22 April 2022
EMA/667840/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tecentriq

International non-proprietary name: atezolizumab

Procedure No. EMEA/H/C/004143/II/0064

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

1/2L	first/second-line
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
BICR	Blinded Independent Central Review
BSC	best supportive care
CCOD	clinical cut-off date
CHMP	Committee for Medicinal Products for Human Use
CSR	clinical study report
DFS	disease-free survival
DHMA	Danish Health and Medicines Authority
EGFR	epidermal growth factor receptor
ESMO	European Society for Medical Oncology
EU	European Union
FDA	U.S. Food and Drug Administration
HCC	hepatocellular carcinoma
HR	hazard ratio
IALT	International Adjuvant Lung Cancer Trial
IC	tumor-infiltrating immune cell
iDCC	independent data coordinating center
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
Ig	Immunoglobulin
ITT	intent to treat
IV	intravenous
KM	Kaplan-Meier
MAA	marketing authorization application
mAb	monoclonal antibody
mUC	metastatic urothelial carcinoma
NCCN	National Comprehensive Cancer Network
NSCLC	non-small cell lung cancer
OS	overall survival
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PEI	Paul-Ehrlich-Institut
PFS	progression-free survival
PK	pharmacokinetics
popPK	population PK
q2/3/4w	every 2/3/4 weeks
SAE	serious adverse event
SBP	Summary of Biopharmaceutical Studies and Associated Analytical Methods
SCE	Summary of Clinical Efficacy
SCLC	small cell lung cancer
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
TC	tumor cell
TNBC	triple-negative breast cancer
TNM	tumor, nodes and metastasis
UC	urothelial cancer
UICC	Union Internationale Contre le Cancer
U.S.	United States

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 28 June 2021 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 and IIIB

C.I.6 (Extension of indication)
Extension of indication to include adjuvant treatment of non-small cell lung cancer (NSCLC) following resection and platinum-based chemotherapy for adult patients whose tumours have PD-L1 expression on ≥ 1% of tumour cells (TC) for Tecentriq as monotherapy based on the results from the pivotal phase III Study GO29527 (IMpower010); as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of both the Tecentriq 840mg concentrate for solution for infusion SmPC and the Tecentriq 1,200mg concentrate for solution for infusion SmPC are updated. Minor editorial changes have been made throughout the SmPC. The Package Leaflets are updated in accordance. Version 21.0 of the RMP has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) 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 received the following Scientific Advice on the clinical development relevant for the indication subject to the present application: EMEA/H/SA/2522/5/2015/II.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Aaron Sosa Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	28 June 2021
Start of procedure:	17 July 2021
CHMP Rapporteur Assessment Report	10 September 2021
PRAC Rapporteur Assessment Report	10 September 2021
PRAC members comments	22 September 2021
CHMP Co-Rapporteur Critique	22 September 2021
PRAC Outcome	30 September 2021
CHMP members comments	04 October 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 October 2021
Request for supplementary information (RSI)	14 October 2021
CHMP Rapporteur Assessment Report	03 March 2022
PRAC Rapporteur Assessment Report	25 February 2022
PRAC members comments	02 March 2022
Updated PRAC Rapporteur Assessment Report	03 March 2022
PRAC Outcome	10 March 2022
CHMP members comments	14 March 2022
Updated CHMP Rapporteur Assessment Report	17 March 2022
2nd Request for Supplementary information	24 Mar 2022
Rapporteur's preliminary assessment report circulated on:	06 April 2022
CHMP members comments	11 April 2022
Updated CHMP Rapporteur Assessment Report	13 April 2022
CHMP Opinion	22 April 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The claimed the therapeutic indication is:

Tecentriq as monotherapy is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression on ≥ 1% of tumour cells (TC).

Epidemiology

Lung cancer is the second most common cancer and the leading cause of cancer death worldwide. Globally lung cancer is responsible for nearly one in five cancer deaths.

Approximately 2.2 million new cases of lung cancer (accounting for 11.4% of total cancers) and 1.8 million deaths occurred worldwide in 2020 (GLOBOCAN 2020). NSCLC is the predominant subtype, accounting for approximately 80%-85% of all cases (Osmani et al. 2018), with 235,760 new cases of lung cancer expected in the United States (U.S.) resulting in 131,880 deaths in 2021 (American Cancer Society Cancer Facts & Figures 2021). Similar data from Europe estimate that there were 477,534 new cases of lung cancer and 384,176 deaths in 2020 (WHO 2020).

Approximately 30% of patients with NSCLC present with resectable disease, however, their outcomes are quite poor. The 5-year overall survival (OS) rate by pathologic stage (per the Union Internationale Contre le Cancer [UICC]/American Joint Committee on Cancer [AJCC] staging, 7th edition) is 71% for Stage IB, 57% for Stage IIA, 49% for Stage IIB, and 36% for Stage IIIA (Goldstraw et al. 2016).

Clinical presentation

Despite progress in early detection and treatment, NSCLC is most often diagnosed at an advanced stage and has a poor prognosis (Herbst et al 2008). Once NSCLC has progressed to a locally advanced or metastatic stage there is no cure and treatment is therefore focused on extending life, delaying disease progression, and improving symptoms and quality of life.

Management

In its early stages, NSCLC is treated surgically with curative intent. For patients with Stage I disease, surgical treatment alone is the standard of care. For Stage II to III disease, with a higher risk of recurrence, platinum-based chemotherapy as an adjuvant or neoadjuvant therapy together with surgery is recommended to improve survival outcomes compared with surgery alone, per NCCN and ESMO guidelines (NCCN 2021; ESMO 2017). Chemotherapy regimens used in the adjuvant and neoadjuvant settings involve platinum-based doublets, which are the same standard of care drugs used in the metastatic setting. According to NCCN and ESMO guidelines, cisplatin is recommended as the preferred platinum agent and carboplatin is used when cisplatin cannot be tolerated or co-morbidities exist. Agents that have been combined with either cisplatin or carboplatin include taxanes, vinorelbine, gemcitabine, etoposide and pemetrexed. Over a follow-up of approximately 5 years, the percentage of patients who have disease recurrence or who die after surgery remains high ranging from approximately 35% among patients with Stage IB disease to 65% among those with Stage III disease, regardless of the use of perioperative chemotherapy (Goldstraw et al. 2016).

The largest evidence for the benefit of adjuvant chemotherapy for resectable NSCLC comes from the International Adjuvant Lung Cancer Trial (IALT). Overall, 1867 patients were randomized to surgery alone or surgery followed by adjuvant chemotherapy. Adjuvant platinum-based chemotherapy had a significantly higher progression free survival (PFS) (39.4% vs. 34.3%) at 5 years, hazard ratio (HR) 0.83 (95% CI, 0.74–0.94, P<0.003) and OS (44.5% vs. 40.4%) at 5 years, HR 0.86 (95% CI, 0.76–0.98, P<0.03) (Arriagada et al. 2004).

In the Phase III Cancer and Leukaemia Group B 9633 study of adjuvant chemotherapy in Stage IB NSCLC, a survival advantage was not observed with paclitaxel and carboplatin in the intent to treat (ITT) Stage IB population (Strauss et al. 2008). However, exploratory analysis demonstrated a significant

survival difference in favour of adjuvant chemotherapy for patients who had tumours ≥ 4 cm in diameter (HR = 0.69; 95% CI: 0.48 to 0.99).

The Phase III adjuvant E1505 study and the JIPANG study suggest that platinum-based chemotherapy continues to be the current standard of care for resectable NSCLC in patients selected by stage alone (Wakelee et al. 2017; Kenmotsu et al. 2020). These more modern studies continue to demonstrate that no platinum-based chemotherapy doublet is superior to another and a clear ceiling has been reached for adjuvant chemotherapy. The results from the Phase III adjuvant E1505 study did not demonstrate improved DFS or OS with the addition of bevacizumab to platinum-based chemotherapy.

The LACE initiative pooled data from five large trials of cisplatin-based chemotherapy in 4584 patients with completely resected NSCLC. Over a median follow-up period of 5.2 years, comparing chemotherapy with no chemotherapy, the HR for OS was 0.89 (95% CI: 0.82, 0.96; p=0.005), corresponding to a 5-year survival benefit of 5.4% from chemotherapy. There was variation observed between the different disease stages per UICC/AJCC staging 7th edition (p=0.04), with the greatest benefit for patients with Stages II and III NSCLC (HR: 0.83 for each), a more moderate effect in Stage IB (HR: 0.93), and a potential deleterious effect in Stage IA (HR: 1.40; Pignon et al. 2008).

Recently, however, for a select patient population with early-stage resectable NSCLC, targeting a specific oncogenic driver, it was shown that improvements upon the modest benefit of platinum-based chemotherapy can be achieved in the adjuvant setting. The ADAURA trial demonstrated that patients whose NSCLC had an activating epidermal growth factor receptor *(EGFR)* mutation achieved significant improvements in DFS (HR = 0.20; p < 0.001) with the addition of adjuvant osimertinib with or without platinum-based chemotherapy after surgery (Wu et al. 2020). Consequently, osimertinib was approved in the U.S. in December 2020 and in the European Union (EU) in May 2021, and represents the first targeted, biomarker-driven treatment option in early-stage EGFR-mutated lung cancer. Thus, with new drugs such as immune checkpoint inhibitors along with patient selection by oncogenic drivers or PD-L1 status, further improvements may be seen after over 16 years without change to the standard of care for these patients with high unmet medical need.

2.1.2. About the product

Pharmacological class

Programmed death-ligand 1 (PD-L1) blocking antibody

Mechanism of action and structure

Atezolizumab is a humanised 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 tumour infiltrating immune cells (ICs) and tumour cells (TCs) and inhibits its interaction with its receptors programmed death1 (PD-1) and B7.1, both of which can provide inhibitory signals to T cells.

Therapeutic indications

Urothelial carcinoma

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC):

- after prior platinum containing chemotherapy, or
- who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%.

Non-small cell lung cancer

Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies.

Tecentriq, in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK positive NSCLC.

Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% TC or ≥ 10% IC and who do not have EGFR mutant or ALK-positive NSCLC.

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK positive NSCLC should also have received targeted therapies before receiving Tecentriq.

Triple-negative breast cancer

Tecentriq in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.

Small cell lung cancer

Tecentriq, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

Hepatocellular carcinoma

Tecentriq, in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

2.1.1. The development programme/compliance with CHMP guidance/scientific advice

CHMP scientific advice on the design of IMpower010 (EMEA/H/SA/2522/5/2015/II):

CHMP advised that patients with IC2/TC2 positive tumors also be included. This has been met.

The CHMP stated that DFS as primary endpoint should, however, be supported by data on OS with adequate maturity (approximately 60% of required events) at the time of marketing authorization application (MAA). The CHMP also specified that although DFS can be considered acceptable as primary endpoint, it is necessary to obtain adequate assessment of the overall survival to exclude late futility effect of the experimental treatment. "An IA after approximately 40% of events is not considered robust enough for adequate assessment of survival benefit. Study maturity will progress differently across prognostic subgroups. This is true for the interim efficacy analysis with an overrepresentation of patients with early progressive disease, and limited relevance in patients with relatively late progression and good prognosis. Since the study will compare an active 1-year treatment vs. observation, a too early analysis may lead to overestimation of the effect and not reflect the cure rate. The submitted OS data are immature, the median OS has not been reached and only ~33% of required OS events have taken place at the current CCOD (interim analysis Jan. 2021).

The provided OS data in the dossier with DCO 21.1.2022 were immature with only 33% of OS events having taken place. Mature OS data are required to assess the benefit/risk in the adjuvant setting and are considered mature when a minimum of 60% of OS events have occurred, preferably 70-80%. This was addressed in the AR and at the clarification TC at 18th November 2021.

The MAH is planning 4 interim analysis (IAs) before the final OS analysis. The MAH clarifies that the time for the first OS interim analysis is projected to occur between May and September 2022. It will be conducted when approximately 254 OS events have been observed in the ITT population (information fraction of approximately 45%). To determine the exact CCOD of the first IA, the MAH is planning to perform an OS sweep in January 2022. The MAH will provide the OS data from this 1st IA and further planned OS analyses post-approval in case of a positive benefit/risk assessment for the now restricted indication statement to ≥50% PD-L1 positive stage II-IIIA (7th edition) patients.

Given the now proposed restriction of the indication to a PD-L1 ≥50% TC Stage II-IIIA NSCLC population, it is considered acceptable to submit further OS data post approval. The efficacy data as submitted with the initial dossier support a favourable benefit risk balance for the PD-L1 high expression subgroup even without mature OS data.

This is based on the large effect size of the treatment effect of DFS (stratified DFS HR 0.47, 95% CI 0.29, 0.75), although this analysis was only a key secondary endpoint and not included in the alpha control of the statistical testing; moreover, the sample size of this subgroup represents only about a quarter of the ITT population (all-comer Stage IB-IIIA; n=1005). However, the DFS benefit in the PD-L1 ≥50% TC Stage II-IIIA was further supported by OS data; although the OS results were exploratory and immature (event rates 10% and 23% in the atezolizumab and BSC arms, respectively), the stratified OS HR of 0.40 (95% CI 0.20, 0.81)) is considered reassuring and it cannot be reasonable expected that the benefit as such would not be confirmed with more follow-up data (though the exact value of the treatment effect cannot be precisely determined with the current data cutoff).

The CHMP noted that the primary endpoint, DFS in all randomized patients (ITT) population, is considered acceptable for filing. The MAH has meanwhile changed the primary endpoint to DFS in the ≥1% PD-L1 stage II-IIIA population. The proposed indication is for all ≥1% PD-L1 patients, regardless of stage, so, the subgroup reflective of the primary endpoint is not identical with the subgroup reflective of the proposed indication.

The CHMP strongly argued in favour of a double-blind design vs. placebo and also stated that at least blinded assessment of relapse should be implemented. IMpower010 was conducted as an open-label trial with BSC in the control arm. Moreover, it remained uncertain whether blinded independent central review (BICR) of the data was conducted, since it was not submitted within the current application dossier. In agreement with the Guideline on the evaluation of anticancer medicinal products in man (p. 23/43), considering the open-label nature of this randomized phase III trial, BICR of the investigator-assessed DFS is considered crucial and the MAH submitted the BICR of approximately 50% of the patients. For the population encompassed by the revised indication (stage II-IIIA ≥50% PD-L1 positive patients), the concordant rate between INV-DFS and BICR-DFS in terms of occurrence of an event was 92.6%. When considering the timing of the DFS events, the concordance was 86.8%. The MAH has also presented the results of the DFS analysis using the BIRC assessment. The results of these preliminary analyses are comparable to those reported using the investigator assessment.

The statistical analysis plan and assumptions were generally acceptable at the time of the advice given. However, the CHMP advised the MAH to consider genotyping (e.g. ALK and EGFR) all patients to make future exploratory analyses in different specific subgroups of patients defined by these gene aberrations possible. Nevertheless, a large fraction of the included patients (in 40.3% of patients EGFR or ALK mutation status is not reported) has not been genotyped leaving ALK and EGFR status undetermined.

The primary endpoint of DFS was considered acceptable for filing. However, the CHMP emphasized, that it is foreseeable that patients will be treated with other active agents upon progression under the study treatments. Namely "cross-over" from the control arm to another anti PD-L1/PD1 is quite probable. Therefore, subsequent treatments and their efficacy must be as thoroughly recorded as possible. The MAH provided subsequent therapies for the ITT population and different subgroups. Generally, a higher proportion of patients received at least one follow-up cancer therapy in the BSC arm compared to the atezolizumab arm (e.g. 26.3% vs. 16.5% for the PD-L1 ≥50% TC Stage II-IIIA population) with the largest difference in the proportion of immunotherapy (16.7% vs. 3.5% in the BSC vs. the atezolizumab arm of the ≥50% Stage II-IIIA population).

In the PD-L1 SP263 ≥50% TC Stage II-IIIA population, 29 (25.4%) patients in the BSC arm and 13 (11.3%) patients in the atezolizumab arm had PFS2 events (unstratified HR 0.37; 95% CI 0.19, 0.72). Although based on low event rates, these results can be considered supportive for the benefit of atezolizumab in the revised indication of high PD-L1 expressors.

2.1.2. General comments on compliance with GCP

IMpower010 was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice. The appropriate Ethics Committees and Institutional Review Boards reviewed and approved the study. No critical audit findings were reported in IMpower010.

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

Atezolizumab is an IgG1 monoclonal antibody produced by recombinant DNA technology, a protein with a molecular mass of ~150 kDa. As an unaltered protein, being extensively degraded in the patient's body by regular proteolytic mechanisms before excretion, atezolizumab is unlikely to result in a significant environmental exposure. Atezolizumab is expected to biodegrade in the environment and does not pose a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), atezolizumab is exempt from the submission of Environmental Risk Assessment studies as the product and excipients do not pose a significant risk to the environment.

2.2.2. Discussion and conclusion on non-clinical aspects

The applicant did not submit studies for the ERA. According to the relevant guideline, in the case of products containing proteins as active pharmaceutical ingredient(s), this is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

IMpower010 is a Phase III, open-label, randomized study to investigate the efficacy and safety of atezolizumab (anti-PD-L1 antibody) compared with best supportive care following adjuvant cisplatin-based chemotherapy in patients with completely resected Stage IB-IIIA NSCLC.

GCP

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

The MAH has provided a statement to the effect 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 1: Clinical studies for popPK analysis

Study	Phase	N treated	N Eval PK	Population	Dose and Schedule
IMpower010 [1] (Study GO29527)	III	Atezo Arm: 495 BSC Arm: 495	Atezo Arm: 493 NA	Patients with complete resection of their NSCLC and eligible to receive one of four regimens of cisplatin-based chemotherapy	Adjuvant: Atezolizumab 1200 mg q3w

Atezo= atezolizumab; BSC=Best Supportive Care; Eval.=evaluable; N=Number of patients; NA=not applicable; q3w=every 3 weeks.

2.3.2. Pharmacokinetics

Atezolizumab pharmacokinetics was assessed by non-compartmental (NCA) and population pharmacokinetic (popPK) analyses.

Analytical methods

The VENTANA PD-L1 assay was used for the qualitative immunohistochemical detection of PD-L1 by light microscopy in sections of formalin-fixed, paraffin embedded tissues. PD-L1 expression in NSCLC was determined as the percentage of tumor cells with any membrane staining above background.

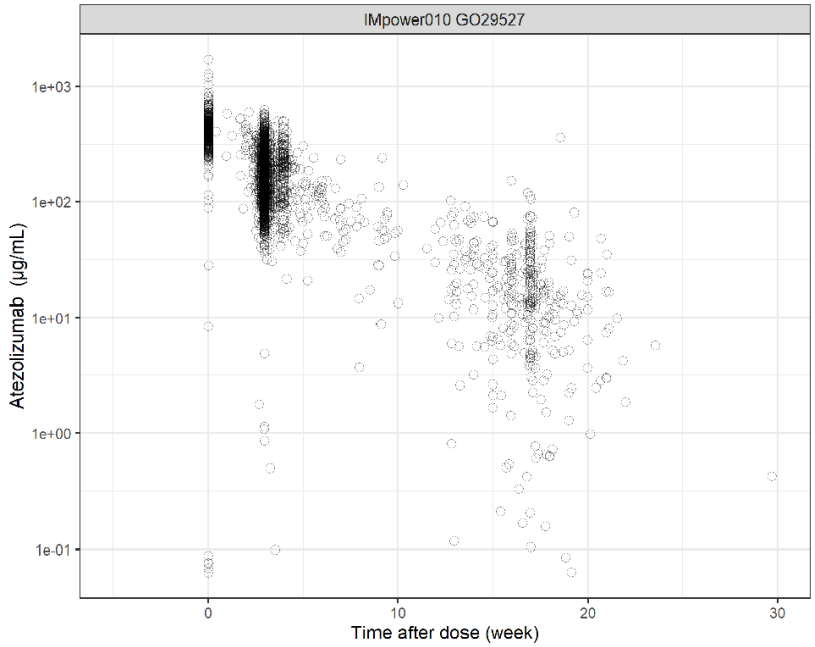
Validated ELISA assays were used to quantify atezolizumab in human serum and for evaluation of immunogenicity status.

Population PK analyses

Pop PK analysis was performed using a non-linear mixed-effects modeling approach with NONMEM, Version 7.3 (ICON, Maryland, USA) and Bayesian post-hoc estimation (MAXEVAL=0). Perl-speaks-NONMEM Version 4.8.1 (Uppsala, Sweden) was used to evaluate/validate the popPK model using predictive checks. Data exploration and visualization, as well as descriptive statistics, were performed using R V3.6.1 in addition to CRAN packages.

In study IMpower010, patients were randomized in a 1:1 ratio to receive either atezolizumab 1200 mg q3w for 16 cycles (Arm A) or best supportive care (Arm B). A total of 3132 atezolizumab serum concentrations from 493 atezolizumab-treated patients were used for the popPK analysis. There were 52 post-dose samples BLQ and 29 samples were excluded for other reasons. In the final data set, 8 observations were associated with a CWRES greater than 5.

Figure 1: Graphical data exploration of atezolizumab concentration data in Impower010



The Phase I popPK model was modified to include an effect of tumor removal after surgery on atezolizumab CL. All other fixed-effects parameters were fixed to the popPK Phase I model. Tumor burden was set to 0 in the dataset after surgery.

Covariate effects (i.e., body weight, ADA status, albumin levels, and gender) in the IMpower010 data were generally consistent with those identified in the modified Phase I popPK model. A 10% decrease in CL was estimated after surgery due to the removal of the tumor before the start of the adjuvant treatment (Table 2).

Table 2: Phase I popPK model parameter estimates for atezolizumab with surgery effect

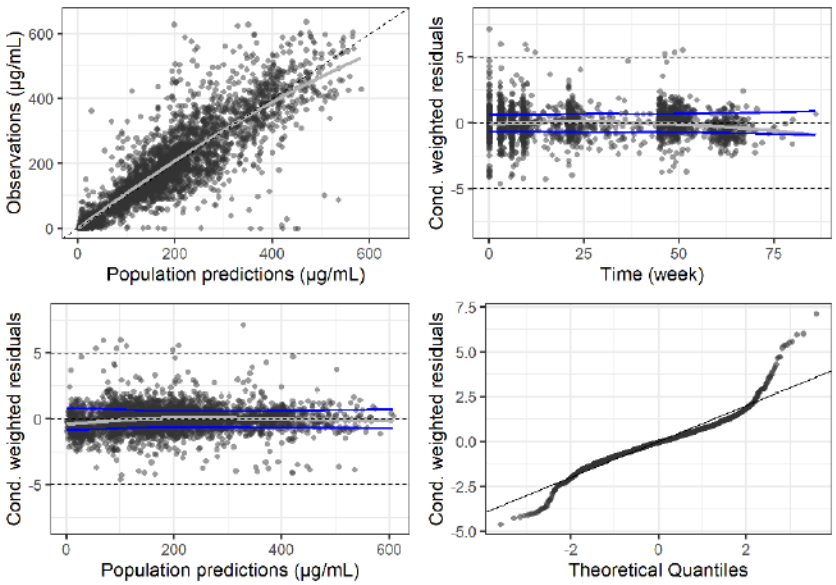
Parameters	Estimate	RSE (%)	Shrinkage (%)	Residual Error or IIV
CL (L/day)	0.200	NA		
V1 (L)	3.28	NA		
V2 (L)	3.63	NA		
Q (L/day)	0.546	NA		
Albumin on CL	-1.12	NA		
Positive ADA on CL	0.159	NA		
Body weight on CL	0.808	NA		
Albumin on V1	-0.350	NA		
Body weight on V1	0.559	NA		
Gender (female) on V1	-0.129	NA		
Gender (female) on V2	-0.272	NA		
Surgery effect[a]	0.897	1.3		
σ^2 Proportional residual error	0.0394	1.5	13	19.8%
σ^2 Additive residual error	16.7	20.1	13	4 µg/mL
ω^2 CL	0.065	5.9	7	26%
ω^2 V1	0.0305	5.5	32	18%
ω^2 V2	0.0455	18	39	22%
Correlation CL.V1	0.257			
Correlation CL.V2	-0.210			
Correlation V1.V2	0.232			
Objective function	26473.238			

CL=clearance; IIV: inter-individual variability; Q=inter-compartmental clearance; RSE= relative standard error; V1= volume of distribution of central compartment; V2=volume of distribution of peripheral compartment; ADA= post-baseline status of anti-drug antibodies; BWT= body weight normalized to 77 kg; Albumin normalized to 40 g/L; Tumor burden normalized to 63 mm; ω^2 =variance of omega; σ^2=variance of sigma.

[a] Surgery effect: impact of tumor removal after the surgery on atezolizumab clearance.

Model diagnostics (pcVPC, goodness-of-fit plots) indicated that the modified Phase I popPK model was adequate to predict atezolizumab pharmacokinetics in IMpower010 patients and to estimate individual exposure parameters in the adjuvant setting (Figures 2-4).

Figure 2: Goodness-of-fit for the PK model of atezolizumab at population level – Impower010



Grey lines are LOESS (locally weighted scatterplot smoothing).
Blue lines are LOESS in positive or negative residuals.

Figure 3: Prediction-corrected VPC of peaks and troughs of atezolizumab (semi-log scale) – after surgery (adjuvant, 1200 mg q3w)

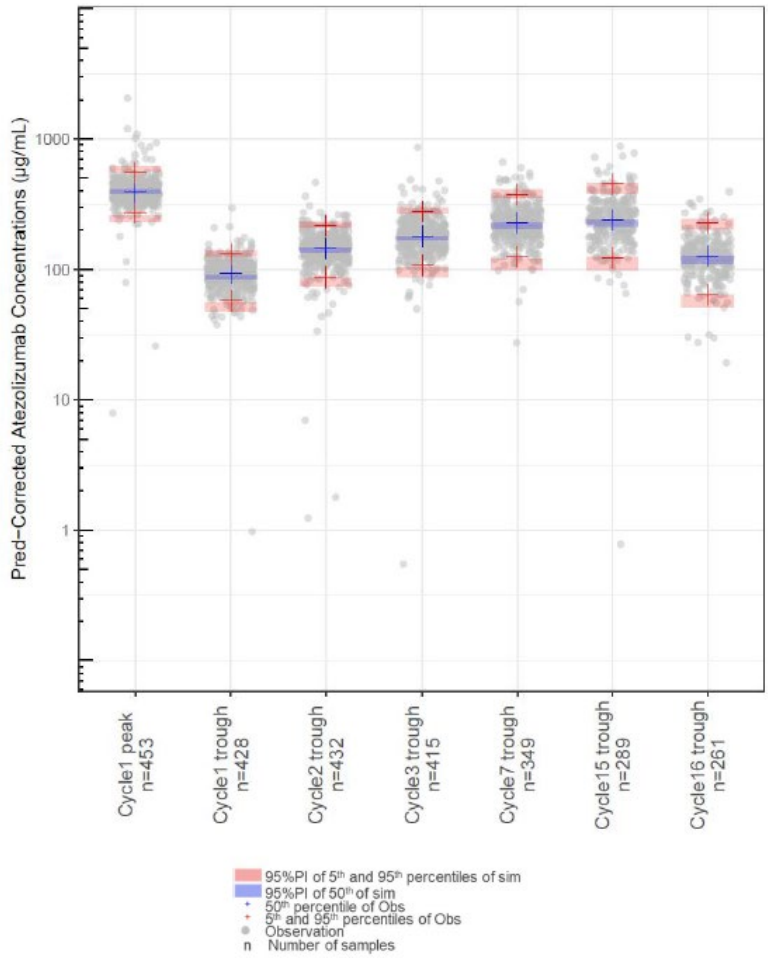
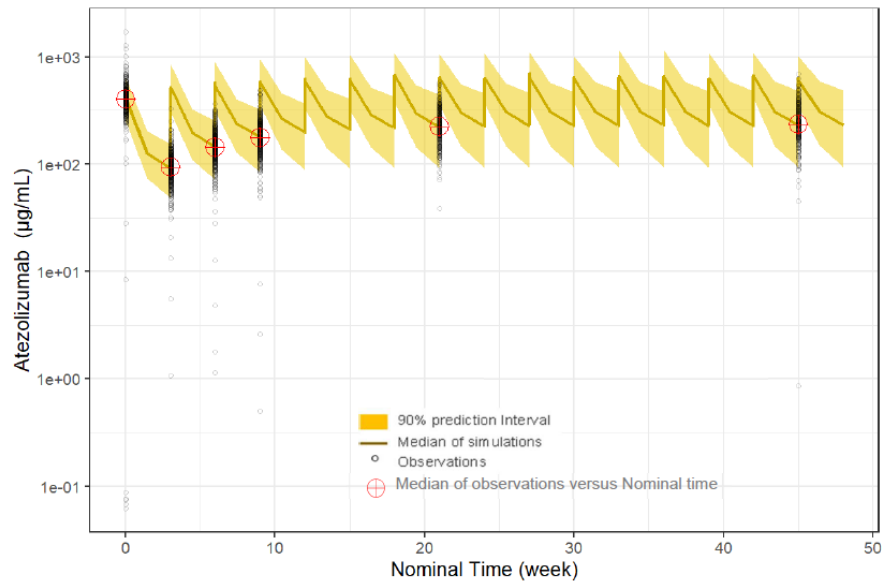


Figure 4: 90% prediction interval of the PK profile using the Phase I popPK model with Impower010 observed concentrations – Impower010



Not all observed data are displayed; x-axis is truncated to 50 weeks.

