (15.0%), immune-mediated hepatitis (lab abnormalities) (9.0%), immune-mediated hypothyroidism (9.0%), immune-mediated pneumonitis (4.3%), immune-mediated hyperthyroidism (2.3%) and immune-mediated hepatitis (diagnosis) (2.3%).
- Grade 3-4 AESIs were reported in 6.7% (20 patients) of patients in the atezolizumab arm and 2.0% (3 patients) in the chemotherapy arm.
- The proportion of patients with at least one SAE was higher in the atezolizumab arm (48.7%) than in the chemotherapy arm (36.1%). The only SAE with a ≥2% higher incidence in the atezolizumab arm compared with the chemotherapy arm was pneumonia (11.0% vs. 7.5%).
- The proportion of patients experiencing AEs leading to discontinuation of study treatment was 13.0% in the atezolizumab arm. The most frequent AEs (≥1% of patients) leading to withdrawal of atezolizumab were pneumonitis (3.0%) and pneumonia (1.0%). All other AEs leading to atezolizumab treatment discontinuation were single occurrences.
- The proportion of patients in the safety-evaluable population who died in the atezolizumab arm (82.7% [248/300 patients]) was lower than that in the chemotherapy arm (87.8% [129/147 patients]). The causes of death were progressive disease (atezolizumab: 59.7% vs. chemotherapy: 70.1%), adverse event (11.7% vs. 8.8%), and 'other' causes (11.3% vs. 8.8%).

## *3.5. Uncertainties and limitations about unfavourable effects*

None.

## 3.6. Effects Table

**Table 59. Effects Table for IPSOS study, Tecentriq (atezolizumab). Data cut-off: 30 April 2022**

| Effect | Short description | Unit | Treatment Atezolizumab mono | Control Vinorelbin or gemcitabine | Hazard Ratio (CI) | Uncertainties / Strength of evidence | Ref |
|---|---|---|---|---|---|---|---|
| **Favourable Effects in ITT population of IPSOS, N=453** | | | | | | | |
| | | | N=302 | N=151 | | | |
| OS in ITT | Overall survival | Months<br><br>(95%CI) | 10.3<br><br>(9.4-11.9) | 9.2<br><br>(5.9-11.2) | 0.78<br><br>(0.63-0.97) | Censoring for OS/mature data, final analysis | Clinical efficacy section |
| **Effect** | **Short description** | **Unit** | **Treatment** Atezolizumab mono | **Control** Chemotherapy | | **Uncertainties / Strength of evidence** | **Ref** |
| **Unfavourable Effects in the ITT population of IPSOS, N=447** | | | | | | | |
| | | | N=300 | N=147 | | | |
| Gr 3-4 | AE | % | 45.3 | 48.3 | | | Clinical safety section |
| SAEs | AE | % | 48.7 | 36.1 | | | |
| AEs leading to discont. | AE | % | 13.0 | 13.6 | | | |
| Death AE | AE | % | 11.7 | 8.8 | | | |

Abbreviations: Abbreviations: NA = not available, NE: not evaluable, HR: hazard ratio, CI: confidence interval, SAE = serious adverse events.

Notes: not applicable.

## 3.7. Benefit-risk assessment and discussion

### 3.7.1. Importance of favourable and unfavourable effects

There exists a high unmet medical need for the targeted frail patient population with advanced NSCLC, who are ineligible for platinum-based chemotherapy.

The primary endpoint of OS in the ITT population shows a median OS of 10.3 months with atezolizumab monotherapy versus a median of 9.2 months in the chemotherapy arm (stratified HR=0.78, 95% CI 0.63, 0.97). From a clinical perspective, the difference of 1 month in OS is considered clinically relevant as it is recognised that the targeted population is frail by definition, and thus an overwhelming improvement of survival was not expected. Response rates and duration of responses also appeared superior in the atezolizumab monotherapy arm in comparison to the chemotherapy choices. The results from the ad hoc platinum ineligible population are supportive of the agreed indication.

There remain some uncertainties and limitations to be considered when interpreting the results of the pivotal IPSOS study, including the definition of platinum-ineligibility, which is not based on validated criteria from international guidelines, as they do not exist for the targeted disease of advanced NSCLC and the limited choices of treatments in the control arm. The control arm included two options of single-agent chemotherapy (vinorelbine or gemcitabine) and the current standard of care options include also pemetrexed and docetaxel, so it remains uncertain whether inclusion of additional possibilities in the

control arm would have led to different study results. However, this issue cannot be further pursued in a concluded trial.

Regarding safety, the toxicity profile of atezolizumab is known and no new ADRs were observed. The higher rate of discontinuation and deaths due to AE in the IPSOS study compared with the atezolizumab monotherapy 2 pooled populations is likely due to the inclusion of older and frailer patients in the IPSOS study.

In conclusion, the Applicant has convincingly argued that a relevant and large subpopulation (89%) of the pivotal IPSOS study can be considered platinum-ineligible from specific criteria, and this is adequately reflected in section 5.1 of the SmPC. Efficacy and safety are comparable for the subgroup and the overall population, and the comparators used are found to be acceptable. Considering the totality of the data, the B/R is positive for the claimed indication.

### 3.7.2. Balance of benefits and risks

The balance of benefits and risks is positive for the applied indication.

### 3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

## *3.8. Conclusions*

The overall B/R of Tecentriq for the applied indication is positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I |

Extension of indication to include first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) who are ineligible for platinum-based therapy (see section 5.1 for selection criteria), for TECENTRIQ, based on final results from study MO29872 (IPSOS); this is a phase 3, open-label, multicenter, randomised study to investigate the efficacy and safety of atezolizumab compared with chemotherapy in patients with treatment naive advanced or recurrent (stage IIIB not amenable for multimodality treatment) or metastatic (stage IV) NSCLC who are deemed unsuitable for platinum-containing therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The new indication has been reflected in the SmPC for the IV and the SC formulations. Version 29.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor

editorial changes to the PI.

The variation leads to amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP).

## *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annex(es) I and to the Risk Management Plan are recommended.