The individual exposure metrics at Cycle 1 and at steady-state following 1200 mg q3w, was predicted using the modified Phase I popPK model and PK data from Cycle 1. See Table 3 and Table 4. Steady-state exposure was assessed after 10 doses.

Table 3: Summary statistics (geometric mean [geometric mean CV%]) of atezolizumab exposure metrics at Cycle 1 predicted using the modified popPK model – adjuvant period

Study (N)/Arm (N)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC (µg.day/mL)	$t_{1/2}$ beta (day)*
IMpower010, Atezo Arm (N=493)	408 [20.5]	89.7 [23.8]	3280 [18.5]	26.9 [22.0]

Atezo Arm=Atezolizumab; AUC=$AUC_{(0\text{-}21)}$ at Cycle 1; C_{max}=C_{max} at Cycle 1; C_{min}=C_{min} at Cycle 1; CV%=coefficient of variation; N=Number of patients.

*t1/2 beta is the terminal half-life based on post-hoc parameter estimates.

Table 4: Summary statistics (geometric mean [geometric mean CV%]) of atezolizumab exposure metrics at steady state predicted using the modified popPK model – adjuvant period

Study (N)/Arm (N)	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)	$AUC_{,ss}$ (µg.day/mL)	Post-hoc accumulation ratio
IMpower010, Atezo Arm (N=493)	640 [23.3]	226 [36.4]	6980 [28.6]	2.13 [14.5]

$AUC_{,ss}$=AUC at steady-state; Atezo Arm=Atezolizumab; CV%=coefficient of variation; N=number of patients; $C_{max,ss}$= C_{max} at steady-state; $C_{min,ss}$=C_{min} at steady-state.

Absorption

Atezolizumab is administered as an IV infusion. There have been no clinical studies performed with other routes of administration.

Distribution

PopPK analysis indicated that V1 was 3.28 L and Vss was 6.91 L in the typical patient.

Elimination

The metabolism of atezolizumab has not been directly studied. PopPK analysis indicated that the typical CL of atezolizumab was 0.200 L/day and the typical terminal t1/2 was 27 days.

Dose proportionality and time dependencies

Non-compartmental analysis indicated that doses ≥1 mg/kg displayed dose-proportional PK. The popPK model estimated geometric mean accumulation ratio for Cmin, Cmax, and AUC was 2.75, 1.46, and 1.91-fold, respectively, following multiple doses of 1200 mg atezolizumab q3w.

Special populations

In the final popPK model, body weight, albumin, tumor burden, and treatment-emergent ADA were statistically significant covariates for CL; body weight and albumin were statistically significant covariates for V1; and gender was a statistically significant covariate for both V1 and V2.

Pharmacokinetic interaction studies

No pharmacokinetic interaction studies have been submitted.

Pharmacokinetics using human biomaterials

Table 5: Arithmetic mean (SD) serum atezolizumab PK concentrations (µg/ml) by study and treatment group following multiple IV doses of atezolizumab 1200 mg given every 3 weeks

		PCD4989g	OAK	IMmotion151[2]	IMmotion150[2]		IMpower150		IMbrave150	IMpower110	IMpower010
Treatment / Visit[1]	Nominal Time (day)	ATZ (N=47)	ATZ (N=606)	ATZ+Bev (N=449)	ATZ+Bev (N=101)	ATZ (N=103)	ATZ+Bev+ Carb+Pac (N=384)	ATZ+ Carb+Pac (N=396)	ATZ + Bev (N=329)	ATZ (N=284)	ATZ (N=493)
Cycle 1 C_{max}/ post-dose C1D1	0.0625	467 (113)	400 (127)	376 (90.2)	331 (92.1)	337 (125)	414 (127)	410 (157)	398 (132)	411 (163)	417 (147)
Cycle 1 C_{min}/ pre-dose C2D1	21	109 (77.9)	83.2 (31.0)	85.6 (35.3)	72.6 (29.5)	79.1 (27.2)	80.8 (41.4)	76.4 (37.7)	79.2 (50.2)	76.7 (57.6)	98.3 (41.8)
Cycle 2 C_{min}/ pre-dose C3D1	42	166 (81.1)	130 (55.8)	127 (49.6)	121 (51.8)	123 (48.9)	130 (57.1)	119 (55.7)	101 (55.4)	121 (57.7)	157 (81.4)
Cycle 3 C_{max}/ post-dose C3D1	42.04	604 (135)	NA	NA	NA	NA	540 (198)	498 (160)	NA	NA	NA
Cycle 3 C_{min}/ pre-dose C4D1	63	149 (57.5)	158 (66.4)	156 (63.4)	150 (67.0)	159 (84.6)	160 (102)	146 (58.9)	131 (63.7)	154 (90.1)	186 (72.5)
Cycle 6 C_{min}/ pre-dose C7D1	126	118 (NE)	NA	202 (78.2)	183 (90.5)	192 (77.6)	NA	NA	NA	NA	NA
Cycle 7 C_{min}/ pre-dose C8D1	147	NA	205 (99.4)	211 (90.4)	190 (86.3)	200 (90.0)	220 (99.0)	219 (89.6)	145 (61.7)	201 (98.6)	239 (90.8)

ATZ=atezolizumab; Bev=bevacizumab; Carb=carboplatin; Pac=paclitaxel; N=number used to calculate statistics; NA=not available; NE=not evaluated; SD=standard deviation.

[1] Visit is denoted by Cycle abbreviated by "C" and Day abbreviated by "D". For example, C1D1 corresponds to Cycle 1, Day 1, etc.

[2] In IMmotion150 and IMmotion151 defined one Cycle as 6 weeks rather than 3 weeks. All studies evaluated atezolizumab administered IV q3w

AM = Arithmetic Mean; SD = standard deviation; NA = Not Available; NE=not evaluable

Sources: CSR PCD4989g (Report No 1064914), CSR OAK (Report No 1070445), CSR IMmotion151 (1080717), CSR IMmotion150 (1073197), CSR IMpower150 (1077726), CSR IMbrave150 (1104177), CSR IMpower110 (Report No. 1091024), CSR IMpower010 (Report No 1106726).

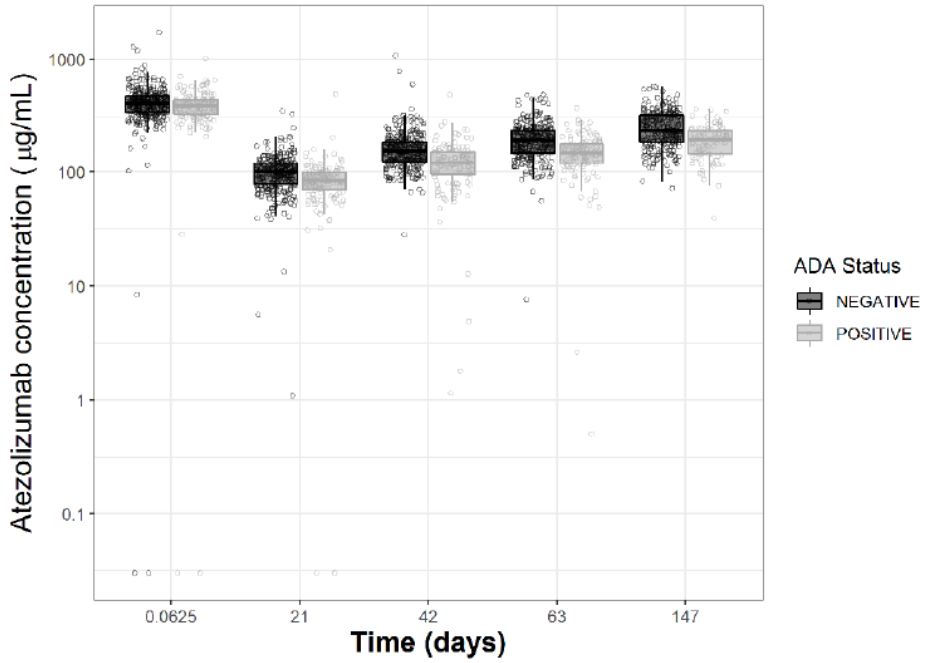
2.3.3. Pharmacodynamics

Primary and secondary pharmacology

Pharmacokinetics by treatment-emergent ADA status

The analysis of observed exposure by ADA status shows that there was lower exposure in the ADA-positive subgroup compared with the ADA-negative subgroup (Figure 5); a statistical t-test of clearance and exposure by ADA was performed and predicted a statistically significant difference between the ADA-positive and ADA-negative subgroups; demonstrating higher clearance and lower exposure in the ADA-positive subgroup (Table 6). However, the vast majority of patients had Cmin above the TE of 6 µg/mL, regardless of ADA status.

Figure 5: Box plots of atezolizumab concentration versus time following multiple IV doses of atezolizumab 1200 mg given every 3 weeks by treatment-emergent ADA status



ADA=anti-drug antibody; IV=intravenous.

The bottom and top of each box represent the 25th and 75th percentiles, respectively. The bold line inside each box represents the median concentration. The whiskers represent the 5th and 95th percentiles.

Note: Time 0.0625 corresponds to Cycle 1 C_{max} and all other timepoints correspond to C_{min}. The figure shows only 7 cycles for presentation purposes; the full concentration versus time profile is appended in the CSR.

Clinical cutoff date: 21 Jan 2021.

Data Source: IMpower010 CSR, Figure 13.

Table 6: Summary statistics (geometric mean [CV%]) and t-test on atezolizumab clearance and exposure metrics by ADA status

Variable (unit)	ADA-Negative N=341*	ADA-Positive N=152	p-value	Ratio 95%CI
Clearance (L/d)	0.162	0.192	1.30E-10	1.19 (1.13,1.25)
Cmax, Cycle 1 (µg/mL)	415	392.4	2.34E-03	0.945 (0.911,0.98)
Cmin, Cycle 1 (µg/mL)	93.4	82.0	2.01E-08	0.877 (0.839,0.917)
$AUC_{0\text{-}21}$, Cycle 1 (µg.day/mL)	3380	3074	2.42E-08	0.909 (0.88,0.94)

AUC0-21=Area under the curve from 0 to 21 days at Cycle 1; Cmin=Individual model-predicted minimum atezolizumab concentration at Cycle 1; Cmax=Individual model-predicted maximum atezolizumab concentration at Cycle 1; CV%=coefficient of variation; CI=confidence interval, the 95% CI for difference/ratio and t-test; N=number of patients in each ADA status group in the popPK population. The two-sided p-value is from a two-sample t-test. P-values for geometric mean ratios are from t-tests on log-transformed PK parameters.

* 6 missing ADA patients were imputed to negative ADA patients.

Data on anti-atezolizumab neutralizing antibodies (NAbs) for the IMpower010 study became available on 5 August 2021. The NAb incidence is being provided for the overall post-treatment anti-drug antibody (ADA)- or NAb-evaluable population, as well as in the programmed death-ligand 1 (PD-L1) SP263 ≥50% tumor cell (TC) Stage II-IIIA population (i.e., intended indicated population) and the PD-L1 SP263 ≥1%

TC Stage II-IIIA population (Table 7, Table 8, and Table 9, respectively). For all populations, the NAb incidence was within the range of 4.3% to 27.5% observed across various atezolizumab Phase II and III studies.

Among the 481 patients who were post-treatment ADA and NAb-evaluable, 107 patients (22%) were ADA-positive/NAb-positive (Table 7). Among the 112 patients who were post-treatment ADA and NAb-evaluable in the PD-L1 SP263 ≥50% TC Stage II-IIIA population, 20 patients (18%) were ADA-positive/NAb-positive (Table 8).

Among the 239 patients who were post-treatment ADA and NAb-evaluable in the PD-L1 SP263 ≥1% TC Stage II-IIIA population, 48 patients (20%) were ADA-positive/NAb-positive (Table 9).

Table 7: Study Impower010: incidence of neutralizing antibodies to atezolizumab (post-treatment ADA or Nab-evaluable population)

Incidence of Treatment Emergent Neutralizing Antibodies (NAbs) to Atezolizumab (RO5541267)
Safety Evaluable Patients
Protocol: GO29527

Unadjusted population	MPDL3280A (N=495)
Treatment-emergent ADA evaluable patients *	487
Post Treatment ADA NAb evaluable patients **	481
ADA+ / Nab+ ***	107 (22%)
ADA+ / Nab- ****	39 (8%)
ADA- *****	335 (70%)

* Pts who received at least one dose of Atezolizumab and have at least one post-baseline ADA sample result
** Tx-e. ADA eval excluding ADA+/NAb missing and ADA+/Nab indet.
*** Patients who are treatment-emergent ADA positive and with at least one post-tx NAb-positive sample.
**** Patients who are treatment-emergent ADA positive and with at least one post-tx NAb-negative sample and no post-tx NAb-positive samples.
Treatment-emergent ADA-positive comprises the following two subgroups:
- Treatment-induced ADA-positive: Patients who are pre-treatment ADA negative or missing pre-treatment ADA data who have at least one post-treatment ADA-positive sample
- Treatment-enhanced ADA-positive: Patients who are pre-treatment ADA positive and who have at least one post-treatment ADA-positive sample with an increase of =0.6 titer units relative to baseline
***** ADA-negative comprises the following two subgroups:
- Patients who are pre-treatment ADA negative or who are missing pre-treatment ADA data and who have all negative post-treatment ADA results
- Treatment-unaffected ADA-negative: Patients who are pre-treatment ADA positive and have at least one post-treatment ADA result but who do not have a post-treatment ADA titer increase of >/= 0.6 titer units relative to baseline
NAb = Anti Therapeutic Neutralizing Antibody

Table 8: Study Impower010: incidence of neutralizing antibodies to atezolizumab (PD-L1 SP263 ≥50% TC stage II-IIIA, post-treatment ADA or Nab-evaluable population)

Incidence of Treatment Emergent Neutralizing Antibodies (NAbs) to Atezolizumab (RO5541267)
Patients with PD-L1 SP263 => 50% TC and with Stage II-IIIA
Protocol: GO29527

Unadjusted population	MPDL3280A (N=113)
Treatment-emergent ADA evaluable patients *	113
Post Treatment ADA NAb evaluable patients **	112
ADA+ / Nab+ ***	20 (18%)
ADA+ / Nab- ****	10 (9%)
ADA- *****	82 (73%)

* Pts who received at least one dose of Atezolizumab and have at least one post-baseline ADA sample result
** Tx-e. ADA eval excluding ADA+/NAb missing and ADA+/Nab indet.
*** Patients who are treatment-emergent ADA positive and with at least one post-tx NAb-positive sample.
**** Patients who are treatment-emergent ADA positive and with at least one post-tx NAb-negative sample and no post-tx NAb-positive samples.
Treatment-emergent ADA-positive comprises the following two subgroups:
- Treatment-induced ADA-positive: Patients who are pre-treatment ADA negative or missing pre-treatment ADA data who have at least one post-treatment ADA-positive sample
- Treatment-enhanced ADA-positive: Patients who are pre-treatment ADA positive and who have at least one post-treatment ADA-positive sample with an increase of =0.6 titer units relative to baseline
***** ADA-negative comprises the following two subgroups:
- Patients who are pre-treatment ADA negative or who are missing pre-treatment ADA data and who have all negative post-treatment ADA results
- Treatment-unaffected ADA-negative: Patients who are pre-treatment ADA positive and have at least one post-treatment ADA result but who do not have a post-treatment ADA titer increase of >/= 0.6 titer units relative to baseline
NAb = Anti Therapeutic Neutralizing Antibody

Table 9: Study Impower010: incidence of neutralizing antibodies to atezolizumab (PD-L1 SP263 ≥1% TC stage II-IIIA, post-treatment ADA or Nab-evaluable population)

Incidence of Treatment Emergent Neutralizing Antibodies (NAbs) to Atezolizumab (RO5541267)
Patients with PD-L1 SP263 => 1% TC and with Stage II-IIIA
Protocol: GO29527

Unadjusted population	MPDL3280A (N=244)
Treatment-emergent ADA evaluable patients *	241
Post Treatment ADA NAb evaluable patients **	239
ADA+ / Nab+ ***	48 (20%)
ADA+ / Nab- ****	17 (7%)
ADA- *****	174 (73%)

* Pts who received at least one dose of Atezolizumab and have at least one post-baseline ADA sample result
** Tx-e. ADA eval excluding ADA+/NAb missing and ADA+/Nab indet.
*** Patients who are treatment-emergent ADA positive and with at least one post-tx NAb-positive sample.
**** Patients who are treatment-emergent ADA positive and with at least one post-tx NAb-negative sample and no post-tx NAb-positive samples.
Treatment-emergent ADA-positive comprises the following two subgroups:
- Treatment-induced ADA-positive: Patients who are pre-treatment ADA negative or missing pre-treatment ADA data who have at least one post-treatment ADA-positive sample
- Treatment-enhanced ADA-positive: Patients who are pre-treatment ADA positive and who have at least one post-treatment ADA-positive sample with an increase of =0.6 titer units relative to baseline
***** ADA-negative comprises the following two subgroups:
- Patients who are pre-treatment ADA negative or who are missing pre-treatment ADA data and who have all negative post-treatment ADA results
- Treatment-unaffected ADA-negative: Patients who are pre-treatment ADA positive and have at least one post-treatment ADA result but who do not have a post-treatment ADA titer increase of >/= 0.6 titer units relative to baseline
NAb = Anti Therapeutic Neutralizing Antibody

2.3.4. Discussion on clinical pharmacology

The bioanalytical reports of sample analysis conducted in clinical study IMpower010 included determination of biomarkers e.g. PD-L1 (SP142), PD-L1 (SP263), serum concentrations of atezolizumab and results of ADA testing.

Samples from 108 patients were evaluated for PD-L1 (SP142), of these 71 patients were determined as negative and 37 were determined as positive. 73 patients were evaluated for PD-L1 (SP263). Upon request of the study team, 933 of the samples initially tested with TC2/IC2 were reanalysed with a different scoring algorithm (TC1/IC1 or TC2/IC2). Due to a Ventana dispenser issue, further 222 samples were retested and rescored. Results of PD-L1 testing were only reported via data transfer.

Validated ELISA assays were used to quantify atezolizumab in human serum and for evaluation of immunogenicity status. The bioanalysis analysis conducted in support of clinical study IMpower010 is considered acceptable with a few minor exceptions.

The Phase I Pop PK model for atezolizumab was fitted to the concentration data from study IMpower010 (3132 atezolizumab serum concentrations from 493 atezolizumab-adjuvant treated patients). The concentrations were predominately sampled within Cycle 1. The model was modified to include an effect of tumor removal and tumor burden was set to zero in the data set. The effect of tumor removal after surgery on CL was estimated to 0.897 (10% decrease in CL). No new covariates were identified. The modified model could adequately describe the IMpower010 data and was used to predict exposure metrics at Cycle 1 and at steady state using Cycle 1 data.

The mean concentrations (Cmax, Cmin) achieved in study IMpower010 were slightly higher compared to concentrations achieved across studies where atezolizumab were given as 1200 mg q3w. This was observed throughout the treatment period. Clearance of atezolizumab is known to be affected by tumor burden and disease status which likely explain the slightly higher serum concentrations observed in IMpower010.

Of 487 atezolizumab treated ADA-evaluable patients in IMpower010, 152 patients were confirmed ADA-positive which is about 30% of the ADA-evaluable population. Exposure was slightly lower in the ADA-positive sub-population compared to the ADA-negative sub-population.

The provided NAB results shows that among 481 ADA and NAb-evaluable patients, 107 patients (22%) were ADA-positive/NAb-positive and 39 patients (8%) were ADA-positive/NAb-negative. In the PD-L1 SP263≥50% TC Stage II-IIIA population, 20 patients (18%) out of 122 patients were ADA positive/NAb positive while 10 patients (9%) were ADA-positive/NAb-negative. In the PD-L1 SP263 ≥1% TC Stage II-IIIA population, 48 patients (20%) were ADA positive/NAb positive while 17 patients (7%) were ADA-positive/NAb-negative. This does not give raise to any concern.

No clinically meaningful ER relationships were identified in previous monotherapy and combination therapies; therefore, no ER analysis was conducted for IMpower010. Furthermore, no new safety finding was observed in IMpower010.

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology of atezolizumab for the intended clinical setting has been adequately described.

2.4. Clinical efficacy

2.4.1. Main study

A Phase III, Open-Label, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab (Anti-PD-L1 Antibody) Compared with Best

Supportive Care Following Adjuvant Cisplatin-Based Chemotherapy in Patients with Completely Resected Stage IB-IIIA Non-Small Cell Lung Cancer.

Methods

IMpower010 is a **Phase III, global, multicenter, open-label, randomized study** comparing the efficacy and safety of atezolizumab versus (best supportive care) BSC in patients with Stage IB (tumors ≥4 cm) - Stage IIIA NSCLC as per the AJCC 7th edition, following complete resection and adjuvant cisplatin-based chemotherapy. The study consists of **two phases**: an enrollment phase and randomized phase.

In the **enrollment phase**, patients who had recently undergone complete resection of their NSCLC were screened, and eligible patients were enrolled to receive one of four regimens of cisplatin-based chemotherapy (cisplatin plus vinorelbine, docetaxel, gemcitabine, or pemetrexed; based on investigator choice).

The **randomized phase** (randomized 1:1) started after patients had completed their cisplatin-based chemotherapy (up to 4 cycles) and were still considered eligible to proceed with randomization.

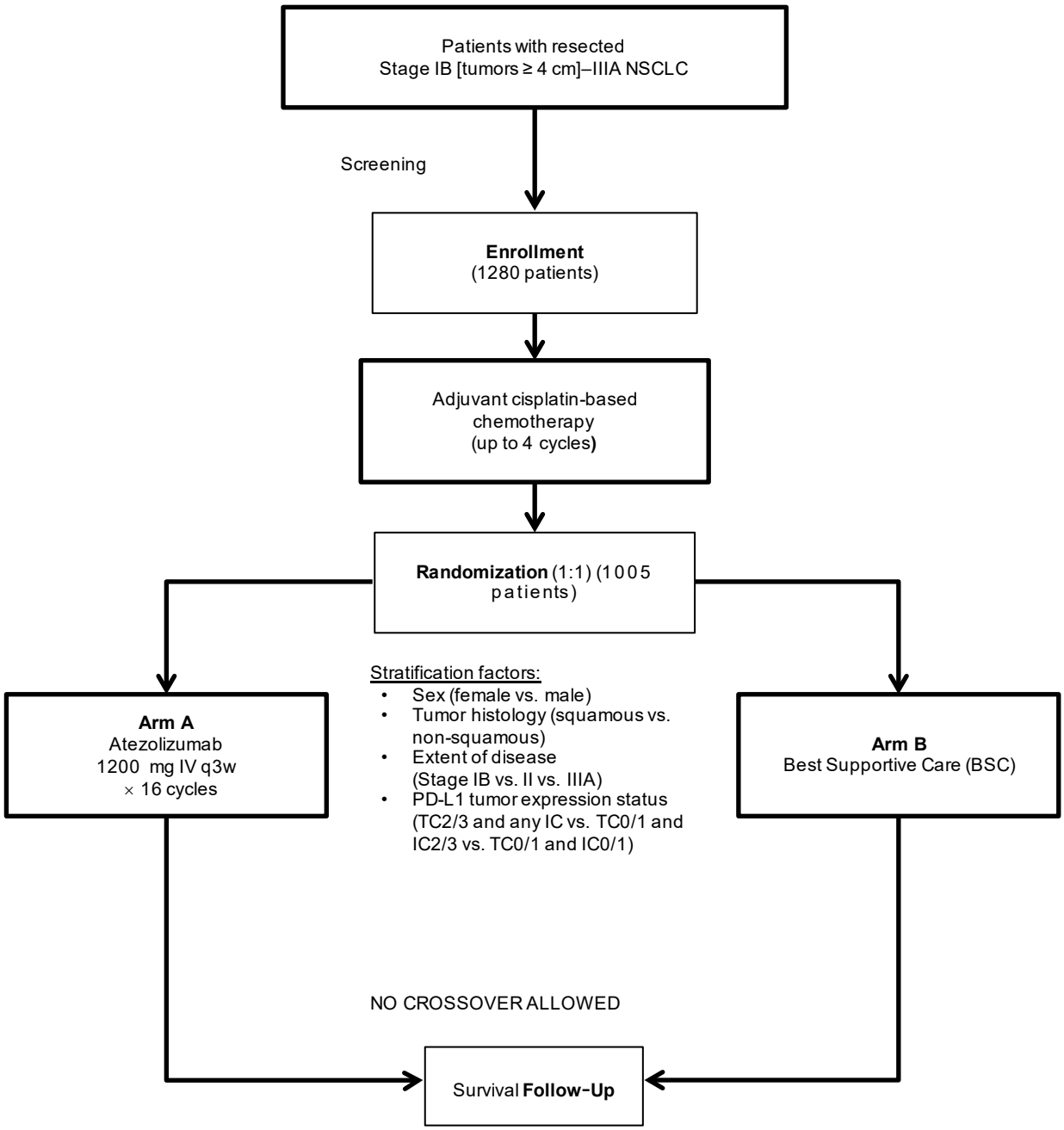
Stratification factors included sex, tumour histology, stage of disease according to AJCC 7th edition and PD-L1 expression according to SP142 testing result.

Patients in the atezolizumab arm received atezolizumab 1200 mg by intravenous (IV) infusion on Day 1 every 3 weeks (q3w) for a total of 16 cycles. Patients in the BSC arm received no treatment during the randomized phase other than best supportive care and were continuously followed starting on Day 1 of each 21-day cycle (considered as observation period) for one year followed by survival follow-up. Cross over to the atezolizumab arm was not permitted.

To ensure the same frequency of study assessments between the treatment arms, including assessments for disease recurrence and safety, patients in the BSC arm were required to undergo medical contact q3w for assessments during the first year for symptom and adverse event (AE) assessment.

The study design is depicted in Figure 6.

Figure 6: IMpower010 Study Schema



IC = tumor-infiltrating immune cell; IV = intravenous; NSCLC = non–small cell lung cancer; PD-L1 = programmed death–ligand 1; q3w = every 3 weeks; TC = tumor cell. **Note:** Patients received up to four cycles of cisplatin-based chemotherapy unless unacceptable toxicity, disease relapse, or patient's decision to discontinue occurred.

Tumour assessments were performed by the investigator every 4 months in the first year and every 6 months in the second year after randomization through Year 5 and annually starting from Year 6. Additional scans could be performed if recurrence of disease was suspected.

Patients from both treatment arms underwent a mandatory tumor biopsy sample collection, unless not clinically feasible as assessed by investigators, at the first evidence of radiographic disease recurrence.

Patients who discontinued treatment before completing the 16 cycles of atezolizumab for reasons other than disease recurrence (e.g., toxicity) continued scheduled tumor assessments until disease recurrence,

death, withdrawal of consent, loss to follow-up, or until the study closes, whichever occurred first, regardless of whether patients started a new anti-cancer therapy.

All patients in the randomized phase were followed for OS and other anti-cancer treatments, approximately every 3 months until death, loss to follow-up, withdrawal of consent or study termination by the Sponsor, whichever occurred first.

Study participants

Key Inclusion criteria

Inclusion criteria for enrollment phase

Patients had to meet all of the following criteria to enter the enrollment phase and receive cisplatin-based chemotherapy regimen in this study:

- A representative formalin-fixed paraffin-embedded (FFPE) tumor specimen in paraffin block (preferred) or 15 (or more) unstained, freshly cut, serial sections (on slides) from an FFPE resected tumor specimen (for further details please see Section 3.5.2.1)
- Histological or cytological diagnosis of Stage IB (tumors≥4 cm)-IIIA (T2-3 N0, T1-3 N1, T1-3 N2, T4 N0-1) NSCLC (per the UICC/AJCC staging system, 7th edition; Detterbeck et al. 2009)
- A complete resection of NSCLC 4-12 weeks (≥28 days and≤84 days) prior to enrollment and adequately recovered from surgery
- Accepted types of resection include any of the following: lobectomy, sleeve lobectomy, bilobectomy, or pneumonectomy. Patients must also have had a protocol-defined mediastinal lymph node evaluation.
- Eligible to receive a cisplatin-based chemotherapy regimen
- Adequate hematologic and end-organ function as defined in the protocol
- For women of childbearing potential and men with partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception during study treatment that resulted in a low failure rate of<1% per year when used consistently and correctly.

Inclusion criteria for randomized phase

Patients had to meet all of the following criteria to be eligible to be randomized to receive either atezolizumab or BSC after completion of the enrollment phase and up to four cycles of cisplatin-based chemotherapy:

- Adequate hematologic and end-organ function as defined in the protocol
- Women who were not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile must have had a negative serum pregnancy test result within 14 days prior to initiation of atezolizumab or BSC

Key exclusion criteria

Exclusion criteria for enrollment phase

Patients who met any of the following criteria were excluded from study enrollment:

- Pregnant and lactating women
- Treatment with prior systemic chemotherapy, with exceptions (see protocol Section 4.1.2)
- Hormonal cancer therapy or radiation therapy as prior cancer treatment within 5 years before enrollment
- Treatment with any other investigational agent with therapeutic intent within 28 days prior to enrollment
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti-PD-1, and anti-PD-L1 therapeutic antibodies
- Malignancies other than NSCLC within 5 years prior to enrollment, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- History of autoimmune disease, (see protocol Section 4.1.2 and Appendix 6 for a more comprehensive list of autoimmune diseases)
- Positive test for HIV
- Patients with active hepatitis B or hepatitis C
- Active tuberculosis
- Significant cardiovascular disease
- History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis
- Prior allogeneic bone marrow transplantation or solid organ transplant
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk from treatment complications
- Known tumor PD-L1 expression status as determined by an IHC assay from other clinical studies (e.g., patients whose PD-L1 expression status was determined during screening for entry into a study with anti-PD-1 or anti-PD-L1 antibodies but were not eligible)
- Patients with squamous cell histology (specific for pemetrexed treatment)

Exclusion criteria for randomized phase

Patients who met any of the following criteria were excluded from study randomization:

- Signs or symptoms of infection within 14 days prior to randomization (severe infection within 28 days prior to randomization), including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Received therapeutic oral or IV antibiotics within 14 days prior to randomization
- Major surgical procedure within 28 days prior to randomization or anticipation of need for a major surgical procedure during the course of the study
- Administration of a live, attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation that such a live attenuated vaccine was required during the study
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferons or interleukin-2) within 4 weeks or 5 drug-elimination half-lives of the drug, whichever was longer, prior to randomization
- Treatment with systemic corticosteroids or other immunosuppressive medications within 14 days prior to randomization

Treatments

Cisplatin-Based Chemotherapy

During the enrollment phase, eligible, surgically resected patients were to receive one of four cisplatin-based chemotherapy options (see Table below). Patients received up to four cycles of cisplatin-based chemotherapy (unless unacceptable toxicity, disease relapse or patient's decision to discontinue occurred), with each cycle being 3 weeks (21 days) in length. The investigator selected the chemotherapy regimen (cisplatin plus either vinorelbine, docetaxel, gemcitabine or pemetrexed) for the patient prior to enrollment.

Cisplatin-Based Chemotherapy Regimens

Regimen	Cisplatin 75 mg/m² IV, Day 1, Plus
1	Vinorelbine 30 mg/m² IV push, Days 1 and 8
2	Docetaxel 75 mg/m² IV, Day 1
3	Gemcitabine 1250 mg/m² IV, Days 1 and 8
4	Pemetrexed 500 mg/m² IV, Day 1 (non-squamous cell NSCLC only)

IV=intravenous; NSCLC=non-small cell lung cancer.

Atezolizumab

During the randomization phase, patients randomized to the atezolizumab arm received 1200 mg atezolizumab by IV infusion on Day 1 of every 21-day cycle. Atezolizumab was infused over 60 (±15) minutes for the first infusion, and if tolerated subsequent infusions were administered over 30 (±10) minutes.

Objectives

The **primary efficacy objective** of the study was as follows:

- To evaluate the efficacy of atezolizumab monotherapy treatment compared with BSC as measured by DFS as assessed by the investigator in the PD-L1 subpopulation (defined as ≥1% TC expression by the SP263 IHC assay) within the Stage II-IIIA population, in all randomized patients with Stage II□IIIA NSCLC, and in the ITT population.

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

- OS in the ITT population
- 3-year and 5-year DFS rates in the PD-L1 subpopulation (defined as ≥1% TC expression by the SP263 IHC assay) within the Stage II-IIIA population, in all randomized patients with Stage II-IIIA NSCLC, and in the ITT population
- DFS in the PD-L1 subpopulation (defined as ≥50% TC expression by the SP263 IHC assay) in patients with Stage II-IIIA NSCLC

Outcomes/endpoints

Primary Efficacy Endpoints

To evaluate the efficacy of atezolizumab monotherapy treatment compared with BSC as measured by **DFS** as assessed by the investigator in

- the PD-L1 ≥1% positive (defined as ≥ 1% TC expression by the SP263 immunohistochemistry [IHC] assay) NSCLC Stage II–IIIA subpopulation
- all randomized patients with Stage II–IIIA NSCLC, any degree of PD-L1 status
- the intent-to-treat (ITT) population; Stage IB (tumour size ≥4 cm)-IIIA, any degree of PD-L1 status

Secondary Efficacy Endpoints

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

- OS in the ITT population
- 3-year and 5-year DFS rates in the PD-L1 subpopulation (defined as ≥ 1% TC expression by the SP263 IHC assay) within the Stage II–IIIA population, in all randomized patients with Stage II–IIIA NSCLC, and in the ITT population
- DFS in the PD-L1 subpopulation (defined as ≥ 50% TC expression by the SP263 IHC assay) in patients with Stage II–IIIA NSCLC

Requested Exploratory Efficacy Analyses

Based on requests at the **pre-submission meeting held on 5 May 2021** between the Sponsor and the (Co-)Rapporteurs, the following post-hoc analyses are included in the submission dossier:

- DFS and OS in the PD-L1 SP263 1-49% TC Stage II-IIIA population
- OS in the PD-L1 SP263 ≥50% TC Stage II-IIIA population
- DFS and OS in the Stage IB population

Subgroup analysis in

- DFS in the PD-L1 SP263 ≥1% TC Stage II IIIA Population
- Disease-Free Survival in the Stage II-IIIA Population by Baseline Characteristics and Biomarker Status

Exploratory analysis

- Disease-Free Survival in the Stage II-IIIA Population by SP142 IHC Test
- Overall Survival in the PD-L1 SP263 ≥1% TC Stage II-IIIA Population
- Overall Survival in the All Randomized Stage II-IIIA Population

Sample size

Approximately 1280 patients are expected to be accrued during the enrollment phase. With an approximate 21% dropout rate during adjuvant cisplatin-based chemotherapy, approximately 1005 patients will enter the randomization phase, including approximately 882 patients in the Stage II-IIIA population, and within Stage II-IIIA NSCLC patients, approximately 474 patients in the PD-L1 subpopulation (≥1% TC expression) defined by the SP263 IHC assay. Emerging data from atezolizumab first-line NSCLC Phase III Study GO29431 (IMpower110; Herbst et al. 2019; Spigel et al. 2019) have

observed clinical benefit with atezolizumab monotherapy in PD-L1 TC-defined subgroups. The TC-based assay SP263 appeared to capture a broader patient population with similar efficacy as compared to SP142. These findings are consistent with results observed in other PD-L1/PD-1 studies. With these data external to Study GO29431 and evolving biomarker landscape, the primary analysis of DFS in the PD-L1 subgroups (TC2/3 or IC2/3, TC1/2/3 or IC1/2/3) defined by SP142 will be replaced with DFS in the PD-L1 subgroup (≥ 1% TC expression) defined by SP263.

The estimates of the number of events required to demonstrate efficacy with regard to DFS are based on the following assumptions:

- 1:1 randomization ratio
- One-sided significance level of 0.025 in the PD-L1 subpopulation defined by SP263 TC ≥ 1% within the Stage II-IIIA population, the randomized Stage II-IIIA population, and the ITT population.

For Stage II-IIIA:

- 89.8% power to detect an HR of 0.65, corresponding to an improvement in median DFS from 34 months to 52 months in the PD-L1 subpopulation defined by SP263 TC ≥ 1% within the Stage II-IIIA population
- 90.7% power to detect an HR of 0.73, corresponding to an improvement in median DFS from 34 months to 46.6 months in the all-randomized Stage II-IIIA population

For Stage IB-IIIA:

- 76.4% power to detect an HR of 0.78, corresponding to an improvement in median DFS from 38 months to 48.7 months in the ITT population
- One DFS interim analysis to be performed when approximately 80% of the total DFS events in the primary efficacy analysis populations required for the primary analysis have occurred.
- Dropout rate of 5% per 24 months

The estimates of the number of events required to demonstrate efficacy with regard to OS are based on the following assumptions:

- 1:1 randomization ratio
- One-sided significance level of 0.025 in the ITT population (i.e., Stage IB-IIIA)
- 77% power to detect an HR of 0.78, corresponding to an improvement in median OS from 66 months to 84.6 months in the ITT population
- Four interim OS analyses to be performed, one at the time of the DFS interim analysis, the second one at the time of DFS final analysis, and the other two when approximately 73% and 88% of the total OS events required for the final analysis have occurred, respectively.
- Dropout rate of 5% per 36 months

With these assumptions, the DFS final analysis will be conducted when approximately 237 DFS events in the PD-L1 subpopulation (defined by SP263 TC≥ 1%) within the Stage II-IIIA population have been observed. This is expected to occur approximately 68 months after the first patient is randomized. This number of events corresponds to a minimum detectable difference in HR of approximately 0. 758 in the PD-L1 subpopulation within the Stage II-IIIA population.

Given the sample size of 1005, the final OS analysis will be conducted when approximately 564 OS events in the all randomized Stage IB-IIIA population have occurred, which is expected at approximately 121 months after the first patient is randomized.

Randomisation

Randomization to the treatment and control arms occured in a 1:1 ratio with use of a permuted-block randomization method. Randomization was stratified by the following factors:

- Sex (female vs. male)
- Tumour histology (squamous vs. non-squamous)
- Extent of disease (Stage IB (tumours ≥4 cm) vs. Stage II vs. Stage IIIA)
- PD-L1 tumour expression status (TC2/3 and any IC vs. TC0/1 and IC2/3 vs. TC0/1 and IC0/1 using the SP142 IHC assay)

Blinding (masking)

The study is open-label.

Statistical methods

Analysis populations

The ITT population is defined as all randomized patients with resected Stage IB (tumours ≥ 4 cm)- IIIA NSCLC, whether or not the patient received the assigned treatment. Patients will be grouped by their assigned treatment at randomization by the IxRS.

The Stage II-IIIA population is defined as all randomized patients with extent of disease as either Stage II or Stage III, and is a subset of the ITT population.

The PD-L1 SP263 biomarker-evaluable population in Stage II-IIIA is defined as all randomized patients from the Stage II-IIIA population who have a valid PD-L1 SP263 measurement at baseline. Similarly, the PD-L1 SP142 biomarker-evaluable population in ITT is defined as all randomized patients from the ITT population who have a valid PD-L1 SP142 measurement at baseline.

Stratification factors in the primary analysis

To manage the small strata size with the consideration of prognostic significance, stratified analyses for DFS in the PD-L1 subpopulation defined by SP263 TC ≥ 1% in Stage II-IIIA NSCLC and stratified analyses for DFS in Stage II-IIIA NSCLC will use the following stratification factors at randomization: stage (II vs. IIIA), sex (female vs. male), and histology (squamous vs. non-squamous).

Stratified analyses for DFS in the ITT population will use the following stratification factors at randomization: stage (IB and II combined vs. IIIA), sex (female vs. male), histology (squamous vs. non-squamous), and PD-L1 tumour expression status by SP142 IHC assay ([TC2/3 and any IC, TC0/1 and IC2/3 combined] vs. TC0/1 and IC0/1).

Stratified analyses of DFS in other PD-L1 subpopulations (e.g., SP263 TC > 50% in Stage II-IIIA NSCLC) will use the same set of stratification factors used for the stratified analyses of DFS in the PD-L1 subpopulation defined by SP263 TC ≥1% in Stage II-IIIA NSCLC.

The set of stratification factors used in the stratified analyses of DFS for a specific analysis population (e.g., the ITT population) will be applied to all other efficacy endpoints where stratified analyses are planned for the same analysis population.

Primary efficacy endpoint DFS

The null and alternative hypotheses regarding DFS in each population can be phrased in terms of the DFS survival functions SA(t) in the atezolizumab arm (Arm A) and SB(t) in the control arm (Arm B), respectively:

H0: SA(t) = SB(t) versus H1: SA(t) > SB(t)

Treatment comparisons will be based on the stratified log-rank test. The HR will be estimated with use of a stratified Cox regression model, including a two-sided 95% CI. The stratification factors used for the analysis are described in Section 4.4. The results for unstratified analysis will also be presented. Kaplan-Meier methodology will be used to estimate the median DFS for each treatment arm and the Kaplan-Meier curve will be constructed to provide a visual description of the difference between the treatment and control arms. Brookmeyer-Crowley methodology will be used to construct the two-sided 95% CI for the median DFS for each treatment arm.

Censoring rules for DFS

Data for patients who are not reported as experiencing disease recurrence, a new primary NSCLC, or death will be censored at the date of the last tumour assessment. If no post-baseline data are available, DFS will be censored at the date of randomization. If recurrence of disease or new primary NSCLC prior to randomization is documented, DFS will be censored at the date of randomization.

Sensitivity analyses for DFS

- Loss to follow-up on DFS: The impact of loss to follow up will be assessed depending on the number of patients who are lost to follow-up. If > 5% of patients are lost to follow-up for DFS in either treatment arm, a sensitivity analysis ("worse-case" analysis) will be performed in which patients who are lost to follow-up will be considered to have recurrent disease at the date of the last tumour assessment.
- Missed Visits for DFS: To evaluate the impact of missed visits, sensitivity analyses with a different censoring rule will be performed for the primary endpoint of DFS. Data for patients with a DFS event who missed two or more scheduled assessments immediately prior to the DFS event will be censored at the last date with adequate radiologic assessment prior to the missed visits.

Secondary endpoint OS

The methodology used for DFS will be applied to OS in the ITT population.

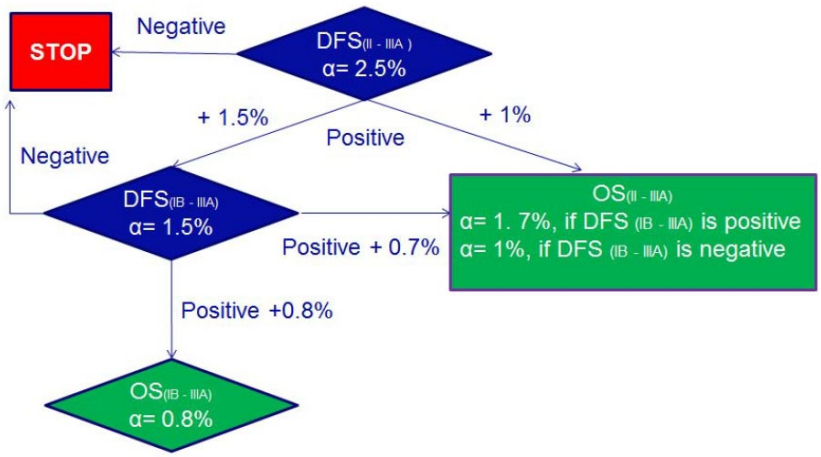
Censoring rules for OS

Data for patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomization.

Type I error control

The overall type I error rate will be controlled for the one-sided test at 0.025. The overview of the alpha control is shown in Figure 2.

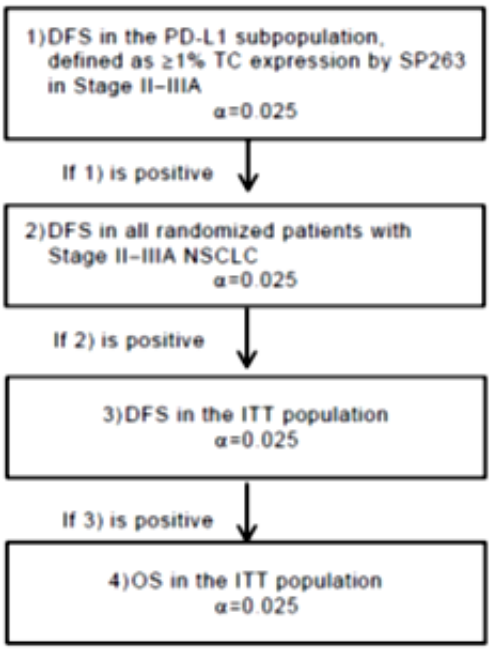
Figure 1: Alpha Control Plan (Protocol Versions 1-4)



DFS = disease-free survival; OS = overall survival.

DFS = disease-free survival; OS overall survival

Figure 2: Overview of the alpha control (one-sided)



DFS = disease-free survival; ITT = intent to treat; OS = overall survival; TC = tumor cells.

Interim analyses for DFS

There will be one planned interim DFS analysis in the study. To control the type I error for DFS at a one-sided alpha of 0.025, the stopping boundaries for the interim and final DFS analyses are to be computed with use of the Hwang-Shih-DeCani alpha spending function with the gamma parameter of -0.9 as shown in Table 10. Boundaries will be adjusted based on observed numbers of DFS events, and the exact timing of this analysis will depend on the occurrence of DFS events.

Table 10: Analysis timing and stopping boundaries for disease-free survival

Type of Analysis	Planned Information Fraction	No. of Events (SP263 TC≥1% in Stage II–IIIA/ Stage II–IIIA/ITT)	Stopping Boundary (one-sided p-value)		
			Stage II–IIIA NSCLC PD-L1 Subpopulation with SP263 TC ≥1%	Stage II–IIIA NSCLC	ITT NSCLC
DFS interim analysis	80%	190/367/394	HR ≤ 0.738 (p ≤ 0.0181)	HR ≤ 0.803 (p ≤ 0.0181)	HR ≤ 0.810 (p ≤ 0.0181)
DFS final analysis	100%	237/459/492	HR ≤ 0.758 (p ≤ 0.0167)	HR ≤ 0.820 (p ≤ 0.0167)	HR ≤ 0.825 (p ≤ 0.0167)

HR = hazard ratio; NSCLC = non–small cell lung cancer; DFS = disease-free survival.

Interim analyses for OS

Four interim OS efficacy analyses are planned. The exact timing of these OS analyses will depend on the occurrence of OS events. If a significantly smaller number of OS events (< 224 events) is observed at the first OS IA, a nominal one-sided type I error of 0.00005 will be assigned to test the first OS IA; all the following OS analyses will be conducted based on the pre-specified number of events in Table 11.

Table 11: Stopping boundaries for overall survival in ITT (Stage IB-IIIA)

Type of Analysis	Analysis Timing (Months from FPI)	Planned Information Fraction (Number of Events)	Stopping Boundary in HR (p-Value)
			One-Sided α=0.025
OS first interim analysis	56	45% (254)	HR ≤ 0.678 (p ≤ 0.0010)
OS second interim analysis	68	59% (333)	HR ≤ 0.780 (p ≤ 0.0119)
OS third interim analysis	83	73% (412)	HR ≤ 0.813 (p ≤ 0.0181)
OS fourth interim analysis	102	88% (497)	HR ≤ 0.809 (p ≤ 0.0093)
OS final analysis	121	100% (564)	HR ≤ 0.811 (p ≤ 0.0063)

FPI = first patient in; HR = hazard ratio; NSCLC = non–small cell lung cancer; OS = overall survival.

SAP Appendix 5: Modification plan

On the basis of results observed from the ongoing Phase III studies as presented in Table 1, the Sponsor may be able to improve the design of the ongoing IMpower010.

The possible modifications to IMpower010 are discussed in Section 2. These modifications include the PD-L1-selected and ITT populations for the primary endpoint of DFS and secondary endpoint of OS to be tested in a different order, and/or with a different alpha control method, and/or different analysis timing than what is specified in Section 6 of the current Protocol GO29527 (Version 8).

The proposed modifications to IMpower010 as outlined in this Modification Plan will be based on data generated outside of the study, with the exception of cumulative population-level PD-L1 expression prevalence data in the combined treatment arms based on ongoing study monitoring. No modifications will be based on any interim analysis of IMpower010. As such, this study is not considered an adaptive design clinical study as defined in the U.S. Food and Drug Administration's February 2010 draft guidance "Adaptive Design Clinical Trials for Drugs and Biologics" and in the European Medicines Agency's October 2007 "Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design." Any modification derived from data entirely outside of IMpower010 will not result in statistical bias (e.g., the type I error will not be inflated).

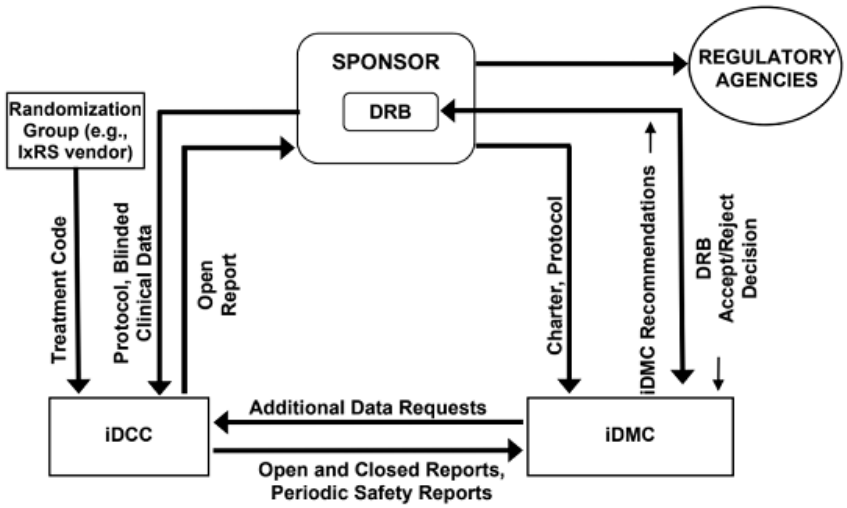
Table 12: Potential modification scenarios in IMpower010

Observed Results from External Data	Potential Modifications to DFS Final Analysis in IMpower010
Treatment effects in adjuvant studies with other agents are stronger than assumed	Decrease study follow-up time for DFS/OS interim and/or final analysis
Delayed treatment effects are observed in adjuvant studies with other agents, or their DFS IA/FA results are negative	Increase study follow-up time for DFS interim and/or final analysis

DFS=disease-free survival; OS=overall survival; IA=interim analysis; FA=final analysis.

Changes in the planned analyses

All changes in the planned analyses for the study that were described in the protocol were implemented in the SAP. This study only has one version of SAP. There were no changes after the SAP was finalized. The analyses described in the SAP supersede those specified in the study protocol, as applicable.



DRB=Data Review Board; iDCC=independent Data Coordinating Center; iDMC=independent Data Monitoring Committee; IxRS=interactive voice or Web-based response system.

Table 13: TC-Based Assays Used in External NSCLC Studies

	HR (95% CI)	Median (months)	Median (months)	Approved Study? (Yes/No)	Reference
KEYNOTE-024					
		Pembrolizumab	Chemo	Yes in TPS ≥50% in the U.S. and EU	
TPS ≥50%	OS: 0.60 (0.41-0.89)	NR	NR		Reck et al. 2016
TPS ≥50%	Updated OS: 0.63 (0.47-0.86)	30	14.2		Reck et al. 2019
KEYNOTE-042					
		Pembrolizumab	Chemo	Yes in TPS ≥1% (U.S.) and in TPS ≥50% (EU)	
TPS ≥50%	OS: 0.69 (0.56-0.85)	20.0	12.2		Lopes et al. 2018
TPS ≥20%	OS: 0.77 (0.64-0.92)	17.7	13.0		
TPS ≥1%	OS: 0.81 (0.71-0.93)	16.7	12.1		
PACIFIC					
		Durvalumab	Chemo		

ITT	PFS: 0.52 (0.42-0.65)	16.8	5.6	Yes in all-comers (U.S.) and in TC ≥1% (EU)	Antonia et al. 2017
ITT	OS: 0.68 (0.53-0.87)	NR	28.7		Antonia et al. 2018
TC ≥1%	OS: 0.53 (0.36-0.77)	NR	29.1		Durvalumab SmPC*

EU=European Union; HR=hazard ratio; ITT=intent to treat; NR=not reached; NSCLC=non-small cell lung cancer; OS=overall survival; TC=tumor cell; TPS=tumor proportion score; U.S.=United States.
Note: These three studies used the following PD-L1 assays: Dako 22C3 in KEYNOTE-024 and KEYNOTE-042, and VENTANA SP263 in PACIFIC.
*SmPC publication date: 25 September 2018.

Results

Participant flow

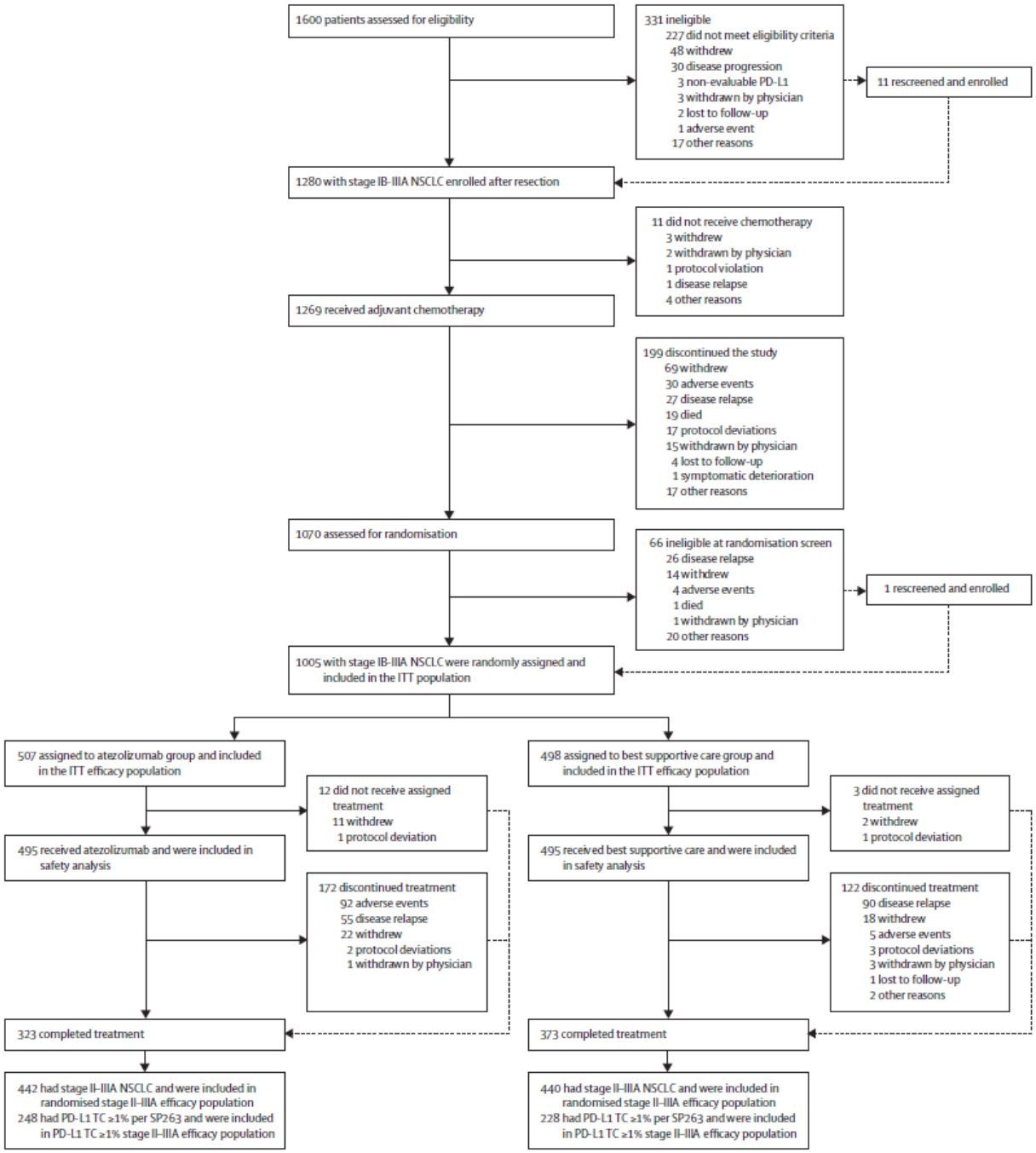
Table 14: Patient Disposition (ITT Population)

Protocol: GO29527
Snapshot Date: 26FEB2021 Clinical Data Cutoff Date: 21JAN2021

	Best Supportive Care (BSC) (N=498)	Atezolizumab (N=507)	All Patients (N=1005)
Received treatment	495 (99.4%)	495 (97.6%)	990 (98.5%)
On study status			
Ongoing	371 (74.5%)	386 (76.1%)	757 (75.3%)
Discontinued	127 (25.5%)	121 (23.9%)	248 (24.7%)
Discontinued study			
Death	88 (17.7%)	91 (17.9%)	179 (17.8%)
Disease relapse	0	1 (0.2%)	1 (<0.1%)
Lost to follow-up	4 (0.8%)	0	4 (0.4%)
Physician decision	3 (0.6%)	0	3 (0.3%)
Protocol deviation	0	2 (0.4%)	2 (0.2%)
Withdrawal by subject	32 (6.4%)	27 (5.3%)	59 (5.9%)

Includes study disposition events occurring on or after the randomization date.

Figure 3: Patient Disposition



Recruitment

Patients in the randomized phase of the study were recruited from 204 centers across 21 countries. The majority of centers each recruited between 1-10 patients; the 5 highest enrolling sites each recruited between 26-44 patients. 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: Russian Federation 153 patients (14 sites), Ukraine 131 (10), Spain 94 (21), Germany 75 (19), France 55 (11), Italy 46 (13), Hungary 45 (4), Portugal 13 (4), Poland 11 (2), Israel 10 (5), United Kingdom 8 (3), Netherlands 6 (3), Romania 4 (1)
- Asia-Pacific: Japan 117 (23), China 75 (11), Taiwan 34 (8), Republic of Korea 5 (1), Australia 2 (1), Hong Kong 2 (1)

- North America: United States of America 112 (47), Canada 7 (2)

The first patient was randomized on 26 February 2016 and the last patient was randomized on 16 January 2019.

Conduct of the study

Protocol amendments:

Table 15: Key protocol changes for study Impower010 (versions 1 to 8)

	Protocol Versions 1–4 (1 April 2015, 8 June 2015, 5 September 2015, 5 October 2015)	Protocol Versions 5-6 (29 June 2016, 2 March 2018)	Protocol Version 7 (30 October 2018)	Protocol Version 8 (11 February, 2020)
Number of randomized patients planned	760	1014	990	1005
Population for enrollment	TC3 or IC3 by SP142	All corners	No change from previous version	No change from previous version
Primary endpoint	INV-assessed DFS	No change from previous version	No change from previous version	No change from previous version
First hypothesis to be tested	DFS for all randomized Stage II-IIIA patients	DFS for the PD-L1 subpopulation defined as TC2/3 or IC2/3 by SP142 in Stage II-IIIA patients	No change from previous version	DFS for the PD-L1 subpopulation defined as TC≥1% by SP263 in Stage II-IIIA patients
Interim analysis for DFS	No interim analysis for DFS	No change from previous version	One interim analysis for DFS	No change from previous version
Alpha spending function	Lan-DeMets O'Brien-Fleming approximation spending function for OS	No change from previous version	Lan-DeMets O'Brien-Fleming approximation spending function for DFS and OS	Hwang-Shih-DeCani alpha-spending function with the gamma parameter of -0.9 for DFS and the alpha spending function with the cumulative one-sided alpha of 0.001, 0.012, 0.022, 0.024, and 0.025 for 4 interim analyses and 1 final analysis for OS
Trigger for the first analysis	The number of DFS events in Stage II-IIIA patients, DFS events in ITT, and the last patient being randomized	The number of DFS events in PD-L1 subpopulations (defined as TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3 by SP142) in Stage II-IIIA patients, DFS events in all randomized Stage II-IIIA patients, DFS events in PD-L1 subpopulations (defined as TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3 by SP142) in ITT, DFS events in ITT, and the last patient being randomized	The number of DFS events in PD-L1 subpopulations (defined as TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3 by SP142) in Stage II-IIIA patients, DFS events in all randomized Stage II-IIIA patients, DFS events in ITT	The number of DFS events in PD-L1 subpopulation (defined as TC≥1% by SP263) in Stage II-IIIA

Secondary efficacy endpoints	OS in all randomized Stage II-IIIA patients and OS in ITT	OS in the PD-L1 subpopulations (defined as TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3 by SP142) in both Stage II-IIIA patients and ITT; OS in all randomized Stage II-IIIA patients, OS in ITT; 3-year DFS and 5-year DFS in PD-L1 subpopulations (defined as TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3 by SP142) in both Stage II-IIIA patients and ITT; 3-year DFS and 5-year DFS in all randomized Stage II-IIIA patients; and 3-year DFS and 5-year DFS in ITT	OS in ITT; DFS in PD-L1 subpopulations defined by SP263 in both Stage II-IIIA patients and ITT; 3-year DFS and 5-year DFS in PD-L1 subpopulations (defined as TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3 by SP142) in both Stage II-IIIA patients and ITT; 3-year DFS and 5-year DFS in both Stage II-IIIA randomized patients and in ITT	OS in ITT; DFS in the PD-L1 subpopulation defined as TC≥50% by SP263 in Stage II-IIIA patients; 3-year DFS and 5-year DFS in PD-L1 subpopulations (defined as TC≥1% and TC≥50% by SP263) in both Stage II-IIIA patients and ITT; 3-year DFS and 5-year DFS in both Stage II-IIIA patients and ITT
Stratification factors	▪ Sex (male vs. female) ▪ Histology (non-squamous vs. squamous) ▪ Stage (IB vs. II vs. IIIA) ▪ PD-L1 tumor expression status (TC3 and any IC vs. TC0/1/2 and IC3)	▪ Sex (male vs. female) ▪ Histology (non-squamous vs. squamous) ▪ Stage (IB vs. II vs. IIIA) ▪ PD-L1 tumor expression status (TC2/3 and any IC vs. TC0/1 and IC2/3 vs. TC0/1 and IC0/1)	No change from previous version	No change from previous version

DFS=disease-free survival; IC=tumor-infiltrating immune cell; INV=investigator; ITT=intent to treat; OS=overall survival; PD–L1=programmed death ligand-1; TC=tumor cell.

Table 16: 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 tumor area occupied by tumor 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 tumor area occupied by tumor 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 tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC2
Presence of discernible PD-L1 staining of any intensity in ICs covering **≥ 10%** of tumor area occupied by tumor 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 = tumor-infiltrating immune cell; IHC = immunohistochemistry; PD-L1 = programmed death–ligand 1; TC = tumor cell.

Table 17: Criteria for PD-L1 expression assessment for the Ventana PD-L1 (SP263) assay

PD-L1 Interpretation	Staining Description
≥1% TC	≥1% of tumor cells with membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control.
<1% TC	<1% of tumor cells with membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control.

TC=tumor cell, PD-L1=programmed death-ligand 1

Table 18: Major protocol deviations (ITT population) (COD: 21 January 2021)

Protocol Deviation Category Protocol Deviation Description	Best Supportive Care (BSC) (N=498)	Atezolizumab (N=507)	All Patients (N=1005)
Total number of patients with at least one deviation	123 (24.7%)	147 (29.0%)	270 (26.9%)
Overall total number of deviations	195	203	398
Inclusion criteria			
Total number of patients with at least one deviation	20 (4.0%)	13 (2.6%)	33 (3.3%)
Total number of events	23	15	38
ICF - Other (e.g. procedural issues)	4 (0.8%)	1 (0.2%)	5 (0.5%)
Inc. criteria procedural issue, e.g. out of window	7 (1.4%)	2 (0.4%)	9 (0.9%)
Inclusion criteria related test not done	5 (1.0%)	5 (1.0%)	10 (1.0%)
Inclusion lab values outside allowed limits	3 (0.6%)	3 (0.6%)	6 (0.6%)
Non-Stage IB (>= 4cm) - IIIA NSCLC	2 (0.4%)	1 (0.2%)	3 (0.3%)
Other inclusion criteria	0	1 (0.2%)	1 (<0.1%)
Exclusion criteria			
Total number of patients with at least one deviation	5 (1.0%)	6 (1.2%)	11 (1.1%)
Total number of events	5	6	11
Ex. criteria procedural issue, e.g. out of window	1 (0.2%)	3 (0.6%)	4 (0.4%)
Exclusion related test not done	1 (0.2%)	0	1 (<0.1%)
History of excluded conditions	1 (0.2%)	0	1 (<0.1%)
Other randomization exclusion criteria	2 (0.4%)	1 (0.2%)	3 (0.3%)
Severe infections w/in 4 w or antibiotics w/ in 2w	0	2 (0.4%)	2 (0.2%)
Medication			
Total number of patients with at least one deviation	2 (0.4%)	21 (4.1%)	23 (2.3%)
Total number of events	2	22	24
Continuation of study Tx in conflict with protocol	0	5 (1.0%)	5 (0.5%)
Dose missed or significantly out of window	0	10 (2.0%)	10 (1.0%)
Received incorrect study medication	1 (0.2%)	2 (0.4%)	3 (0.3%)
Received prohibited concomitant therapy/ medication	1 (0.2%)	3 (0.6%)	4 (0.4%)
Significant deviation from planned chemotherapy dose	0	1 (0.2%)	1 (<0.1%)
Procedural			
Total number of patients with at least one deviation	107 (21.5%)	116 (22.9%)	223 (22.2%)
Total number of events	165	160	325
Error with stratification or randomization	14 (2.8%)	28 (5.5%)	42 (4.2%)
Fail to report SAE/pregnancy according to protocol	6 (1.2%)	7 (1.4%)	13 (1.3%)
ICF - Other (e.g. procedural issues)	39 (7.8%)	61 (12.0%)	100 (10.0%)
Omission of any tumor assessment	9 (1.8%)	14 (2.8%)	23 (2.3%)
Omission of non-tumor study assessment	50 (10.0%)	25 (4.9%)	75 (7.5%)
On study disease assessment outside of window during treatment	4 (0.8%)	2 (0.4%)	6 (0.6%)

Includes protocol deviations occurring on or after the randomization date.

Baseline data

Table 19: Summary of baseline demographic characteristics (ITT population) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=498)	Atezolizumab (N=507)	All Patients (N=1005)
Age (yrs) at randomization*			
n	498	507	1005
Mean (SD)	61.1 (9.2)	61.2 (8.4)	61.2 (8.8)
Median	62.0	62.0	62.0
Min - Max	26 - 84	33 - 83	26 - 84
Age group 1 (yrs) at randomization*			
n	498	507	1005
< 65	300 (60.2%)	323 (63.7%)	623 (62.0%)
>= 65	198 (39.8%)	184 (36.3%)	382 (38.0%)
Age group 2 (yrs) at randomization*			
n	498	507	1005
< 65	300 (60.2%)	323 (63.7%)	623 (62.0%)
65 - 74	173 (34.7%)	164 (32.3%)	337 (33.5%)
75 - 84	25 (5.0%)	20 (3.9%)	45 (4.5%)
Sex per eCRF			
n	498	507	1005
Male	335 (67.3%)	337 (66.5%)	672 (66.9%)
Female	163 (32.7%)	170 (33.5%)	333 (33.1%)
Sex per IxRS			
n	498	507	1005
Male	334 (67.1%)	337 (66.5%)	671 (66.8%)
Female	164 (32.9%)	170 (33.5%)	334 (33.2%)
Race			
n	498	507	1005
Asian	112 (22.5%)	130 (25.6%)	242 (24.1%)
Black or African American	1 (0.2%)	5 (1.0%)	6 (0.6%)
Native Hawaiian or other Pacific Islander	1 (0.2%)	1 (0.2%)	2 (0.2%)
White	376 (75.5%)	362 (71.4%)	738 (73.4%)
Multiple	1 (0.2%)	0	1 (<0.1%)
Unknown	7 (1.4%)	9 (1.8%)	16 (1.6%)
Ethnicity			
n	498	507	1005
Hispanic or Latino	9 (1.8%)	5 (1.0%)	14 (1.4%)
Not Hispanic or Latino	478 (96.0%)	484 (95.5%)	962 (95.7%)
Not Stated	7 (1.4%)	13 (2.6%)	20 (2.0%)
Unknown	4 (0.8%)	5 (1.0%)	9 (0.9%)
Weight (kg) at randomization*			
n	495	495	990
Mean (SD)	74.45 (15.80)	73.62 (16.53)	74.03 (16.17)
Median	73.00	71.50	72.35
Min - Max	43.1 - 140.0	39.6 - 132.5	39.6 - 140.0
ECOG performance status at randomization*			
n	498	507	1005
0	283 (56.8%)	273 (53.8%)	556 (55.3%)
1	214 (43.0%)	232 (45.8%)	446 (44.4%)
2	1 (0.2%)	2 (0.4%)	3 (0.3%)
Tobacco use history			
n	498	507	1005
Never	108 (21.7%)	114 (22.5%)	222 (22.1%)
Current	86 (17.3%)	76 (15.0%)	162 (16.1%)
Previous	304 (61.0%)	317 (62.5%)	621 (61.8%)

*At randomization is defined as the last assessment value before the start of treatment date in the randomization period.

Table 20: Summary of baseline disease characteristics (ITT population) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=498)	Atezolizumab (N=507)	All Patients (N=1005)
Stage per eCRF			
n	498	507	1005
STAGE IB	58 (11.6%)	65 (12.8%)	123 (12.2%)
STAGE IIA	148 (29.7%)	147 (29.0%)	295 (29.4%)
STAGE IIB	84 (16.9%)	90 (17.8%)	174 (17.3%)
STAGE IIIA	208 (41.8%)	205 (40.4%)	413 (41.1%)
Stage per IxRS			
n	498	507	1005
STAGE IB	47 (9.4%)	49 (9.7%)	96 (9.6%)
STAGE II	237 (47.6%)	244 (48.1%)	481 (47.9%)
STAGE IIIA	214 (43.0%)	214 (42.2%)	428 (42.6%)
Histology per eCRF			
n	498	507	1005
Squamous	167 (33.5%)	179 (35.3%)	346 (34.4%)
Non-squamous	331 (66.5%)	328 (64.7%)	659 (65.6%)
Histology per IxRS			
n	498	507	1005
Squamous	169 (33.9%)	179 (35.3%)	348 (34.6%)
Non-squamous	329 (66.1%)	328 (64.7%)	657 (65.4%)
Time since initial NSCLC diagnosis to first treatment in randomisation (months)			
n	493	491	984
Mean (SD)	5.43 (1.27)	5.47 (1.13)	5.45 (1.20)
Median	5.19	5.29	5.22
Min - Max	2.3 - 13.2	2.4 - 10.0	2.3 - 13.2
EGFR mutation status			
n	498	507	1005
Detected	64 (12.9%)	53 (10.5%)	117 (11.6%)
Not Detected	266 (53.4%)	261 (51.5%)	527 (52.4%)
Unknown	168 (33.7%)	193 (38.1%)	361 (35.9%)
ALK mutation status			
n	498	507	1005
Yes	18 (3.6%)	15 (3.0%)	33 (3.3%)
No	294 (59.0%)	280 (55.2%)	574 (57.1%)
Unknown	186 (37.3%)	212 (41.8%)	398 (39.6%)
EGFR mutation or ALK mutation			
n	498	507	1005
Yes	82 (16.5%)	67 (13.2%)	149 (14.8%)
No	230 (46.2%)	221 (43.6%)	451 (44.9%)
Unknown	186 (37.3%)	219 (43.2%)	405 (40.3%)
KRAS mutation			
n	498	507	1005
Detected	17 (3.4%)	21 (4.1%)	38 (3.8%)
Not Detected	35 (7.0%)	45 (8.9%)	80 (8.0%)
Unknown	446 (89.6%)	441 (87.0%)	887 (88.3%)
Patients not tested for a specific mutation are listed with "unknown" status.			
Largest Tumor Diameter (cm)			
n	498	507	1005
Mean (SD)	4.46 (2.25)	4.42 (2.14)	4.44 (2.20)
Median	4.20	4.00	4.10
Min - Max	0.6 - 16.0	0.6 - 14.2	0.6 - 16.0
Site of Primary Tumor			
n	498	507	1005
BILATERAL	1 (0.2%)	0	1 (<0.1%)
LEFT	239 (48.0%)	227 (44.8%)	466 (46.4%)
RIGHT	258 (51.8%)	280 (55.2%)	538 (53.5%)
Subtype Histology in Non-Squamous			
n	331	328	659
ADENOCARCINOMA	308 (93.1%)	300 (91.5%)	608 (92.3%)
ADENOCARCINOMA WITH NEUROENDOCRINE FEATURES	2 (0.6%)	4 (1.2%)	6 (0.9%)
ADENOSQUAMOUS	5 (1.5%)	7 (2.1%)	12 (1.8%)
BRONCHIOLOALVEOLAR CARCINOMA	2 (0.6%)	4 (1.2%)	6 (0.9%)
LARGE CELL	11 (3.3%)	8 (2.4%)	19 (2.9%)
NOT APPLICABLE	0	3 (0.9%)	3 (0.5%)
SARCOMATOID	1 (0.3%)	0	1 (0.2%)
UNDIFFERENTIATED	2 (0.6%)	1 (0.3%)	3 (0.5%)
UNKNOWN	0	1 (0.3%)	1 (0.2%)
Primary Tumor Stage			
n	498	507	1005
T1A	46 (9.2%)	36 (7.1%)	82 (8.2%)
T1B	37 (7.4%)	51 (10.1%)	88 (8.8%)
T2A	191 (38.4%)	206 (40.6%)	397 (39.5%)
T2B	81 (16.3%)	72 (14.2%)	153 (15.2%)
T3	116 (23.3%)	120 (23.7%)	236 (23.5%)
T4	26 (5.2%)	22 (4.3%)	48 (4.8%)
TX	1 (0.2%)	0	1 (<0.1%)
Regional Lymph Node Stage (pN)			
n	498	507	1005
N0	169 (33.9%)	183 (36.1%)	352 (35.0%)
N1	178 (35.7%)	170 (33.5%)	348 (34.6%)
N2	151 (30.3%)	154 (30.4%)	305 (30.3%)
Regional Lymph Node Positive			
n	498	507	1005
Yes	329 (66.1%)	324 (63.9%)	653 (65.0%)
No	169 (33.9%)	183 (36.1%)	352 (35.0%)
Distant Metastasis Stage (pM)			
n	498	507	1005
M0	498 (100%)	507 (100%)	1005 (100%)

Table 21: Baseline PD-L1 expression status (ITT population) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=498)	Atezolizumab (N=507)	All Patients (N=1005)
PD-L1 Status by SP142			
n	498	507	1005
TC0/1 and IC0/1	231 (46.4%)	231 (45.6%)	462 (46.0%)
TC0/1 and IC2/3	145 (29.1%)	146 (28.8%)	291 (29.0%)
TC2/3 and any IC	122 (24.5%)	130 (25.6%)	252 (25.1%)
SP142 TC3/IC3			
n	498	507	1005
TC3 or IC3	153 (30.7%)	153 (30.2%)	306 (30.4%)
TC0/1/2 and IC0/1/2	345 (69.3%)	354 (69.8%)	699 (69.6%)
SP142 TC23/IC23			
n	498	507	1005
TC2/3 or IC2/3	267 (53.6%)	276 (54.4%)	543 (54.0%)
TC0/1 and IC0/1	231 (46.4%)	231 (45.6%)	462 (46.0%)
SP142 TC123/IC123			
n	498	507	1005
TC1/2/3 or IC1/2/3	461 (92.6%)	463 (91.3%)	924 (91.9%)
TC0 and IC0	37 (7.4%)	44 (8.7%)	81 (8.1%)
PD-L1 status by SP263 Cut-off 1			
n	486	493	979
>= 1%	252 (51.9%)	283 (57.4%)	535 (54.6%)
< 1%	234 (48.1%)	210 (42.6%)	444 (45.4%)
PD-L1 status by SP263 Cut-off 3			
n	486	493	979
>= 50%	127 (26.1%)	131 (26.6%)	258 (26.4%)
< 50%	359 (73.9%)	362 (73.4%)	721 (73.6%)

Table 22: Baseline PD-L1 Expression Status (PD-L1 SP263 ≥1% TC Stage II-IIIA Population) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=228)	Atezolizumab (N=248)	All Patients (N=476)
PD-L1 Status by SP142			
n	228	248	476
TC0/1 and IC0/1	66 (28.9%)	77 (31.0%)	143 (30.0%)
TC0/1 and IC2/3	61 (26.8%)	66 (26.6%)	127 (26.7%)
TC2/3 and any IC	101 (44.3%)	105 (42.3%)	206 (43.3%)
SP142 TC3/IC3			
n	228	248	476
TC3 or IC3	108 (47.4%)	109 (44.0%)	217 (45.6%)
TC0/1/2 and IC0/1/2	120 (52.6%)	139 (56.0%)	259 (54.4%)
SP142 TC23/IC23			
n	228	248	476
TC2/3 or IC2/3	162 (71.1%)	171 (69.0%)	333 (70.0%)
TC0/1 and IC0/1	66 (28.9%)	77 (31.0%)	143 (30.0%)
SP142 TC123/IC123			
n	228	248	476
TC1/2/3 or IC1/2/3	220 (96.5%)	236 (95.2%)	456 (95.8%)
TC0 and IC0	8 (3.5%)	12 (4.8%)	20 (4.2%)
PD-L1 status by SP263 Cut-off 3			
n	228	248	476
>= 50%	114 (50.0%)	115 (46.4%)	229 (48.1%)
< 50%	114 (50.0%)	133 (53.6%)	247 (51.9%)

Table 23: Summary of Baseline Demographic Characteristics (PD-L1 SP263 ≥50% TC Stage II-IIIA Population) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=114)	Atezolizumab (N=115)	All Patients (N=229)
Age (yrs) at randomization			
n	114	115	229
Mean (SD)	61.3 (9.2)	61.1 (8.5)	61.2 (8.8)
Median	62.0	62.0	62.0

Min - Max	36 - 84	34 - 77	34 - 84
Age group 1 (yrs) at randomization			
n	114	115	229
< 65	68 (59.6%)	70 (60.9%)	138 (60.3%)
>= 65	46 (40.4%)	45 (39.1%)	91 (39.7%)
Age group 2 (yrs) at randomization			
n	114	115	229
< 65	68 (59.6%)	70 (60.9%)	138 (60.3%)
65 - 74	40 (35.1%)	43 (37.4%)	83 (36.2%)
75 - 84	6 (5.3%)	2 (1.7%)	8 (3.5%)
Sex per eCRF			
n	114	115	229
Male	78 (68.4%)	89 (77.4%)	167 (72.9%)
Female	36 (31.6%)	26 (22.6%)	62 (27.1%)
Sex per IxRS			
n	114	115	229
Male	78 (68.4%)	89 (77.4%)	167 (72.9%)
Female	36 (31.6%)	26 (22.6%)	62 (27.1%)
Race			
n	114	115	229
Asian	26 (22.8%)	36 (31.3%)	62 (27.1%)
Black or African American	0	1 (0.9%)	1 (0.4%)
Native Hawaiian or other Pacific Islander	0	1 (0.9%)	1 (0.4%)
White	86 (75.4%)	75 (65.2%)	161 (70.3%)
Unknown	2 (1.8%)	2 (1.7%)	4 (1.7%)
Ethnicity			
n	114	115	229
Hispanic or Latino	3 (2.6%)	2 (1.7%)	5 (2.2%)
Not Hispanic or Latino	106 (93.0%)	111 (96.5%)	217 (94.8%)
Not Stated	3 (2.6%)	2 (1.7%)	5 (2.2%)
Unknown	2 (1.8%)	0	2 (0.9%)
Weight (kg) at randomization*			
n	112	113	225
Mean (SD)	76.15 (18.08)	74.54 (17.39)	75.34 (17.72)
Median	74.00	71.50	73.00
Min - Max	43.5 - 126.3	46.6 - 132.5	43.5 - 132.5
ECOG performance status at randomization*			
n	114	115	229
0	60 (52.6%)	71 (61.7%)	131 (57.2%)
1	53 (46.5%)	44 (38.3%)	97 (42.4%)
2	1 (0.9%)	0	1 (0.4%)
Tobacco use history			
n	114	115	229
Never	15 (13.2%)	16 (13.9%)	31 (13.5%)
Current	22 (19.3%)	16 (13.9%)	38 (16.6%)
Previous	77 (67.5%)	83 (72.2%)	160 (69.9%)

*At randomization is defined as the last assessment value before the start of treatment date in the randomization period.

Table 24: Summary of Baseline Disease Characteristics (PD-L1 SP263 ≥50% TC Stage II-IIIA Population) (COD: 21 January 2021)

	Best Supportive Care(BSC) (N=114)	Atezolizumab (N=115)	All Patients (N=229)
Stage per eCRF			
n	114	115	229
STAGE IIA	41 (36.0%)	35 (30.4%)	76 (33.2%)
STAGE IIB	16 (14.0%)	27 (23.5%)	43 (18.8%)
STAGE IIIA	57 (50.0%)	53 (46.1%)	110 (48.0%)
Stage per IxRS			
n	114	115	229
STAGE IB	0	1 (0.9%)	1 (0.4%)
STAGE II	54 (47.4%)	61 (53.0%)	115 (50.2%)
STAGE IIIA	60 (52.6%)	53 (46.1%)	113 (49.3%)
Histology per eCRF			
n	114	115	229
Squamous	45 (39.5%)	47 (40.9%)	92 (40.2%)
Non-squamous	69 (60.5%)	68 (59.1%)	137 (59.8%)
Histology per IxRS			
n	114	115	229
Squamous	45 (39.5%)	48 (41.7%)	93 (40.6%)
Non-squamous	69 (60.5%)	67 (58.3%)	136 (59.4%)
Time since initial NSCLC diagnosis to first treatment in randomization (months)			
n	112	112	224
Mean (SD)	5.37 (1.27)	5.59 (1.09)	5.48 (1.19)
Median	5.24	5.36	5.29
Min - Max	2.6 - 10.1	3.7 - 8.9	2.6 - 10.1
EGFR mutation status			
n	114	115	229
Detected	8 (7.0%)	6 (5.2%)	14 (6.1%)
Not Detected	64 (56.1%)	60 (52.2%)	124 (54.1%)
Unknown	42 (36.8%)	49 (42.6%)	91 (39.7%)
ALK mutation status			
n	114	115	229
Yes	3 (2.6%)	3 (2.6%)	6 (2.6%)
No	62 (54.4%)	62 (53.9%)	124 (54.1%)
Unknown	49 (43.0%)	50 (43.5%)	99 (43.2%)
EGFR mutation or ALK mutation			
n	114	115	229
Yes	11 (9.6%)	9 (7.8%)	20 (8.7%)
No	54 (47.4%)	52 (45.2%)	106 (46.3%)
Unknown	49 (43.0%)	54 (47.0%)	103 (45.0%)
KRAS mutation			
n	114	115	229
Detected	4 (3.5%)	7 (6.1%)	11 (4.8%)
Not Detected	6 (5.3%)	7 (6.1%)	13 (5.7%)
Unknown	104 (91.2%)	101 (87.8%)	205 (89.5%)
Type of surgery			
n	114	115	229
Lobectomy	85 (74.6%)	85 (73.9%)	170 (74.2%)
Sleeve lobectomy	1 (0.9%)	2 (1.7%)	3 (1.3%)
Bilobectomy	7 (6.1%)	7 (6.1%)	14 (6.1%)
Pneumonectomy	20 (17.5%)	20 (17.4%)	40 (17.5%)
Other	1 (0.9%)	1 (0.9%)	2 (0.9%)

Patients not tested for a specific mutation are listed with "unknown" status.

Table 25: Baseline PD-L1 Expression Status (PD-L1 SP263 ≥50% TC Stage II-IIIA Population) (COD: 21 January 2021)

	Best Supportive Care(BSC) (N=114)	Atezolizumab (N=115)	All Patients (N=229)
PD-L1 Status by SP142			
n	114	115	229
TC0/1 and IC0/1	12 (10.5%)	12 (10.4%)	24 (10.5%)
TC0/1 and IC2/3	16 (14.0%)	22 (19.1%)	38 (16.6%)
TC2/3 and any IC	86 (75.4%)	81 (70.4%)	167 (72.9%)
SP142 TC3/IC3			
n	114	115	229
TC3 or IC3	81 (71.1%)	77 (67.0%)	158 (69.0%)
TC0/1/2 and IC0/1/2	33 (28.9%)	38 (33.0%)	71 (31.0%)
SP142 TC23/IC23			
n	114	115	229
TC2/3 or IC2/3	102 (89.5%)	103 (89.6%)	205 (89.5%)
TC0/1 and IC0/1	12 (10.5%)	12 (10.4%)	24 (10.5%)
SP142 TC123/IC123			
n	114	115	229
TC1/2/3 or IC1/2/3	110 (96.5%)	115 (100%)	225 (98.3%)
TC0 and IC0	4 (3.5%)	0	4 (1.7%)

Table 26: Baseline PD-L1 Expression Status by SP263 (ITT Population)

PD-L1 Status by SP263	BSC N = 498	Atezolizumab N = 507	Total N = 1005
	n = 486	n = 493	n = 979[a]
≥1%	252 (51.9%)	283 (57.4%)	535 (54.6%)
1-49%	125 (25.7%[b])	152 (30.8%[b])	277 (28.3%[b])
≥50%	127 (26.1%)	131 (26.6%)	258 (26.4%)

BSC=best supportive care; ITT=intent-to-treat; PD-L1=programmed death-ligand 1.
[a] Number of patients who had a valid PD-L1 status based on the SP263 assay
[b] The percentages have been calculated manually here using the small 'n'

Table 27: Baseline PD-L1 Expression Status by SP263 (Stage II-IIIA Population)

PD-L1 Status by SP263	BSC N = 440	Atezolizumab N = 442	Total N = 882
	n = 430	n = 429	n = 859[a]
≥1%	228 (53.0%)	248 (57.8%)	476 (55.4%)
1-49%	114 (26.5%[b])	133 (31.0%[b])	247 (28.8%[b])
≥50%	114 (26.5%)	115 (26.8%)	229 (26.7%)

BSC=best supportive care; PD-L1=programmed death-ligand.
[a] Number of patients who had a valid PD-L1 status based on the SP142 assay
[b] The percentages have been calculated manually here using the small 'n'

Subsequent Non-Protocol Anti-Cancer Therapy

In the ITT population, more patients in the BSC arm (27%) compared with the atezolizumab arm (21%) received at least one non-protocol anti-cancer systemic therapy at any time during the course of the study with the most commonly used agent being carboplatin (12% vs. 9%).

Follow-up radiotherapy was received by more patients on BSC (17%) compared with atezolizumab (11%), with the most common sites being to the brain, lungs, bone and lymph nodes.

Follow-up surgery was reported for a similar proportion of patients in both arms (7% BSC vs 5% atezolizumab), with the most common sites being to the brain (2%) and lungs (3%).

Numbers analysed

Table 28: Overview of Analysis Populations (ITT Population) (COD: 21 January 2021)

Analysis Populations	Best Supportive Care (BSC) (N=498)	Atezolizumab (N=507)	All Patients (N=1005)
Intent-to-Treat Patients	498	507	1005
Intent-to-Treat Stage II-IIIA (eCRF) Patients	440	442	882
Intent-to-Treat Stage II-IIIA (eCRF) Patients with SP263 TC >=1%	228	248	476
Randomized Safety-Evaluable Patients (BSC vs Atezolizumab)	495	495	990
PK Evaluable Patients	0	493	493
Randomized ADA Evaluable Patients	0	487	487

Median duration of survival follow-up at CCOD in both arms: 32 months

Table 29: Duration of Survival Follow-up (ITT Population) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=498)	Atezolizumab (N=507)	All Patients (N=1005)
Duration of follow-up (months)			
n	498	507	1005
Mean (SD)	31.35 (11.29)	31.47 (10.78)	31.41 (11.03)
Median	32.31	32.00	32.20
25% and 75%-ile	27.60 - 38.64	27.40 - 38.24	27.50 - 38.37
Min - Max	0.2 - 58.5	0.0 - 58.8	0.0 - 58.8

Overall, 75% (373/498) of patients in the BSC arm completed the observation period and 64% (323/507) in the treatment arm received all 16 planned doses of atezolizumab. As of the CCOD, all patients were either in survival follow-up (74% [371/498] BSC vs. 76% [386/507] atezolizumab) or had discontinued the study (26% [127/498] vs 24% [121/507], respectively).

Outcomes and estimation

Data are based on an interim analysis for DFS (CCOD **21 Jan 2021**) with a median duration of survival **follow-up of 32 months**.

	BSC	**Atezolizumab**
Primary Endpoint		
DFS in PD-L1 SP263 ≥1% TC Stage II-IIIA	N=228	N=248
Patients with event (%)	105 (46.1%)	88 (35.5%)
Median DFS (95% CI), months	35.3 (29.0, NE)	NE (36.1, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	

p-value (Stratified Log-rank)		0.0039
3-year DFS % (95% CI)	48.2 (40.7, 55.7)	60.0 (52.8, 67.1)
DFS in Stage II-IIIA	N=440	N=442
Patients with event (%)	198 (45.0%)	173 (39.1%)
Median DFS (95% CI), months	35.3 (30.4, 46.4)	42.3 (36.0, NE)
Stratified HR (95% CI)		0.79 (0.64, 0.96)
p-value (Stratified Log-rank)		0.0205
DFS in ITT (Stage IB-IIIA)	N=498	N=507
Patients with event (%)	212 (42.6%)	187 (36.9%)
Median DFS (95% CI), months	37.2 (31.6, NE)	NE (36.1, NE)
Stratified HR (95% CI)		0.81 (0.67, 0.99)
p-value (Stratified Log-rank)		0.0395
Key Secondary Endpoints		
OS ITT (Stage IB-IIIA)	N=498	N=507
Patients with event (%)	90 (18.1%)	97 (19.1%)
Median OS (95% CI), months	NE (NE)	NE (NE)
Stratified HR (95% CI)		1.07 (0.80, 1.42)
DFS in PD-L1 SP263 ≥50% TC Stage II-IIIA	N=114	N=115
Patients with event (%)	52 (45.6%)	28 (24.3%)
Median DFS (95% CI), months	35.7 (29.7, NE)	NE (42.3, NE)
Unstratified HR (95% CI)		0.43 (0.27, 0.68)
Key Exploratory Endpoint		
OS in PD-L1 SP263 ≥1% TC Stage II-IIIA	N=228	N=248
Patients with event (%)	48 (21.1%)	42 (16.9%)
Median OS (95% CI), months	NE (NE)	NE (NE)
Stratified HR (95% CI)		0.77 (0.51, 1.17)

BSC=best supportive care; DFS=disease-free survival; HR=hazard ratio; INV=investigator; ITT=intent-to-treat; NE=not estimable; OS=overall survival; TC=tumor cell.

Note: Key results in the PD-L1 SP263 ≥1% TC Stage II-IIIA (population of interest for this submission) are presented in black. Key results in other populations are presented in grey for reference.

Primary Efficacy Endpoints

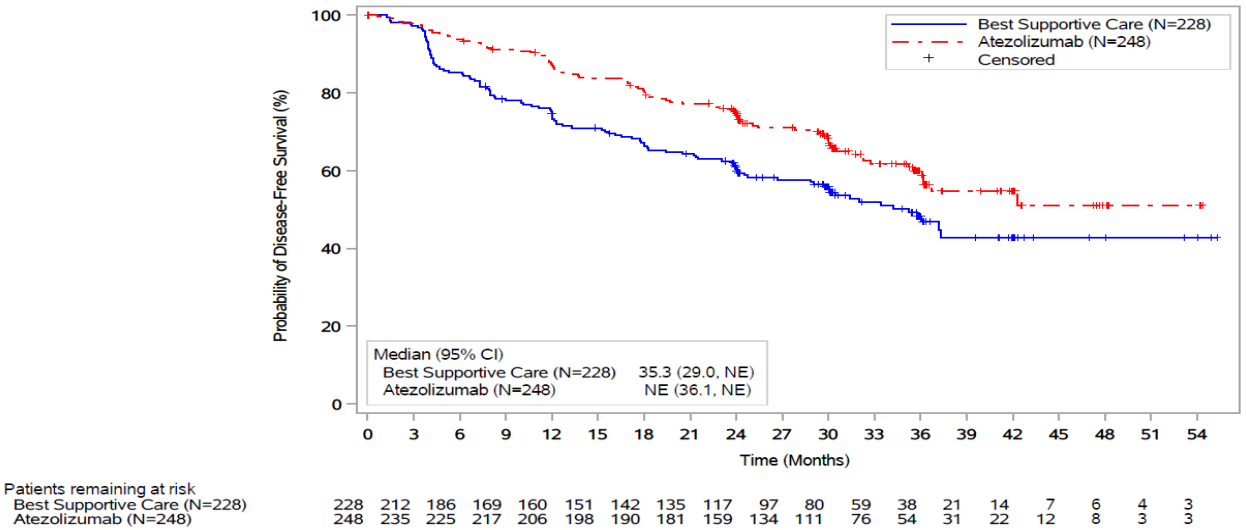
Disease-Free Survival in the PD-L1 SP263 ≥ 1% TC Stage II-IIIA Population

Table 30: Time to Event Summary of Disease-Free Survival (PD-L1 SP263 ≥1% TC Stage II-IIIA Population, ITT population) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=228)		Atezolizumab (N=248)
Patients with event (%)	105 (46.1%)		88 (35.5%)
Earliest contributing event			
Death	3		15
Disease Recurrence	102		73
Patients without event (%)	123 (53.9%)		160 (64.5%)
Time to event (months)			
Median	35.3		NE
95% CI	(29.0, NE)		(36.1, NE)
25% and 75%-ile	12.0 - NE		24.0 - NE
Range	0.0* - 55.3*		0.0* - 54.3*
Stratified Analysis			
p-value (log-rank)		0.0039	
Hazard Ratio		0.659	
95% CI		(0.495, 0.877)	
Unstratified Analysis			
p-value (log-rank)		0.0032	
Hazard Ratio		0.655	
95% CI		(0.493, 0.870)	
Time Point Analysis			
3 Years			
Patients remaining at risk	38		54
Event Free Rate (%)	48.22		59.96
95% CI	(40.73, 55.71)		(52.82, 67.10)
Difference in Event Free Rate		11.74	
95% CI		(1.39, 22.08)	
p-value (Z-test)		0.0262	
5 Years			
Patients remaining at risk	NE		NE
Event Free Rate (%)	NE		NE
95% CI	NE		NE
Difference in Event Free Rate		NE	
95% CI		NE	
p-value (Z-test)		NE	

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley.
Hazard ratios were estimated by Cox regression.
* Censored, NE = Not estimable.
Stratification factors: stage from eCRF (II vs. IIIA), sex from eCRF (female vs. male), and histology from eCRF (squamous vs. non-squamous)

Table 31: Kaplan-Meier Plot of Disease-Free Survival (PD-L1 SP263 ≥1% TC, Stage II-IIIA Population, ITT population) (COD: 21 January 2021)



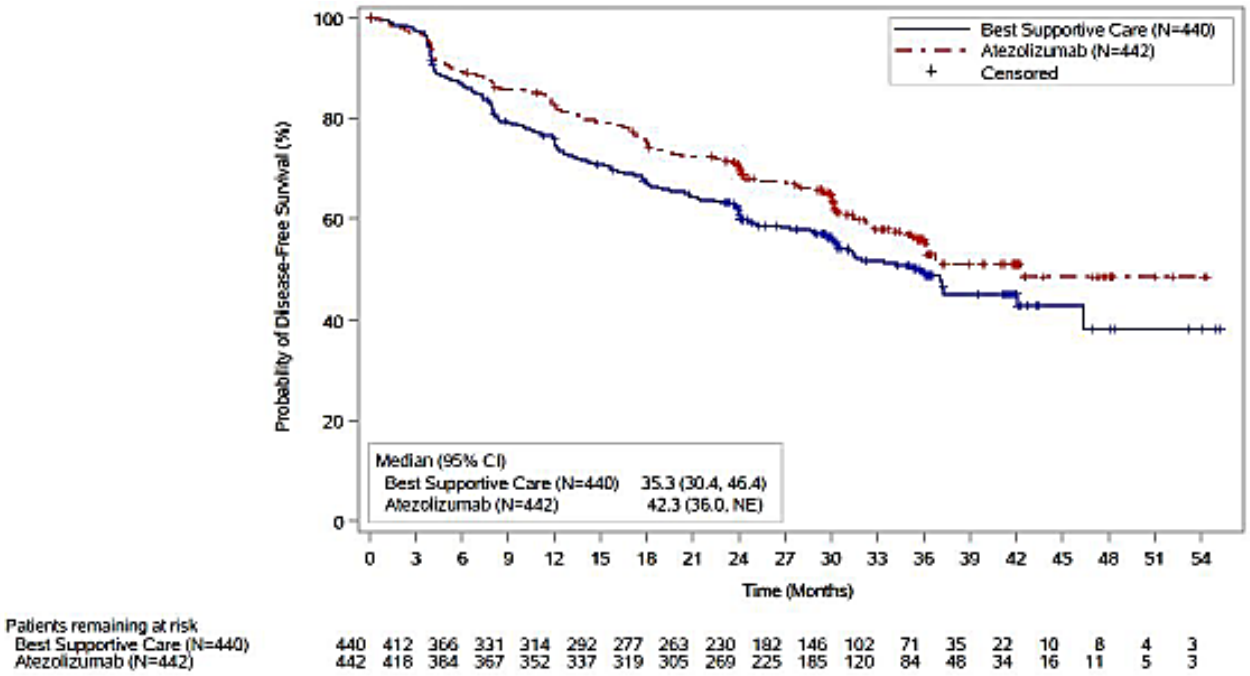
Disease-Free Survival in the All Randomized Stage II-IIIA Population

Table 32: Time to Event Summary of Disease-Free Survival (Stage II-IIIA Population, ITT population) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=440)		Atezolizumab (N=442)
Patients with event (%)	198 (45.0%)		173 (39.1%)
Earliest contributing event			
Death	9		26
Disease Recurrence	189		147
Patients without event (%)	242 (55.0%)		269 (60.9%)
Time to event (months)			
Median	35.3		42.3
95% CI	(30.4, 46.4)		(36.0, NE)
25% and 75%-ile	12.0 - NE		18.0 - NE
Range	0.0* - 55.3*		0.0* - 54.3*
Stratified Analysis			
p-value (log-rank)		0.0205	
Hazard Ratio		0.785	
95% CI		(0.639, 0.964)	
Unstratified Analysis			
p-value (log-rank)		0.0160	
Hazard Ratio		0.778	
95% CI		(0.634, 0.954)	
Time Point Analysis			
3 Years			
Patients remaining at risk	71		84
Event Free Rate (%)	49.41		55.74
95% CI	(43.95, 54.87)		(50.29, 61.18)
Difference in Event Free Rate		6.33	
95% CI		(-1.38, 14.04)	
p-value (Z-test)		0.1076	
5 Years			
Patients remaining at risk	NE		NE
Event Free Rate (%)	NE		NE
95% CI	NE		NE
Difference in Event Free Rate		NE	
95% CI		NE	
p-value (Z-test)		NE	

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley.
Hazard ratios were estimated by Cox regression.
* Censored, NE = Not estimable.
Stratification factors: stage from eCRF (II vs. IIIA), sex from eCRF (female vs. male), and histology from eCRF (squamous vs. non-squamous)

Figure 4: Kaplan-Meier Plot of Disease-Free Survival (Stage II-IIIA Population, ITT population) (COD: 21 January 2021)



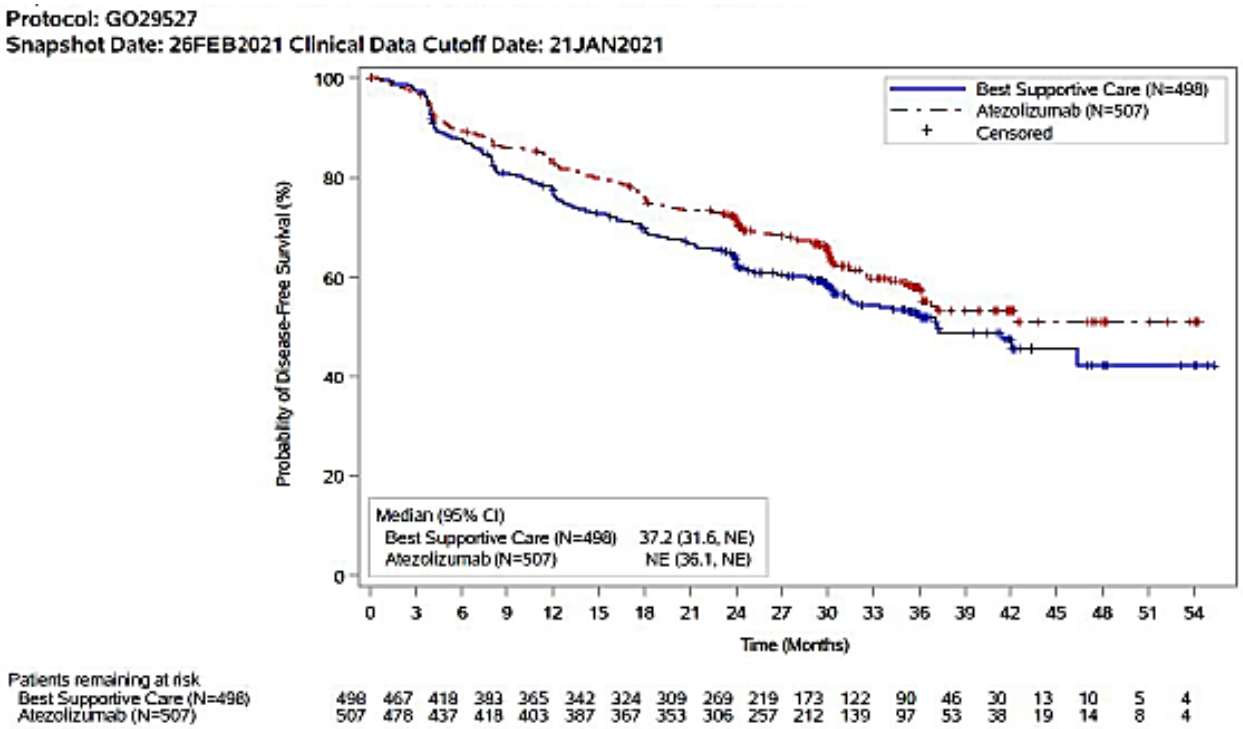
Disease-Free Survival in the ITT Population

Table 33: Time to Event Summary of Disease-Free Survival (ITT Population) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=498)		Atezolizumab (N=507)
Patients with event (%)	212 (42.6%)		187 (36.9%)
Earliest contributing event			
Death	9		31
Disease Recurrence	203		156
Patients without event (%)	286 (57.4%)		320 (63.1%)
Time to event (months)			
Median	37.2		NE
95% CI	(31.6, NE)		(36.1, NE)
25% and 75%-ile	12.7 - NE		18.1 - NE
Range	0.0* - 55.3*		0.0* - 54.3*
Stratified Analysis			
p-value (log-rank)		0.0395	
Hazard Ratio		0.812	
95% CI		(0.665, 0.990)	
Unstratified Analysis			
p-value (log-rank)		0.0271	
Hazard Ratio		0.801	
95% CI		(0.658, 0.975)	
Time Point Analysis			
3 Years			
Patients remaining at risk	90		97
Event Free Rate (%)	52.57		57.94
95% CI	(47.51, 57.64)		(52.89, 62.99)
Difference in Event Free Rate		5.37	
95% CI		(-1.79, 12.52)	
p-value (Z-test)		0.1416	
5 Years			
Patients remaining at risk	NE		NE
Event Free Rate (%)	NE		NE
95% CI	NE		NE
Difference in Event Free Rate		NE	
95% CI		NE	
p-value (Z-test)		NE	

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley.
Hazard ratios were estimated by Cox regression.
* Censored, NE = Not estimable.
Stratification factors: stage from eCRF (IB/II vs. IIIA), sex from eCRF (female vs. male), histology from eCRF (squamous vs. non-squamous) and PD-L1 tumor expression status by SP142 IHC assay from IxRS (TC2/3 or IC2/3 vs. TC0/1 and IC0/1)

Figure 5: Kaplan-Meier Plot of Disease-Free Survival (ITT Population)



Secondary Efficacy Endpoints

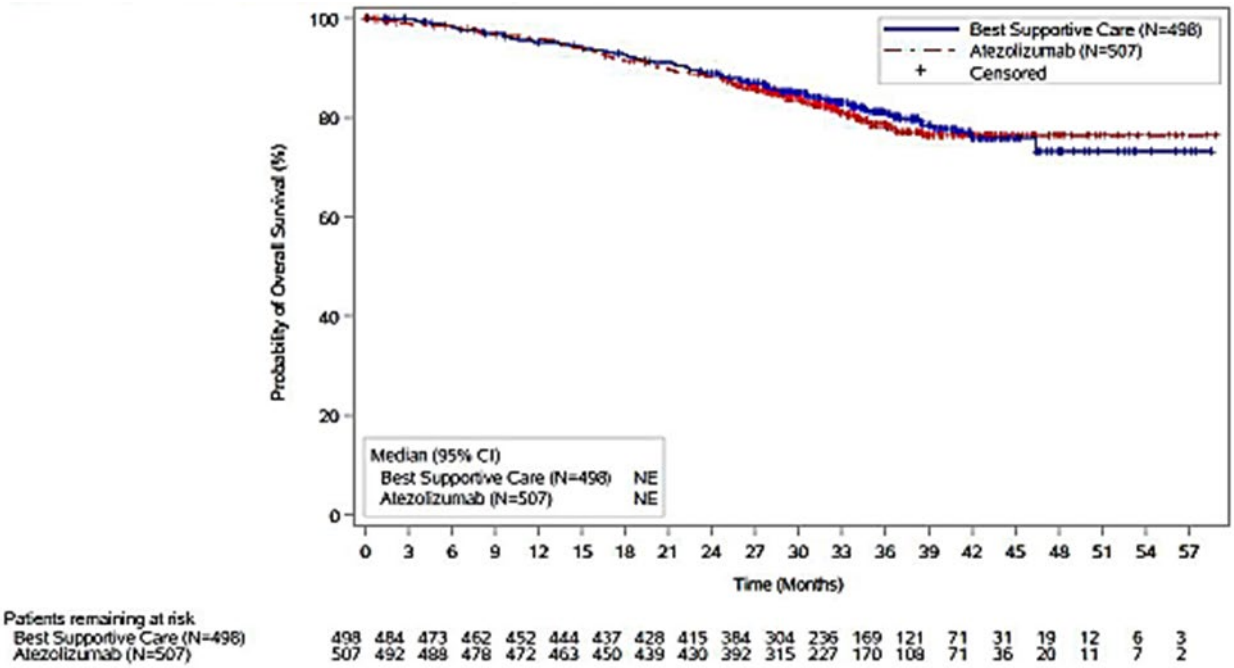
Overall Survival in the ITT Population

Table 34: Overall Survival (ITT Population) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=498)		Atezolizumab (N=507)
Patients with event (%)	90 (18.1%)		97 (19.1%)
Earliest contributing event			
Death	90		97
Patients without event (%)	408 (81.9%)		410 (80.9%)
Time to event (months)			
Median	NE		NE
95% CI	NE		NE
25% and 75%-ile	46.4 - NE		NE
Range	0.2* - 58.5*		0.0* - 58.8*
Stratified Analysis			
p-value (log-rank)		0.6651	
Hazard Ratio		1.066	
95% CI		(0.799, 1.421)	
Unstratified Analysis			
p-value (log-rank)		0.6983	
Hazard Ratio		1.058	
95% CI		(0.794, 1.410)	
Time Point Analysis			
3 Years			
Patients remaining at risk	169		170
Event Free Rate (%)	81.18		78.63
95% CI	(77.37, 84.99)		(74.61, 82.65)
Difference in Event Free Rate		-2.55	
95% CI		(-8.09, 2.99)	
p-value (Z-test)		0.3666	
5 Years			
Patients remaining at risk	NE		NE
Event Free Rate (%)	NE		NE
95% CI	NE		NE
Difference in Event Free Rate		NE	
95% CI		NE	
p-value (Z-test)		NE	

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley.
Hazard ratios were estimated by Cox regression.
* Censored, NE = Not estimable.
Stratification factors: stage from eCRF (IB/II vs. IIIA), sex from eCRF (female vs. male), histology from eCRF (squamous vs. non-squamous) and PD-L1 tumor expression status by SP142 IHC assay from IxRS (TC2/3 or IC2/3 vs. TC0/1 and IC0/1)

Figure 6: Kaplan-Meier Plot of Overall Survival (ITT Population) (COD: 21 January 2021)



Disease-Free Survival 3-Year and 5-Year Landmark Analyses

In the PD-L1 SP263 ≥1% TC Stage II-IIIA, Stage II-IIIA, and ITT populations, the 3-year DFS rates were higher in the atezolizumab arm compared with the BSC arm. The corresponding 5-year DFS rates were not estimable and require longer follow-up.

Table 35: 3-year Disease-Free Survival Rates (All Populations)

	PD-L1 SP263 ≥1% TC Stage II-IIIA		Stage II-IIIA		ITT	
	BSC N=228	Atezolizumab N=248	BSC N=440	Atezolizumab N=442	BSC N=498	Atezolizumab N=507
3-year DFS % (95% CI)	48.2 (40.7, 55.7)	60.0 (52.8, 67.1)	49.4 (44.0, 54.9)	55.7 (50.3, 61.2)	52.6 (47.5, 57.6)	57.9 (52.9, 63.0)
Difference (95% CI)	11.7 (1.4, 22.1)		6.3 (-1.4, 14.0)		5.4 (-1.8, 12.5)	

BSC=best supportive care; DFS=disease-free survival; ITT=intent-to-treat; TC=tumor cell; PD-L1=programmed death-ligand 1.

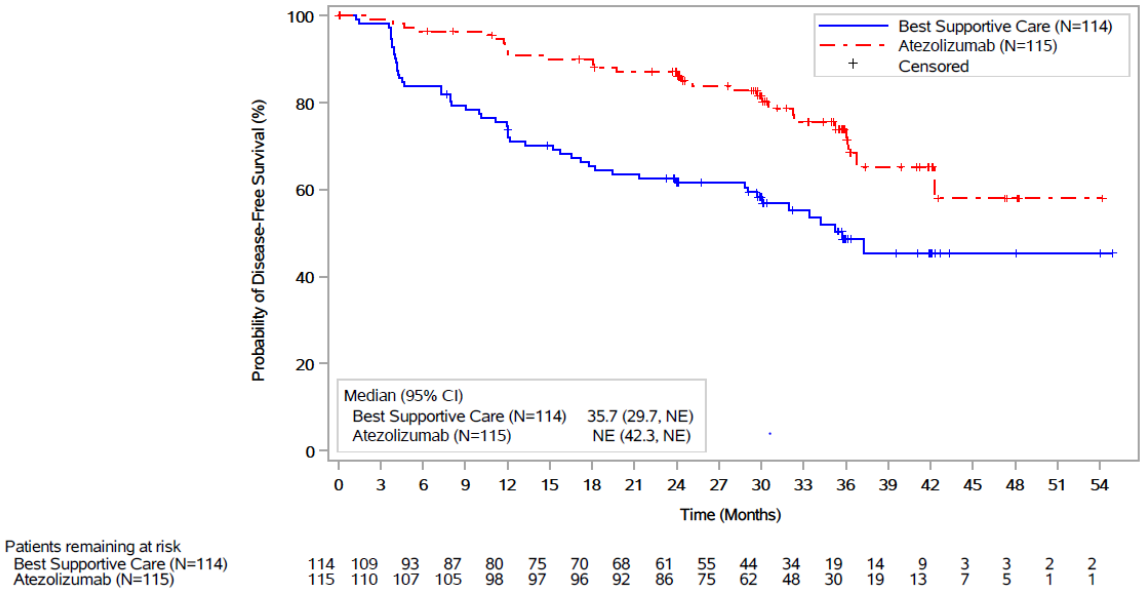
DFS in the PD-L1 SP263 ≥ 50% TC Stage II–IIIA Population

Table 36: Time to Event Summary of Disease-Free Survival (PD-L1 SP263 ≥ 50% TC Expression Stage II-IIIA Population) (COD: 21 January 2021)

	Best Supportive Care(BSC) (N=114)		Atezolizumab (N=115)
Patients with event (%)	52 (45.6%)		28 (24.3%)
Earliest contributing event			
Death	2		3
Disease Recurrence	50		25
Patients without event (%)	62 (54.4%)		87 (75.7%)
Time to event (months)			
Median	35.7		NE
95% CI	(29.7, NE)		(42.3, NE)
25% and 75%-ile	12.0 - NE		35.3 - NE
Range	0.0* - 54.9*		0.0* - 54.2*
Stratified Analysis			
p-value (log-rank)		0.0012	
Hazard Ratio		0.467	
95% CI		(0.292, 0.748)	
Unstratified Analysis			
p-value (log-rank)		0.0002	
Hazard Ratio		0.432	
95% CI		(0.272, 0.684)	
Time Point Analysis			
3 Years			
Patients remaining at risk	19		30
Event Free Rate (%)	48.61		73.79
95% CI	(38.03, 59.18)		(64.35, 83.23)
Difference in Event Free Rate		25.18	
95% CI		(11.01, 39.36)	
p-value (Z-test)		0.0005	
5 Years			
Patients remaining at risk	NE		NE
Event Free Rate (%)	NE		NE
95% CI	NE		NE
Difference in Event Free Rate		NE	
95% CI		NE	
p-value (Z-test)		NE	

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley.
Hazard ratios were estimated by Cox regression.
* Censored, NE = Not estimable.
Stratification factors: stage from eCRF (II vs. IIIA), sex from eCRF (female vs. male), and histology from eCRF (squamous vs. non-squamous)

Figure 7: Kaplan-Meier Plot of Disease-Free Survival (PD-L1 SP263 ≥ 50% TC Stage II-IIIA Population) (COD: 21 January 2021)



Ancillary analyses

BICR

Table 37: Summary of INV-DFS and BICR-DFS (ITT Population)

	Updated BICR analysis (Data Transfer: 22 December 2021)			
	Investigator		**BICR**	
	BSC N=253	**Atezo N=261**	**BSC N=253**	**Atezo N=261**
Patients with event, n (%)	107 (42.3%)	101 (38.7%)	96 (37.9%)	98 (37.5%)
Median DFS (95% CI), months	NE (30.0, NE)	NE (36.0, NE)	44.4 (34.9, NE)	42.1 (35.5, NE)
Unstratified HR (95% CI)*	0.85 (0.65, 1.12)		0.91 (0.68, 1.20)	

Atezo=atezolizumab; BICR=blinded independent central review; BSC=best supportive care; CI=confidence interval; DFS=disease-free survival; HR=hazard ratio; INV-DFS=investigator-assessed disease-free survival; NE=not estimable

*Unstratified HR reported due to small sample size

Table 38: Summary of INV-DFS and BICR-DFS (PD-L1 SP263 ≥50% TC Stage II-IIIA Population)

	Updated BICR analysis (Data Transfer: 22 December 2021)	
	Investigator	**BICR**

	BSC N=58	**Atezo N=63**	**BSC N=58**	**Atezo N=63**
Patients with event, n (%)	26 (44.8%)	16 (25.4%)	25 (43.1%)	16 (25.4%)
Median DFS (95% CI), months	NE (23.9, NE)	NE (36.1, NE)	50.3 (28.8, NE)	NE (38.5, NE)
Unstratified HR (95% CI)*	0.50 (0.27, 0.94)		0.53 (0.28, 0.99)	

Atezo=atezolizumab; BICR=blinded independent central review; BSC=best supportive care; CI=confidence interval; DFS=disease-free survival; HR=hazard ratio; INV-DFS=investigator-assessed disease-free survival; NE=not estimable

*Unstratified HR reported due to small sample size.

Requested Exploratory Efficacy Endpoints

The following post-hoc analyses have been included in the application:

- DFS and OS in the PD-L1 SP263 1-49% TC Stage II-IIIA population
- OS in the PD-L1 SP263 ≥50% TC Stage II-IIIA population
- DFS and OS in the Stage IB population

Disease-Free Survival in the PD-L1 SP263 1-49% TC Stage II–IIIA Population

Table 39: Time to Event Summary of Disease-Free Survival (PD-L1 SP263 1-49% TC Expression Stage II–IIIA Population) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=114)		Atezolizumab (N=133)
Patients with event (%)	53 (46.5%)		60 (45.1%)
Earliest contributing event			
Death	1		12
Disease Recurrence	52		48
Patients without event (%)	61 (53.5%)		73 (54.9%)
Time to event (months)			
Median	31.4		32.8
95% CI	(24.0, NE)		(29.4, NE)
25% and 75%-ile	12.0 - NE		17.1 - NE
Range	0.0* - 55.3*		0.0* - 54.3*
Stratified Analysis			
p-value (log-rank)		0.3826	
Hazard Ratio		0.846	
95% CI		(0.581, 1.232)	
Unstratified Analysis			
p-value (log-rank)		0.4521	
Hazard Ratio		0.868	
95% CI		(0.600, 1.256)	
Time Point Analysis			
3 Years			
Patients remaining at risk	19		24
Event Free Rate (%)	48.09		48.00
95% CI	(37.59, 58.59)		(37.86, 58.15)
Difference in Event Free Rate		-0.09	
95% CI		(-14.69, 14.51)	
p-value (Z-test)		0.9906	
5 Years			
Patients remaining at risk	NE		NE
Event Free Rate (%)	NE		NE
95% CI	NE		NE
Difference in Event Free Rate		NE	
95% CI		NE	
p-value (Z-test)		NE	

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley.
Hazard ratios were estimated by Cox regression.
* Censored, NE = Not estimable.
Stratification factors: stage from eCRF (II vs. IIIA), sex from eCRF (female vs. male), and histology from eCRF (squamous vs. non-squamous)

Figure 8: Kaplan-Meier Plot of Disease-Free Survival (PD-L1 SP263 1-49% TC Stage II–IIIA Population) (COD: 21 January 2021)

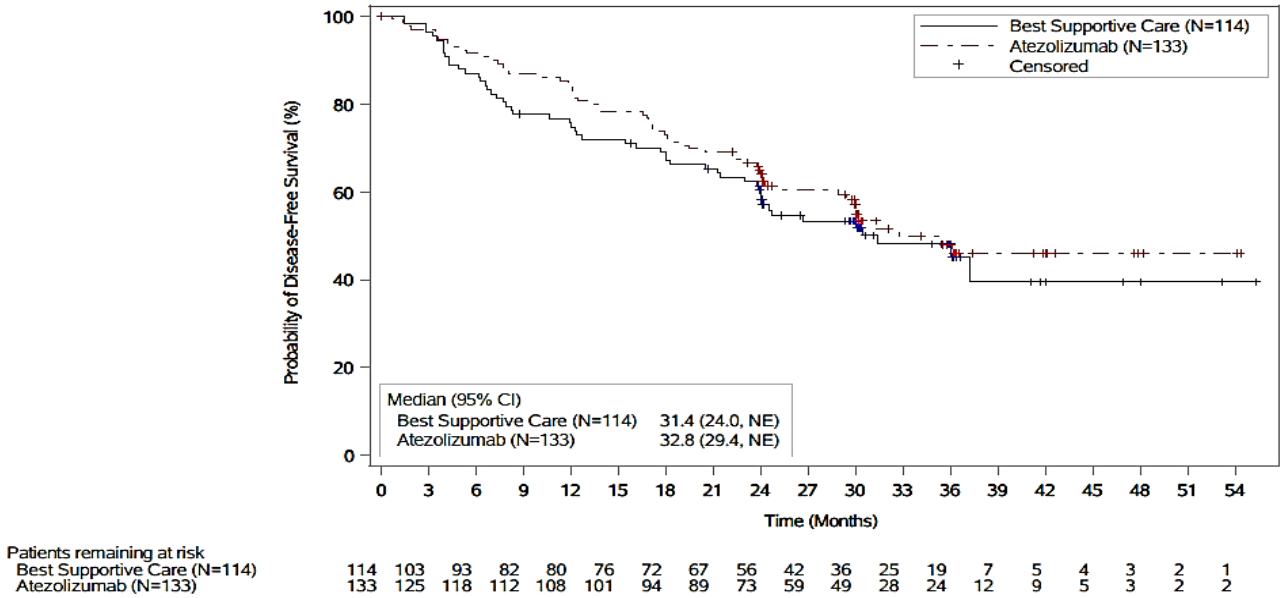


Table 40: Overall Survival in the PD-L1 SP263 1-49% TC Stage II–IIIA Population (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=114)	Atezolizumab (N=133)
Patients with event (%)	22 (19.3%)	31 (23.3%)
Earliest contributing event		
Death	22	31
Patients without event (%)	92 (80.7%)	102 (76.7%)
Time to event (months)		
Median	NE	NE
95% CI	NE	NE
25% and 75%-ile	38.5 - NE	34.9 - NE
Range	1.4* - 57.1*	0.1* - 56.4*
Stratified Analysis		
p-value (log-rank)	0.5804	
Hazard Ratio	1.168	
95% CI	(0.673, 2.027)	
Unstratified Analysis		
p-value (log-rank)	0.4787	
Hazard Ratio	1.218	
95% CI	(0.705, 2.104)	
Time Point Analysis		
3 Years		
Patients remaining at risk	37	43
Event Free Rate (%)	80.41	73.97
95% CI	(72.32, 88.50)	(65.56, 82.38)
Difference in Event Free Rate	-6.44	
95% CI	(-18.11, 5.23)	
p-value (Z-test)	0.2794	
5 Years		
Patients remaining at risk	NE	NE
Event Free Rate (%)	NE	NE
95% CI	NE	NE
Difference in Event Free Rate	NE	
95% CI	NE	
p-value (Z-test)	NE	

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley.
Hazard ratios were estimated by Cox regression.
* Censored, NE = Not estimable.
Stratification factors: stage from eCRF (II vs. IIIA), sex from eCRF (female vs. male), and histology from eCRF (squamous vs. non-squamous)

Figure 9: Kaplan-Meier Plot of overall survival (PD-L1 SP263 1-49% TC Stage II–IIIA Population) (COD: 21 January 2021)

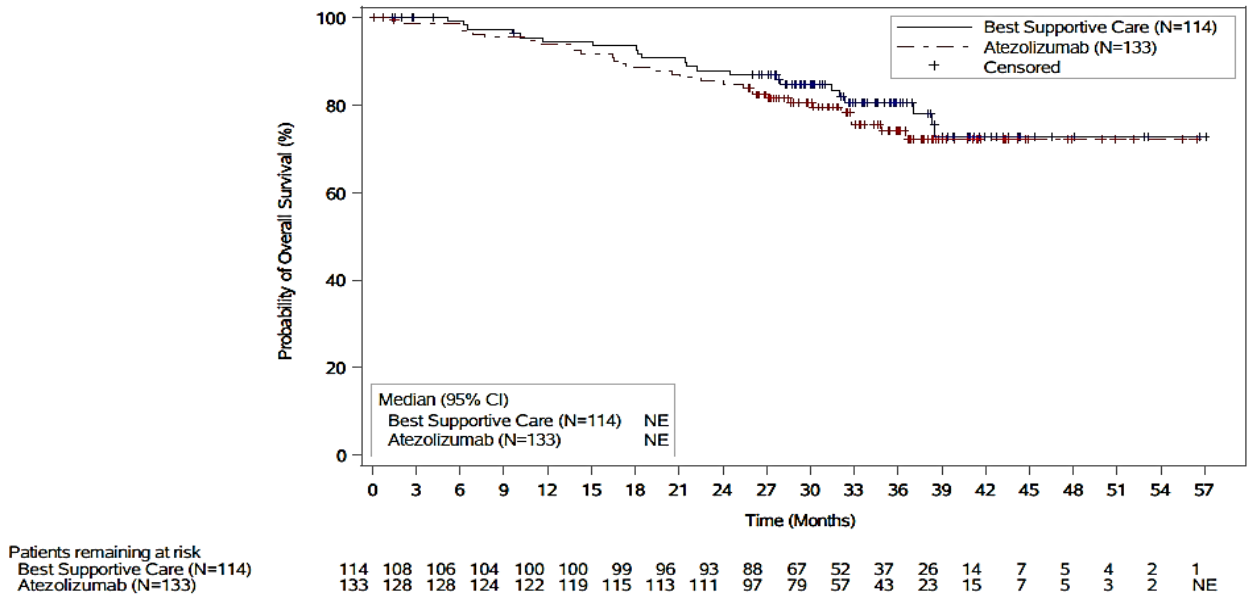


Table 41: Overall Survival in the PD-L1 SP263 ≥50% TC Stage II-IIIA Population (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=114)	Atezolizumab (N=115)
Patients with event (%)	26 (22.8%)	11 (9.6%)
Earliest contributing event		
Death	26	11
Patients without event (%)	88 (77.2%)	104 (90.4%)
Time to event (months)		
Median	NE	NE
95% CI	NE	NE
25% and 75%-ile	36.4 - NE	NE
Range	0.2* - 57.5*	0.2* - 54.2*
Stratified Analysis		
p-value (log-rank)	0.0089	
Hazard Ratio	0.398	
95% CI	(0.195, 0.812)	
Unstratified Analysis		
p-value (log-rank)	0.0036	
Hazard Ratio	0.366	
95% CI	(0.181, 0.742)	
Time Point Analysis		
3 Years		
Patients remaining at risk	43	56
Event Free Rate (%)	76.67	90.94
95% CI	(68.38, 84.97)	(85.21, 96.67)
Difference in Event Free Rate	14.27	
95% CI	(4.19, 24.35)	
p-value (Z-test)	0.0055	
5 Years		
Patients remaining at risk	NE	NE
Event Free Rate (%)	NE	NE
95% CI	NE	NE
Difference in Event Free Rate	NE	
95% CI	NE	
p-value (Z-test)	NE	

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley.
Hazard ratios were estimated by Cox regression.
* Censored, NE = Not estimable.
Stratification factors: stage from eCRF (II vs. IIIA), sex from eCRF (female vs. male), and histology from eCRF (squamous vs. non-squamous)

Figure 10: Kaplan-Meier Plot of overall survival (PD-L1 SP263 ≥50% TC Stage II–IIIA Population) (COD: 21 January 2021)

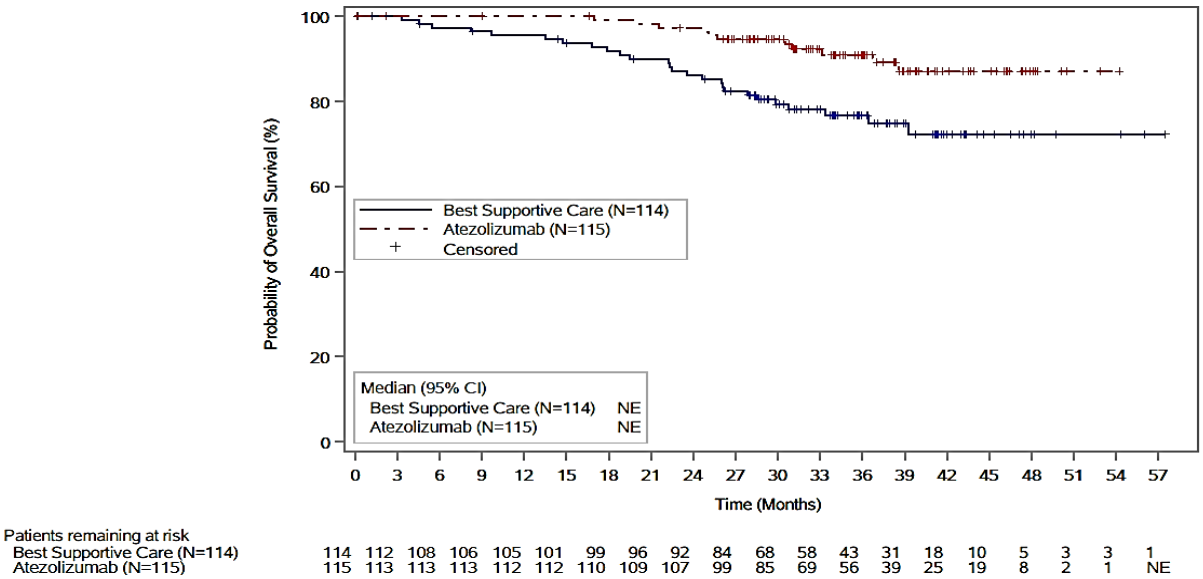


Table 42: Disease-Free Survival in the Stage IB Population (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=58)		Atezolizumab (N=65)
Patients with event (%)	14 (24.1%)		14 (21.5%)
Earliest contributing event			
Death	0		5
Disease Recurrence	14		9
Patients without event (%)	44 (75.9%)		51 (78.5%)
Time to event (months)			
Median	NE		NE
95% CI	NE		NE
25% and 75%-ile	41.4 - NE		NE
Range	0.0* - 54.1*		0.0* - 54.1*
Stratified Analysis			
p-value (log-rank)		0.7231	
Hazard Ratio		1.149	
95% CI		(0.533, 2.477)	
Unstratified Analysis			
p-value (log-rank)		0.9776	
Hazard Ratio		1.011	
95% CI		(0.480, 2.126)	
Time Point Analysis			
3 Years			
Patients remaining at risk	19		13
Event Free Rate (%)	75.85		75.15
95% CI	(64.28, 87.42)		(63.63, 86.67)
Difference in Event Free Rate		-0.70	
95% CI		(-17.03, 15.63)	
p-value (Z-test)		0.9330	
5 Years			
Patients remaining at risk	NE		NE
Event Free Rate (%)	NE		NE
95% CI	NE		NE
Difference in Event Free Rate		NE	
95% CI		NE	
p-value (Z-test)		NE	

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley.
Hazard ratios were estimated by Cox regression.
* Censored, NE = Not estimable.
Stratification factors: sex from eCRF (female vs. male), histology from eCRF (squamous vs. non-squamous) and PD-L1 tumor expression status by SP142 IHC assay from IxRS (TC2/3 or IC2/3 vs. TC0/1 and IC0/1)

Figure 11: Kaplan-Meier Plot of disease free survival in Stage IB Patients (COD: 21 January 2021)

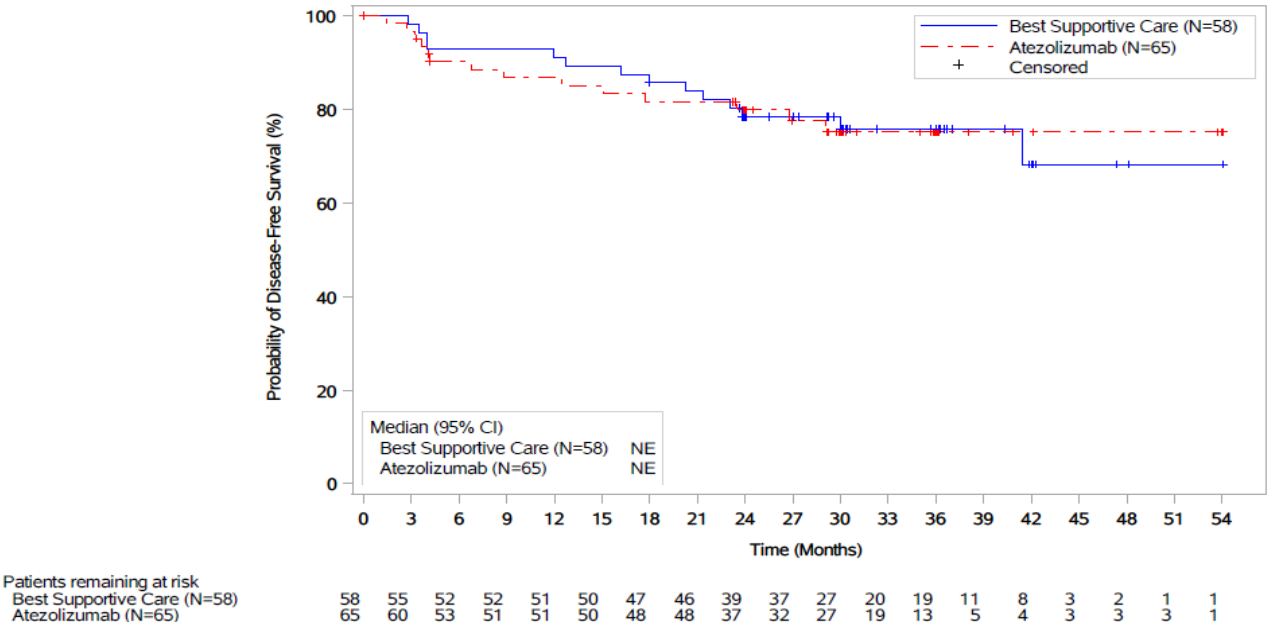


Table 43: Overall Survival in the Stage IB Population (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=58)		Atezolizumab (N=65)
Patients with event (%)	4 (6.9%)		10 (15.4%)
Earliest contributing event			
Death	4		10
Patients without event (%)	54 (93.1%)		55 (84.6%)
Time to event (months)			
Median	NE		NE
95% CI	NE		NE
25% and 75%-ile	NE		NE
Range	4.1* - 58.5*		1.0* - 58.8*
Stratified Analysis			
p-value (log-rank)		0.0652	
Hazard Ratio		2.977	
95% CI		(0.892, 9.936)	
Unstratified Analysis			
p-value (log-rank)		0.0932	
Hazard Ratio		2.609	
95% CI		(0.816, 8.342)	
Time Point Analysis			
3 Years			
Patients remaining at risk	26		18
Event Free Rate (%)	94.64		83.72
95% CI	(88.73, 100.00)		(74.47, 92.98)
Difference in Event Free Rate		-10.91	
95% CI		(-21.89, 0.07)	
p-value (Z-test)		0.0514	
5 Years			
Patients remaining at risk	NE		NE
Event Free Rate (%)	NE		NE
95% CI	NE		NE
Difference in Event Free Rate		NE	
95% CI		NE	
p-value (Z-test)		NE	

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley.
Hazard ratios were estimated by Cox regression.
* Censored, NE = Not estimable.
Stratification factors: sex from eCRF (female vs. male), histology from eCRF (squamous vs. non-squamous) and PD-L1 tumor expression status by SP142 IHC assay from IxRS (TC2/3 or IC2/3 vs. TC0/1 and IC0/1)

Figure 12: Kaplan-Meier Plot of overall survival in Stage IB Patients (COD: 21 January 2021)

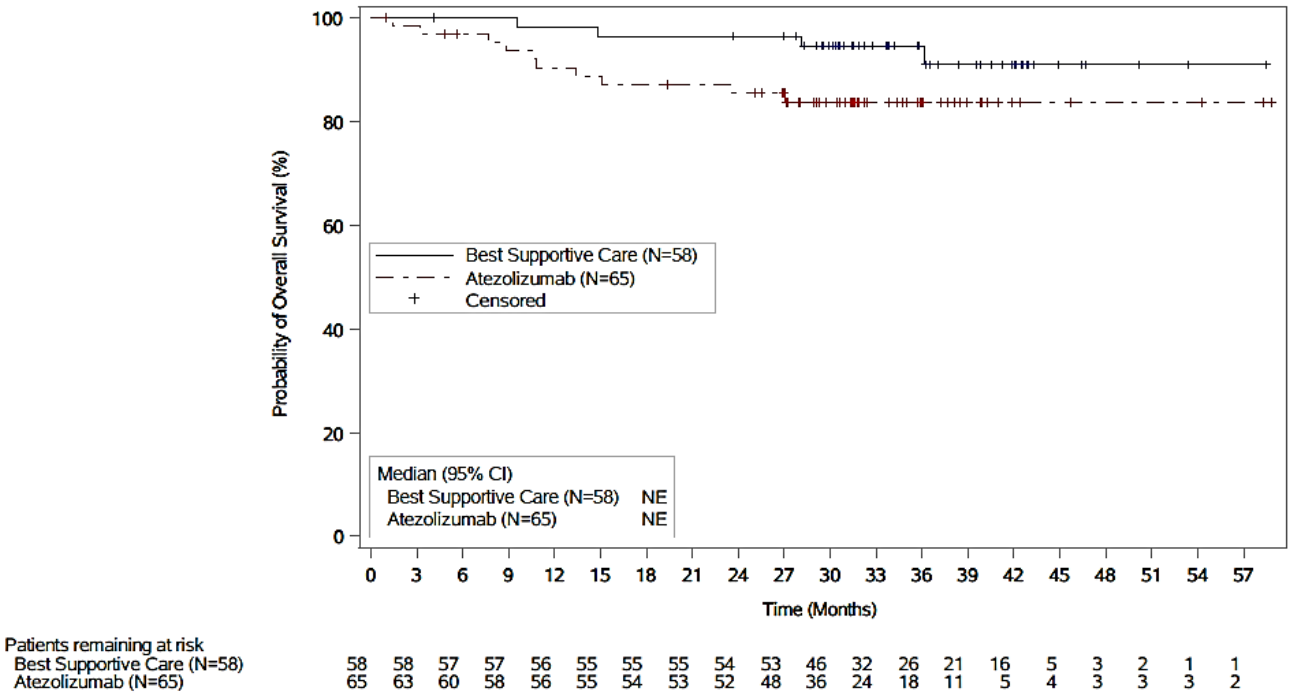


Table 44: Summary of Metastasis-Free Survival and Disease-Free Survival in PD-L1 SP263 ≥50% TC Stage II-IIIA, PD-L1 SP263 ≥1% TC Stage II-IIIA, Stage II-IIIA, ITT, PD-L1 SP263 1-49% TC Stage II-IIIA Populations (COD: 21 January 2021)

	Metastasis-Free Survival		Disease-Free Survival	
	BSC	Atezolizumab	BSC	Atezolizumab
PD-L1 SP263 ≥50% TC Stage II-IIIA population				
	n = 114	n = 115	n = 114	n = 115
Patients with event (%)	39 (34.2%)	18 (15.7%)	52 (45.6%)	28 (24.3%)
Median (months) (95% CI)	NE (35.3, NE)	NE (42.3, NE)	35.7 (29.7, NE)	NE (42.3, NE)
Stratified HR (95% CI)	0.42 (0.24, 0.74)		0.47 (0.29, 0.75)	
PD-L1 SP263 ≥1% TC Stage II-IIIA population				
	n = 228	n = 248	n = 228	n = 248
Patients with event (%)	72 (31.6%)	66 (26.6%)	105 (46.1%)	88 (35.5%)
Median (months) (95% CI)	NE (38.3, NE)	NE (42.3, NE)	35.3 (29.0, NE)	NE (36.1, NE)
Stratified HR (95% CI)	0.72 (0.51, 1.01)		0.66 (0.50, 0.88)	
Stage II-IIIA population				
	n = 440	n = 442	n = 440	n = 442
Patients with event (%)	144 (32.7%)	138 (31.2%)	198 (45.0%)	173 (39.1%)
Median (months) (95% CI)	46.4 (40.9, NE)	NE (38.5, NE)	35.3 (30.4, 46.4)	42.3 (36.0, NE)
Stratified HR (95% CI)	0.86 (0.68, 1.09)		0.79 (0.64, 0.96)	
ITT population				
	n = 498	n = 507	n = 498	n = 507
Patients with event (%)	155 (31.1%)	151 (29.8%)	212 (42.6%)	187 (36.9%)
Median (months) (95% CI)	NE (41.9, NE)	NE (42.3, NE)	37.2 (31.6, NE)	NE (36.1, NE)

Stratified HR (95% CI)	0.90 (0.72, 1.13)		0.81 (0.67, 0.99)	
PD-L1 SP263 1-49% TC Stage II-IIIA population				
	n = 114	n = 133	n = 114	n = 133
Patients with event (%)	33 (28.9%)	48 (36.1%)	53 (46.5%)	60 (45.1%)
Median (months) (95% CI)	NE (38.3, NE)	36.5 (32.8, NE)	31.4 (24.0, NE)	32.8 (29.4, NE)
Stratified HR (95% CI)	1.00 (0.64, 1.57)		0.85 (0.58, 1.23)	

BSC = best supportive care, CI = confidence interval, HR = hazard ratio, ITT = intent-to-treat; NE = not estimable, PD-L1 = programmed death-ligand 1, TC = tumor cells

Subgroup Analyses

Figure 13: Subgroup Analysis of Overall Survival in the PD-L1 SP263 ≥50% TC Stage II-IIIA Population by Baseline Characteristics and Biomarker Status (COD: 21 January 2021)

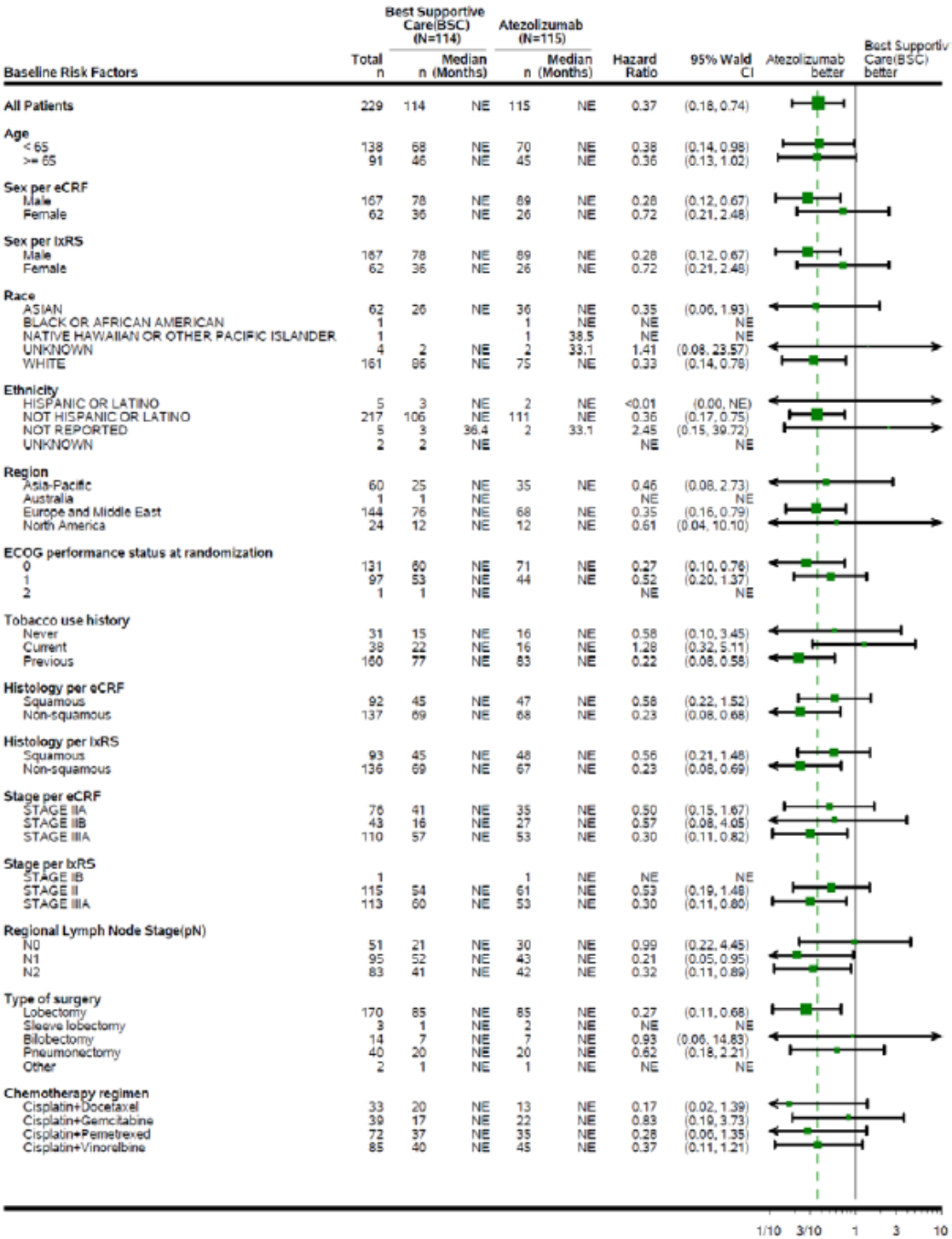


Table 45: Summary of DFS and OS Results in PD-L1 SP263 ≥50% TC Stage II and Stage III Population with Non-Squamous and Squamous Histology

	Stage II		Stage III	
Endpoints by Histology	BSC	Atezolizumab	BSC	Atezolizumab
DFS – Non-Squamous	n = 34	n = 32	n = 35	n = 36
Median	NE	NE	21.4	NE
Unstratified HR (95% CI)	0.33 (0.12, 0.93)		0.35 (0.17, 0.74)	
DFS – Squamous	n = 23	n = 30	n = 22	n = 17
Median	NE	36.7	35.3	NE
Unstratified HR (95% CI)	0.80 (0.31, 2.09)		0.40 (0.11, 1.46)	
OS – Non-Squamous	n = 34	n = 32	n = 35	n = 36
Median	NE	NE	NE	NE
Unstratified HR (95% CI)	0.12 (0.01, 0.93)		0.33 (0.09, 1.24)	
OS – Squamous	n = 23	n = 30	n = 22	n = 17
Median	NE	NE	NE	NE
Unstratified HR (95% CI)	1.88 (0.36, 9.68)		0.28 (0.06, 1.31)	

BSC=best supportive care; CI=confidence interval; DFS=disease-free survival; HR=hazard ratio; ITT=intent-to-treat; NE=not estimable; TC=tumor cell; OS=overall survival; PD-L1=programmed death-ligand 1.

Table 46: Summary of DFS and OS Results in PD-L1 SP263 ≥1% TC Stage II and Stage III Population with Non-Squamous and Squamous Histology

	Stage II		Stage III	
Endpoints by Histology	BSC	Atezolizumab	BSC	Atezolizumab
DFS – Non-Squamous	n = 67	n = 74	n = 76	n = 78
Median	NE	NE	24.7	42.3
Unstratified HR (95% CI)	0.59 (0.34, 1.03)		0.60 (0.39, 0.94)	
DFS – Squamous	n = 46	n = 57	n = 39	n = 39
Median	NE	NE	33.4	NE
Unstratified HR (95% CI)	1.06 (0.51, 2.22)		0.64 (0.32, 1.28)	
OS – Non-Squamous	n = 67	n = 74	n = 76	n = 78
Median	NE	NE	NE	NE
Unstratified HR (95% CI)	0.31 (0.12, 0.80)		1.08 (0.52, 2.28)	
OS – Squamous	n = 46	n = 57	n = 39	n = 39
Median	NE	NE	NE	NE
Unstratified HR (95% CI)	2.01 (0.63, 6.41)		0.70 (0.33, 1.54)	

BSC=best supportive care; CI=confidence interval; DFS=disease-free survival; HR=hazard ratio; ITT=intent-to-treat; NE=not estimable; TC=tumor cell; OS=overall survival; PD-L1=programmed death-ligand 1.

Exploratory analyses

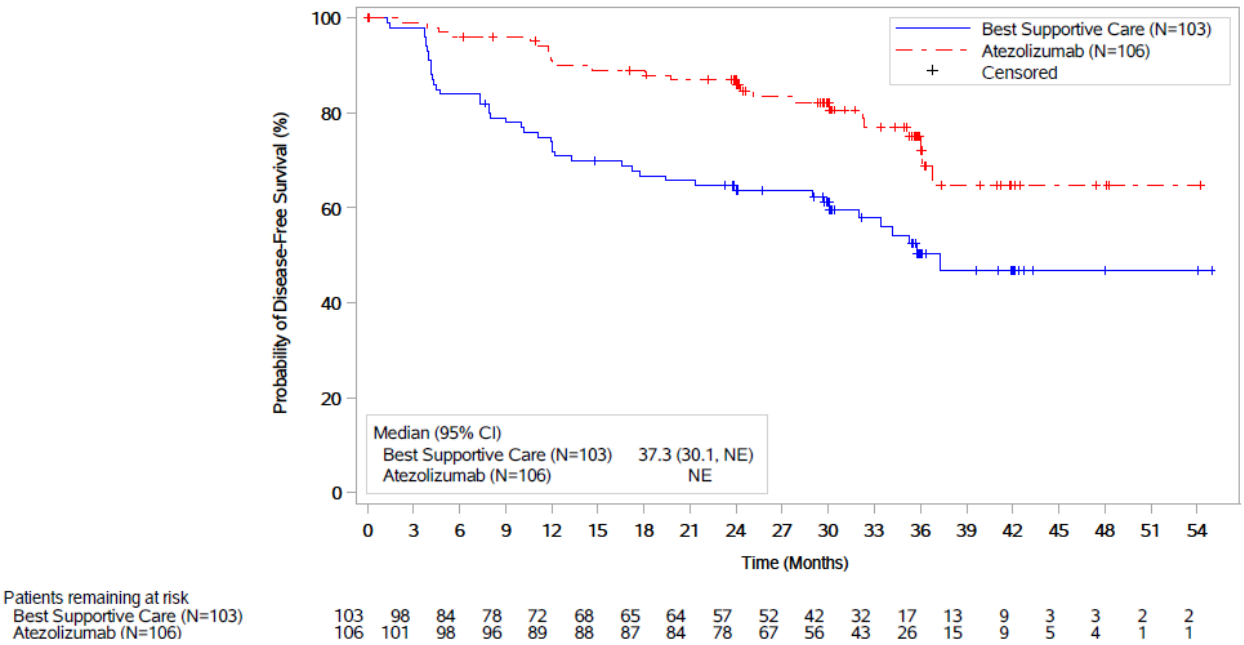
Analysis of DFS and OS in the stage II-IIIA PD-L1≥50% patient population excluding patients with no EGFR mutations or ALK rearrangements

Table 47: Investigator-assessed DFS in the PD-L1 expression ≥ 50% TC stage II – IIIA patient population without EGFR mutations or ALK rearrangements (IMpower010) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=103)		Atezolizumab (N=106)
Patients with event (%)	45 (43.7%)		24 (22.6%)
Earliest contributing event			
Death	2		3
Disease Recurrence	43		21
Patients without event (%)	58 (56.3%)		82 (77.4%)
Time to event (months)			
Median	37.3		NE
95% CI	(30.1, NE)		NE
25% and 75%-ile	11.1 - NE		36.0 - NE
Range	0.0* - 54.9*		0.0* - 54.2*
Stratified Analysis			
p-value (log-rank)		0.0045	
Hazard Ratio		0.488	
95% CI		(0.294, 0.808)	
Unstratified Analysis			
p-value (log-rank)		0.0007	
Hazard Ratio		0.435	
95% CI		(0.265, 0.714)	
Time Point Analysis			
3 Years			
Patients remaining at risk	17		26
Event Free Rate (%)	50.43		75.08
95% CI	(39.22, 61.65)		(65.36, 84.81)
Difference in Event Free Rate		24.65	
95% CI		(9.80, 39.50)	
p-value (Z-test)		0.0011	
5 Years			
Patients remaining at risk	NE		NE
Event Free Rate (%)	NE		NE
95% CI	NE		NE
Difference in Event Free Rate		NE	
95% CI		NE	
p-value (Z-test)		NE	

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley.
Hazard ratios were estimated by Cox regression.
* Censored, NE = Not estimable.
Stratification factors: sex from eCRF (female vs male), histology from eCRF (squamous vs. non-squamous), and stage from eCRF (II vs IIIA).

Figure 14: Kaplan-Meier curve for disease-free survival in the PD-L1 expression ≥ 50% TC stage II – IIIA patient population without EGFR mutations or ALK rearrangements (IMpower010) (COD: 21 January 2021)



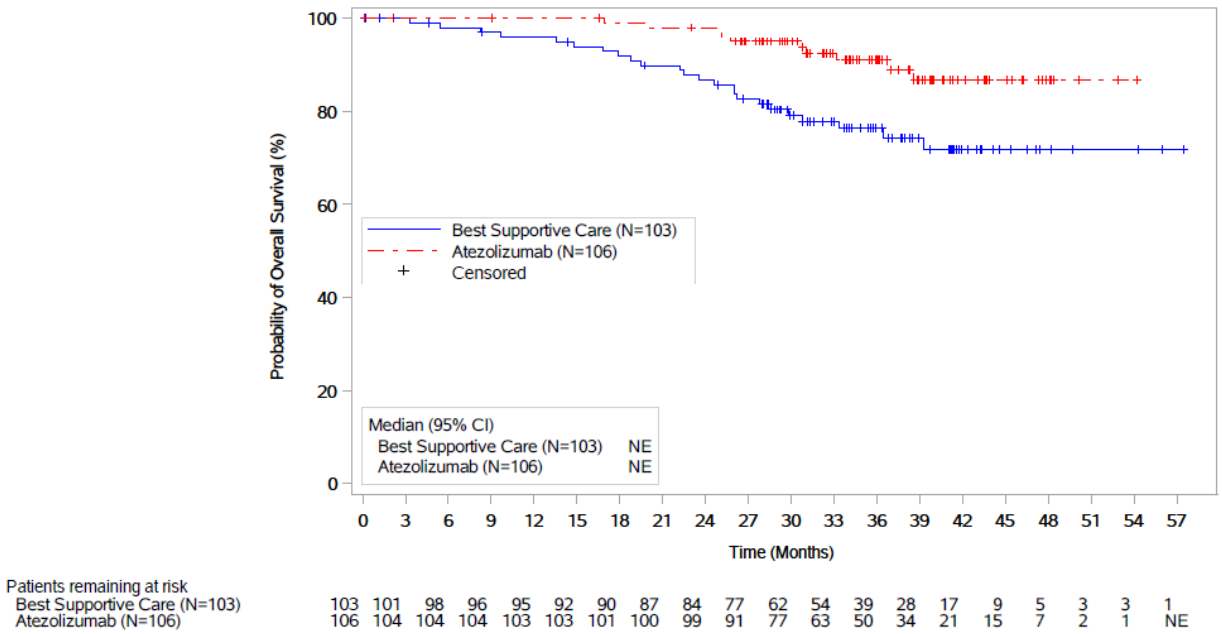
The observed DFS improvement in the atezolizumab arm compared with the BSC arm was consistently shown across the majority of pre-specified subgroups in the PD-L1 ≥ 50% TC stage II – IIIA patient population without EGFR mutations or ALK rearrangements, including both non-squamous NSCLC patients (unstratified HR of 0.35, 95% CI: 0.18, 0.69; median DFS NE vs. 35.7 months) and squamous NSCLC patients (unstratified HR of 0.60, 95% CI: 0.29, 1.26; median DFS 36.7 vs. NE months).

Table 48. Overall survival in the PD-L1 expression ≥ 50% TC stage II – IIIA patient population without EGFR mutations or ALK rearrangements (IMpower010) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=103)		Atezolizumab (N=106)
Patients with event (%)	24 (23.3%)		10 (9.4%)
Earliest contributing event			
Death	24		10
Patients without event (%)	79 (76.7%)		96 (90.6%)
Time to event (months)			
Median	NE		NE
95% CI	NE		NE
25% and 75%-ile	36.4 - NE		NE
Range	0.2* - 57.5*		0.2* - 54.2*
Stratified Analysis			
p-value (log-rank)		0.0100	
Hazard Ratio		0.388	
95% CI		(0.184, 0.818)	
Unstratified Analysis			
p-value (log-rank)		0.0045	
Hazard Ratio		0.359	
95% CI		(0.172, 0.752)	
Time Point Analysis			
3 Years			
Patients remaining at risk	39		50
Event Free Rate (%)	76.37		91.05
95% CI	(67.62, 85.11)		(85.03, 97.07)
Difference in Event Free Rate		14.68	
95% CI		(4.06, 25.30)	
p-value (Z-test)		0.0067	
5 Years			
Patients remaining at risk	NE		NE
Event Free Rate (%)	NE		NE
95% CI	NE		NE
Difference in Event Free Rate		NE	
95% CI		NE	
p-value (Z-test)		NE	

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley.
Hazard ratios were estimated by Cox regression.
* Censored, NE = Not estimable.
Stratification factors: sex from eCRF (female vs male), histology from eCRF (squamous vs. non-squamous), and stage from eCRF (II vs IIIA).

Figure 15: Kaplan-Meier curve for overall survival in the PD-L1 expression ≥ 50% TC stage II – IIIA patient population without EGFR mutations or ALK rearrangements (IMpower010) (COD: 21 January 2021)



Analysis of DFS according to PD-L1 subgroups

Table 49: Disease-Free Survival across PD-L1 SP142 Subgroups (Stage II-IIIA Population)

	BSC	Atezolizumab
TC3 or IC3	n=139	n=135
Patients with event (%)	54 (38.8%)	34 (25.2%)
Median DFS (95% CI), months	46.4 (35.7, NE)	NE (NE)
Unstratified HR (95% CI)	0.59 (0.38, 0.90)	
TC2/3 or IC2/3	n=242	n=244
Patients with event (%)	100 (41.3%)	75 (30.7%)
Median DFS (95% CI), months	42.1 (33.4, NE)	NE (NE)
Unstratified HR (95% CI)	0.65 (0.48, 0.88)	
TC1/2/3 or IC1/2/3	n=406	n=406
Patients with event (%)	181 (44.6%)	153 (37.7%)
Median DFS (95% CI), months	35.7 (30.4, 46.4)	42.3 (36.1, NE)
Unstratified HR (95% CI)	0.76 (0.61, 0.94)	

BSC=best supportive care; DFS=disease free survival; IC=immune cell; NE=not estimable; TC=tumor cell.

Analysis of DFS and OS in the stage II-IIIA PD-L1≥1% patient population

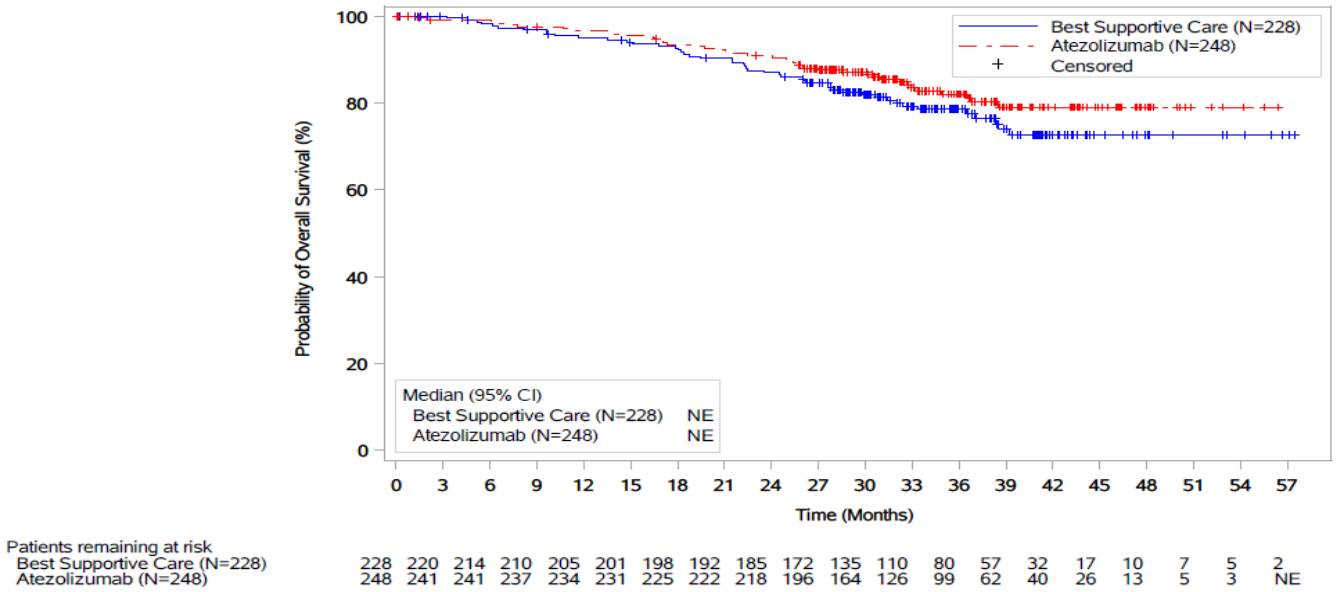
Table 50: Overall Survival in the PD-L1 SP263 ≥1% TC Stage II-IIIA Population

Protocol: GO29527
Snapshot Date: 26FEB2021 Clinical Data Cutoff Date: 21JAN2021

	Best Supportive Care (BSC) (N=228)		Atezolizumab (N=248)
Patients with event (%)	48 (21.1%)		42 (16.9%)
Earliest contributing event			
Death	48		42
Patients without event (%)	180 (78.9%)		206 (83.1%)
Time to event (months)			
Median	NE		NE
95% CI	NE		NE
25% and 75%-ile	38.5 - NE		NE
Range	0.2* - 57.5*		0.1* - 56.4*
Stratified Analysis			
p-value (log-rank)		0.2207	
Hazard Ratio		0.772	
95% CI		(0.509, 1.170)	
Unstratified Analysis			
p-value (log-rank)		0.1905	
Hazard Ratio		0.759	
95% CI		(0.502, 1.148)	
Time Point Analysis			
3 Years			
Patients remaining at risk	80		99
Event Free Rate (%)	78.53		82.04
95% CI	(72.73, 84.33)		(76.78, 87.30)
Difference in Event Free Rate		3.50	
95% CI		(-4.32, 11.33)	
p-value (Z-test)		0.3802	
5 Years			
Patients remaining at risk	NE		NE
Event Free Rate (%)	NE		NE
95% CI	NE		NE
Difference in Event Free Rate		NE	
95% CI		NE	
p-value (Z-test)		NE	

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley.
Hazard ratios were estimated by Cox regression.
* Censored, NE = Not estimable.
Stratification factors: stage from eCRF (II vs. IIIA), sex from eCRF (female vs. male), and histology from eCRF (squamous vs. non-squamous)

Figure 16: Kaplan-Meier Plot of overall survival (PD-L1 SP263 ≥1% TC Stage II–IIIA Population)



Analysis of DFS and OS in the all randomised stage II-IIIA PD-L1≥1% patient population

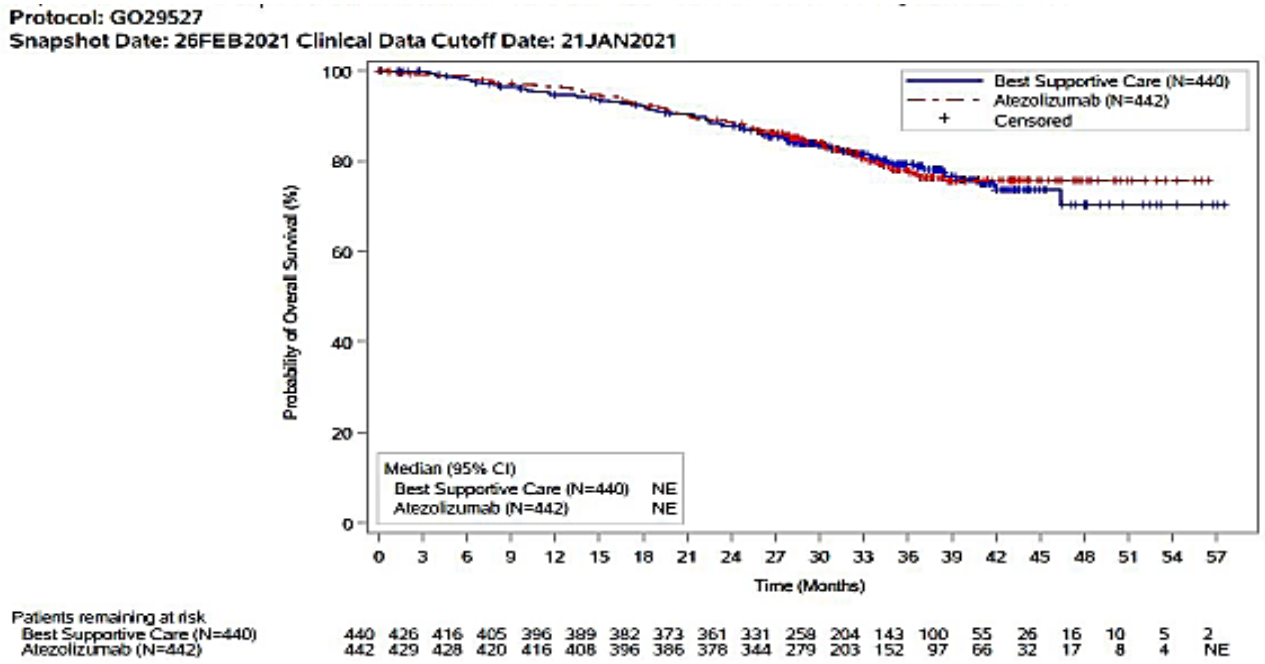
Table 51: Overall Survival in the All Randomised Stage II-IIIA Population

Protocol: GO29527
Snapshot Date: 26FEB2021 Clinical Data Cutoff Date: 21JAN2021

	Best Supportive Care (BSC) (N=440)		Atezolizumab (N=442)
Patients with event (%)	86 (19.5%)		87 (19.7%)
Earliest contributing event			
Death	86		87
Patients without event (%)	354 (80.5%)		355 (80.3%)
Time to event (months)			
Median	NE		NE
95% CI	NE		NE
25% and 75%-ile	40.9 - NE		NE
Range	0.2* - 57.5*		0.0* - 56.4*
Stratified Analysis			
p-value (log-rank)		0.9418	
Hazard Ratio		0.989	
95% CI		(0.733, 1.333)	
Unstratified Analysis			
p-value (log-rank)		0.8771	
Hazard Ratio		0.977	
95% CI		(0.725, 1.316)	
Time Point Analysis			
3 Years			
Patients remaining at risk	143		152
Event Free Rate (%)	79.31		78.04
95% CI	(75.08, 83.55)		(73.68, 82.39)
Difference in Event Free Rate		-1.28	
95% CI		(-7.35, 4.79)	
p-value (Z-test)		0.6799	
5 Years			
Patients remaining at risk	NE		NE
Event Free Rate (%)	NE		NE
95% CI	NE		NE
Difference in Event Free Rate		NE	
95% CI		NE	
p-value (Z-test)		NE	

Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley.
Hazard ratios were estimated by Cox regression.
* Censored, NE = Not estimable.
Stratification factors: stage from eCRF (II vs. IIIA), sex from eCRF (female vs. male), and histology from eCRF (squamous vs. non-squamous)

Figure 17: Kaplan-Meier Plot of overall survival (Stage II–IIIA Population)



Analyses of DFS and OS in EGFR or ALK mutated patients

Figure 18: Subgroup Analysis of Disease-Free Survival in PD-L1 SP263 ≥ 50% TC Stage II-IIIA Population by Biomarker Status

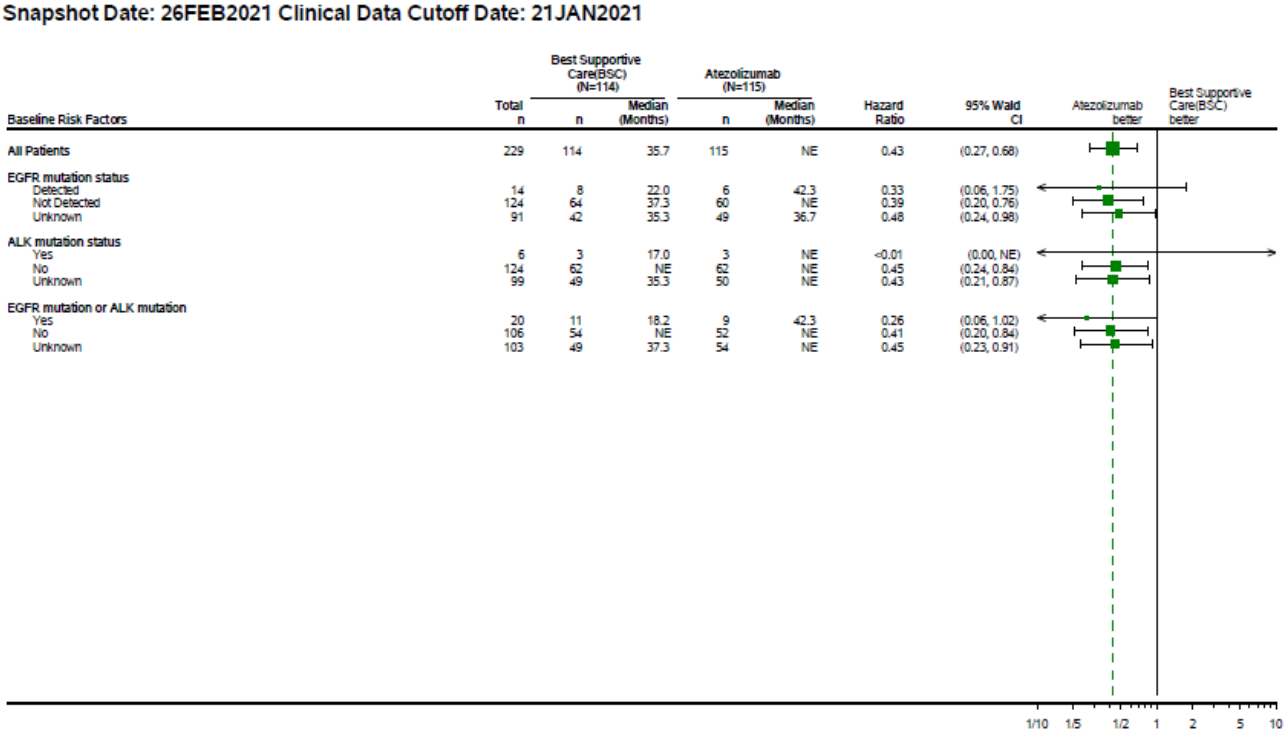
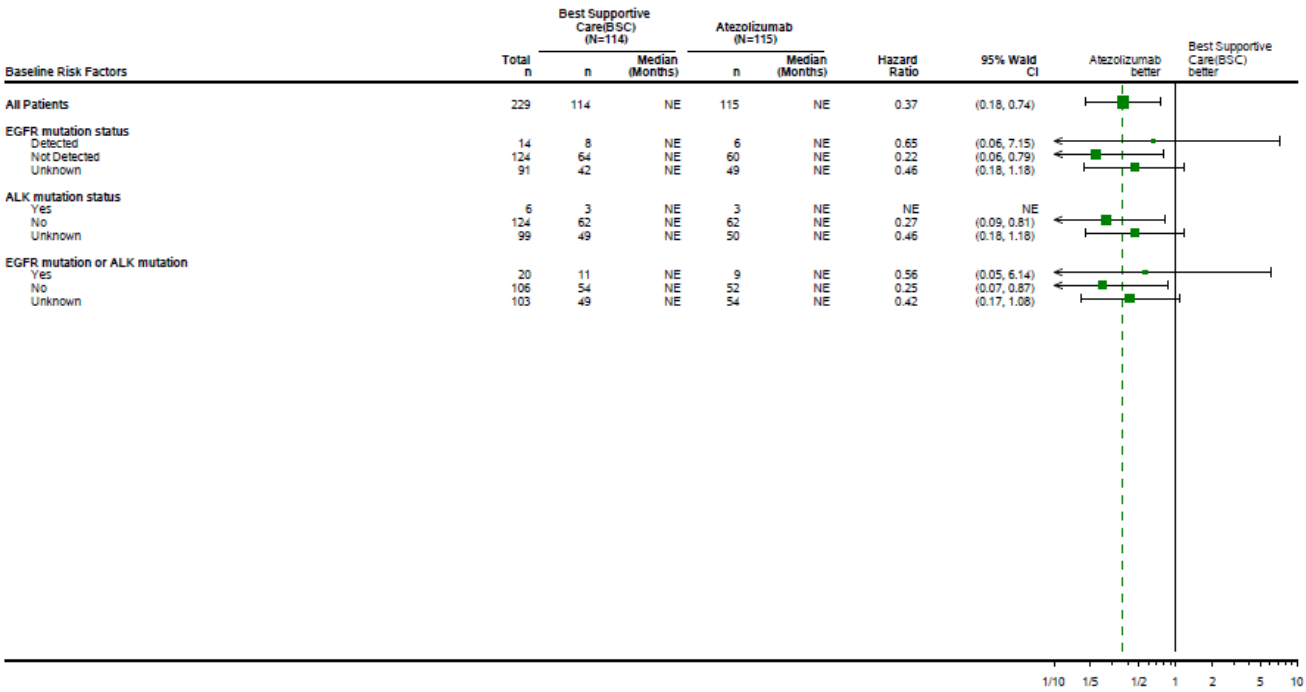


Figure 19: Subgroup Analysis of Overall Survival in PD-L1 SP263 ≥ 50% TC Stage II-IIIA Population by Biomarker Status

Protocol: GO29527
Snapshot Date: 26FEB2021 Clinical Data Cutoff Date: 21JAN2021



Analyses of subsequent therapies and PFS2

Table 52: Summary of Follow-Up Cancer Therapy

	Best supportive care	Atezolizumab
PD-L1 SP263 ≥50% TC Stage II-IIIA population	n = 114	n = 115
At least one follow-up cancer therapy	30 (26.3%)	19 (16.5%)
Chemotherapy	16 (14.0%)	15 (13.0%)
Immunotherapy	19 (16.7%)	4 (3.5%)
Targeted Therapy, TKI	5 (4.4%)	5 (4.3%)
Targeted Therapy, Monoclonal Antibody	2 (1.8%)	2 (1.7%)
PD-L1 SP263 ≥1% TC Stage II-IIIA population	n = 228	n = 248
At least one follow-up cancer therapy	68 (29.8%)	51 (20.6%)
Chemotherapy	47 (20.6%)	40 (16.1%)
Immunotherapy	36 (15.8%)	8 (3.2%)
Targeted Therapy, TKI	14 (6.1%)	12 (4.8%)
Targeted Therapy, Monoclonal Antibody	6 (2.6%)	7 (2.8%)
Stage II-IIIA population	n = 440	n = 442
At least one follow-up cancer therapy	125 (28.4%)	99 (22.4%)
Chemotherapy	87 (19.8%)	70 (15.8%)
Immunotherapy	61 (13.9%)	19 (4.3%)
Targeted Therapy, TKI	28 (6.4%)	29 (6.6%)
Targeted Therapy, Monoclonal Antibody	16 (3.6%)	17 (3.8%)
Unknown	5 (1.1%)	1 (0.2%)
Bisphosphonate	1 (0.2%)	0
ITT population	n = 498	n = 507
At least one follow-up cancer therapy	131 (26.3%)	102 (20.1%)
Chemotherapy	92 (18.5%)	72 (14.2%)
Immunotherapy	65 (13.1%)	19 (3.7%)
Targeted Therapy, TKI	29 (5.8%)	29 (5.7%)
Targeted Therapy, Monoclonal Antibody	17 (3.4%)	17 (3.4%)
PD-L1 SP263 1-49% TC Stage II-IIIA population	n = 114	n = 133
At least one follow-up cancer therapy	38 (33.3%)	32 (24.1%)
Chemotherapy	31 (27.2%)	25 (18.8%)
Immunotherapy	17 (14.9%)	4 (3.0%)
Targeted Therapy, TKI	9 (7.9%)	7 (5.3%)
Targeted Therapy, Monoclonal Antibody	4 (3.5%)	5 (3.8%)

- ITT=intent-to-treat; PD-L1 = programmed death-ligand 1; TC = tumor cells; TKI=tyrosine kinase inhibitor

PFS2 data in the PD-L1 SP263 ≥50% TC Stage II-IIIA population is presented in the table below.

Table 53: Summary of Progression-Free Survival after Next Line of Cancer Immunotherapy (PFS2)

	Best supportive care	Atezolizumab
PD-L1 SP263 ≥50% TC Stage II-IIIA population	n = 114	n = 115
PFS2 events	29 (25.4%)	13 (11.3%)
Death	20	10
Disease Progression	9	3
Median (Months), 95% CI	NE	NE
Unstratified HR, 95% CI	0.37 (0.19, 0.72)	
PD-L1 SP263 ≥1% TC Stage II-IIIA population	n = 228	n = 248
PFS2 events	57 (25.0%)	44 (17.7%)
Death	35	38
Disease Progression	22	6
Median (Months), 95% CI	NE	NE
Unstratified HR, 95% CI	0.62 (0.42, 0.92)	
Stage II-IIIA population	n = 440	n = 442
PFS2 events	103 (23.4%)	89 (20.1%)
Death	67	81
Disease Progression	36	8
Median (Months), 95% CI	NE	NE
Unstratified HR, 95% CI	0.79 (0.59, 1.04)	
ITT population	n = 498	n = 507
PFS2 events	109 (21.9%)	99 (19.5%)
Death	71	91
Disease Progression	38	8
Median (Months), 95% CI	NE	NE
Unstratified HR, 95% CI	0.84 (0.64, 1.10)	
PD-L1 SP263 1-49% TC Stage II-IIIA population	n = 114	n = 133
PFS2 events	28 (24.6%)	31 (23.3%)
Death	15	28
Disease Progression	13	3
Median (Months), 95% CI	NE	NE
Unstratified HR, 95% CI	0.86 (0.52, 1.43)	

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; PD-L1 = programmed death-ligand 1; TC = tumor cells

Summary of main study

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

Table 54: Summary of Efficacy for trial Impower010

Title: A Phase III, Open-Label, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab (Anti-PD-L1 Antibody) Compared with Best Supportive Care Following Adjuvant Cisplatin-Based Chemotherapy in Patients With Completely Resected Stage IB-IIIA Non-Small Cell Lung Cancer	
Study identifier	IMpower010, GO29527, EudraCT 2014-003205-15, NCT02486718
Design	Phase III, randomized, global, multicenter, open-label, two-arm study. Enrolment phase: Patients with Stage IB - Stage IIIA NSCLC (as per UICC/AJCC staging system, 7th edition) who had recently undergone complete resection received one of four regimens of cisplatin-based chemotherapy (cisplatin plus vinorelbine, docetaxel, gemcitabine, or pemetrexed; based on investigator choice) for up to 4 cycles. Randomized phase: Following cisplatin-based chemotherapy patients were randomized 1:1 to receive atezolizumab or best supportive care (BSC). Cross over to the atezolizumab arm was not permitted.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		59 months: first patient randomized 26 February 2016 to clinical cut-off date (CCOD) 21 January 2021 Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Atezolizumab		1200 mg by IV infusion on Day 1 every 3 weeks for a total of 16 cycles unless there was disease recurrence or unacceptable toxicity, followed by survival follow-up. N = 507 patients.
	BSC		No treatment other than best supportive care. Patients were followed starting on Day 1 of each 21-day cycle for one year followed by survival follow-up. N = 498 patients.
Endpoints and definitions	Primary endpoint	Disease-free survival (DFS)	DFS as assessed by the investigator in the PD-L1 subpopulation (defined as ≥ 1% tumour cell expression by the SP263 assay) within the Stage II-IIIA population, in all randomized patients with Stage II-IIIA NSCLC, and in the ITT population. DFS defined as time from randomization to the date of occurrence of any of the following, whichever occurs first: • First recurrence of NSCLC, as determined by the investigator after an integrated assessment of radiographic data, biopsy sample results (if available), and clinical status • Occurrence of new primary NSCLC, as assessed by the investigator • Death from any cause
	Key secondary endpoint	Overall survival (OS)	OS in the ITT population. OS defined as time from randomization to death from any cause.
Database lock	CCOD: 21 January 2021		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Randomized patients within the PD-L1 subpopulation (PD-L1 ≥1% tumour cell expression by the SP263 assay) within the Stage II-IIIA population. CCOD: 21 January 2021		
	Treatment group	Atezolizumab	BSC

Descriptive statistics and estimate variability	Number of subjects	248	228
	DFS (median, months)	NE (not estimable)	35.3
	95% confidence interval	36.1, NE	29.0, NE
Effect estimate per comparison	DFS	Comparison groups	Atezolizumab vs. BSC
		Hazard ratio	0.66
		95% CI	0.50, 0.88
		P-value	0.0039
Notes	The OS data in the ITT population was immature with low event-to-patient ratios (18% BSC vs. 19% atezolizumab) and not formally tested at the time of the CCOD. An exploratory analysis of OS suggested a trend in favour of atezolizumab over BSC in the PD-L1 SP263 ≥ 1% TC Stage II-IIIA population (stratified HR of 0.77; 95% CI: 0.51, 1.17).		

Clinical studies in special populations

No dedicated studies were conducted in special populations.

In IMpower 010, the ≥65 years population was: 198 (39.8%) in the arm BSC and 184 (36.3%) in the atezolizumab arm, a total of 382/1005 (38.0%) patients.

2.4.2. Discussion on clinical efficacy

The Applicant is seeking an extension of indication to include treatment with atezolizumab monotherapy for one year as adjuvant treatment with the following initial indication:

Tecentriq as monotherapy is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression on ≥ 1% of tumour cells (TC).

Design and conduct of clinical studies

The Applicant submitted an interim analysis of the pivotal study, Impower010, a phase III, open label, multi-centre, randomised study, GO29527 (IMpower010), was conducted to evaluate the efficacy and safety of atezolizumab for the adjuvant treatment of patients with stage IB (tumours ≥ 4 cm) - IIIA NSCLC (per the Union for International Cancer Control/American Joint Committee on Cancer staging system, 7th edition). Patients were recruited from 204 centers across 21 countries.

The stratification factors (stage, sex, histology and PD-L1 status according to SP142) are considered relevant. The number of patients in PD-L1 subgroups defined by the SP263 immunohistochemistry (IHC) assay were generally balanced between treatment arms in the ITT population (n= 1005).

The demographics and baseline disease characteristics in the ITT population were well balanced between the treatment arms. The median age was 62 years (range: 26 to 84), and 67% of patients were male. The majority of patients were White (73%), and 24% were Asian. Most patients were current or previous smokers (78%) and baseline ECOG performance status in patients was 0 (55%) or 1 (44%). Overall, 12% of patients had stage IB, 47% had stage II and 41% had stage IIIA disease. The percentage of patients who had tumours with PD-L1 expression ≥ 1% and ≥ 50% on TC as measured by the VENTANA PD-L1 (SP263) Assay was 55% and 26%, respectively.

The open-label design of the phases III randomized study was not recommended by the Rapporteurs, and the applicant was advised to implement a blinded independent central review (BICR). The primary efficacy endpoint is investigator-assessed DFS and a retrospective blinded independent central review of DFS was performed.

The primary endpoint of DFS was accepted, although clarifying, that it would be of major importance that a gain in DFS translated into a gain in OS. The MAH presented preliminary BIRC results for approximately 50% of the original ITT population (514 patients of 1005 included in the ITT). The concordant rate between INV-DFS and BICR-DFS in terms of occurrence of an event was 92.6%. When considering the timing of the DFS events, the concordance was 86.8%. The MAH also presented results of the DFS analysis using the BIRC assessment. These preliminary analyses are comparable to those reported using the investigator assessment and therefore considered valid. The statistical methods implemented to analyse DFS and OS are endorsed.

The provided OS data in the dossier with DCO 21.01.2021 were granted immature (33% of OS events). The MAH plans to perform additional interim analyses (IAs) of OS before the final OS analysis, and has accepted to submit final DFS and updated and final OS data post-approval.

Seven (7) amendments, were made to the protocol during the study period. Changes in study population, primary endpoint, testing hierarchy, and the addition and timing of interim analyses were made, in addition to changing the PD-L1 testing method (from SP142 to SP263). According to the MAH, the changes were guided only by external data from other studies on atezolizumab. The MAH presented the analyses that would have been performed according to protocol versions 1-4, 5-6 and 7. The results for the DFS analyses were concordant, i.e. in all cases, the primary test remained statistically significant. These analyses do not raise concerns regarding data-driven protocol changes, but suggest the lack of benefit for patients with stage IB and confirm the association of better efficacy outcomes with higher PD-L1 expression status.

Overall, the design and conduct of the study are acceptable. The patient population was adequately selected without an age limit for inclusion, the comparator arm was considered appropriate.

Efficacy data and additional analyses

The primary endpoints of DFS in PD-L1 ≥1% positive stage II-IIIA NSCLC patients, and DFS in all randomized stage II-IIIA any degree of PD-L1 status NSCLC patients, were both met. The Primary endpoint of DFS in the ITT population (Stage IB (tumour size ≥4 cm)-IIIA, any degree of PD-L1 status) was not met. Furthermore, more deaths were observed in the atezolizumab arm compared to the BSC arm in the OS analysis. This indicated that certain subgroups (patients with: stage IB (by 7th edition AJCC), <50% PD-L1 expression, EGFR and ALK mutations) in the ITT population did not seem to benefit from the experimental arm.

The MAH provided data of subsequent therapies and PFS2 for the ITT population and subgroups. Generally, a higher proportion of patients received at least one follow-up cancer therapy in the BSC arm compared to the atezolizumab arm (e.g. 26.3% vs. 16.5% for the PD-L1 ≥50% TC Stage II-IIIA population) with the largest difference in the proportion of immunotherapy (16.7% vs. 3.5% in the BSC vs. the atezolizumab arm of the ≥50% Stage II-IIIA population). In the PD-L1 ≥50% TC Stage II-IIIA population, 29 (25.4%) patients in the BSC arm and 13 (11.3%) patients in the atezolizumab arm had PFS2 events (unstratified HR 0.37; 95% CI 0.19, 0.72). Although based on low event rates, these results can be considered supportive for the benefit of atezolizumab in the subgroup of patients with high PD-L1 expression.

In view of the immature OS data, the MAH was asked for metastasis-free survival (MFS) data and could provide results of MFS as exploratory analyses for the ITT and different subpopulations. In the PD-L1 ≥ 50% TC stage II-IIIA population, results support the DFS benefit (MFS HR 0.42; 95% CI 0.24, 0.74; event rates 34.2% vs 15.7% in the SOC vs the atezolizumab arm). A MFS benefit was less clear in other populations (HR 0.72 for PD-L1≥1% TC Stage II-IIIA, 0.86 for Stage II-IIIA, 0.90 for ITT and notably 1.0 for 1-49% TC II-IIIA). In the subgroup of the stage IB and the PD-L1 1-49% positive patients, more deaths were seen in the atezolizumab arm than in the BSC arm and no differences were seen in DFS.

At the SA meeting, the MAH was advised to test all included patients for driver mutations (ALK and EGFR). In the submitted data EGFR and ALK status was known for 60% of the patients. From the forest plots, it seems that patients with EGFR or ALK mutations do not benefit from adjuvant treatment with atezolizumab.

The patient group that seems to drive the DFS benefit from adjuvant atezolizumab encompasses 209 of the initial 1005 randomized patients; 106 in the atezolizumab arm and 103 in the BSC arm. Median DFS was NE (NE-NE) in the atezolizumab arm and 37.3 (30.1-NE) months in the BSC arm, stratified HR=0.49 95% CI: (0.29-0.81) and the 3-year DFS proportions are 75.1% and 50.4%, respectively. An exploratory analysis of OS suggested a trend in favor of atezolizumab over BSC, with a stratified HR of 0.39 (95% CI: 0.18, 0.82). The OS forest plot of subgroups in these patient pool showed point estimates <1 for all subgroups except for the small group of current smokers (HR 1.28; 95% CI 0.32, 5.11).

Based on clinical interpretation from the abovementioned subgroup analyses, it was agreed with the MAH to restrict the indication to patients who exhibited a favourable benefit/risk balance from adjuvant atezolizumab, i.e., stage II-IIIA (7th edition AJCC), PD-L1 high (≥50%) and without EGFR or ALK mutations. This is based on the large effect size of the treatment on DFS (stratified DFS HR 0.49, 95% CI 0.29-0.81), acknowledging this analysis was only a key secondary endpoint and not included in the alpha control of the statistical testing; moreover, the sample size of this subgroup (n=209) represents only about 20% of the ITT population (n=1005). However, the DFS benefit was further supported by OS data; although exploratory and immature (event rates 9% and 23% in the atezolizumab and BSC arms, respectively), with a stratified OS HR of 0.39 (95% CI 0.18-0.82). This is considered reassuring, and it can be reasonably expected that the benefit supports the restricted indication. Nevertheless, OS data are immature and final DFS and updated OS data are requested to reassure these conclusions, also because data come from analyses in a subgroup of the ITT. The MAH has committed to provide final analysis of DFS and 2nd interim analysis of OS as a recommendation, expected in August 2024.

The indication wording agreed upon the previous discussion states:

Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1 for selection criteria).

The following selection criteria define patients with high risk of recurrence who are included in the therapeutic indication and are reflective of the patient population with stage II – IIIA according to the 7th edition staging system:

Tumour size ≥ 5 cm; or tumours of any size that are either accompanied by N1 or N2 status; or tumours that are invasive of thoracic structures (directly invade the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve the main bronchus < 2 cm distal to the carina but without involvement of the carina; or tumours that are associated with atelectasis or obstructive pneumonitis of the entire lung; or tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary.

The study did not include patients who had N2 status with tumours invading the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, or with separate tumour nodule(s) in a different ipsilateral lobe.

2.4.3. Conclusions on the clinical efficacy

The data presented in the interim analysis (CCOD January 2021) support the adjuvant treatment with atezolizumab as monotherapy for one year following resection and platinum-based adjuvant chemotherapy for adult patients with stage II-IIIA (7th edition AJCC) ≥50% PD-L1 positive NSCLC although, OS is still immature. Furthermore, the very limited data of the EGFR and ALK mutated patients showed no benefit for this patient group which is excluded from the approved indication. The MAH is recommended to submit final data on DFS and updated and final OS data post-approval.

2.5. Clinical safety

Introduction

Tecentriq received a marketing authorisation valid throughout the EU on 21 September 2017.

For this application, the safety of Tecentriq (atezolizumab) monotherapy in subjects with Stage IB (tumors ≥4 cm)-Stage IIIA non-small cell lung cancer (NSCLC) (as per UICC/AJCC staging system, 7th edition) following complete resection and up to 4 cycles of adjuvant cisplatin-based chemotherapy is based on the Study GO29527 (hereinafter IMpower010).

In addition to IMpower010, pooled safety data for the following populations are provided as part of the comprehensive safety evaluation:

- Single-agent atezolizumab regardless of tumour type (n=2616); hereinafter referred to as Atezo Mono 1 population. The Atezo Mono 1 comprises safety data which informs the Warnings and Precautions section of the currently approved U.S. Prescribing Information.

- Single-agent atezolizumab regardless of tumour type (n=3178); hereinafter referred to as Atezo Mono 2 population (Atezo Mono 1 + GO29294 (IMVIGOR211) + wo29074 (IMMOTION150 RCC ATEZO MONO ARM B prior to crossover)).

Safety data from the atezolizumab arm and BSC arm of IMpower010 are summarized and displayed side by side with the two pooled atezolizumab monotherapy populations described above. The pooled populations allow for a comprehensive characterization of the safety profile of atezolizumab when given as monotherapy.

The enrolled safety-evaluable population is defined as all eligible patients who entered the enrollment phase and who received at least one dose of chemotherapy (cisplatin, vinorelbine, docetaxel, gemcitabine, or pemetrexed), regardless of whether they are subsequently randomized or not.

The randomized safety evaluable population is defined as all randomized patients who received at least one dose of atezolizumab and all randomized patients who were randomized to the control arm and did not receive any dose of atezolizumab but who had at least one post baseline safety assessment (e.g., adverse events, laboratory tests, vital signs), regardless of their assigned treatment at randomization (atezolizumab/BSC).

Table 55: Patient disposition (safety evaluable population)

	IMPOWER010		Pooled Population	
	Best Supportive Care (BSC) (N=495)	Atezolizumab (N=495)	Atezo Mono[1] (N=2616)	Atezo Mono[2] (N=3178)
Study Status				
n	495 (100%)	495 (100%)	2616 (100%)	3178 (100%)
Ongoing	370 (74.7%)	381 (77.0%)	911 (34.8%)	1108 (34.9%)
Discontinued study	125 (25.3%)	114 (23.0%)	1705 (65.2%)	2070 (65.1%)
Reason for Study Discontinuation				
All Reasons	125 (25.3%)	114 (23.0%)	1705 (65.2%)	2070 (65.1%)
Death	88 (17.8%)	91 (18.4%)	1535 (58.7%)	1887 (59.4%)
Progressive disease	0	0	3 (0.1%)	3 (<0.1%)
Lost to follow-up	4 (0.8%)	0	67 (2.6%)	70 (2.2%)
Other	0	0	1 (<0.1%)	1 (<0.1%)
Physician decision	3 (0.6%)	0	1 (<0.1%)	1 (<0.1%)
Protocol violation	0	0	11 (0.4%)	11 (0.3%)
Protocol Deviation	0	1 (0.2%)	0	0
Withdrawal by subject	30 (6.1%)	21 (4.2%)	87 (3.3%)	97 (3.1%)
Disease relapse	0	1 (0.2%)	0	0

Atezo=Atezolizumab. Atezo Mono[1]: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR Arm A) + GO28754(BIRCH) +
GO28915(OAK Arm A) + GO29293(IMVIGOR210); Atezo Mono[2]: Atezo Mono[1] + GO29294(IMVIGOR211) + WO29074(IMMOTION150 RCC ATEZO MONO
ARM B prior to crossover).
Note: The safety population from IMpower010 reflects safety evaluable patients from the randomized phase(BSC vs atezolizumab) of the
study.
Actual treatment arms are presented.
Clinical cut-off dates: GO29527:21JAN2021, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015,
GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, WO29074:17OCT2016.

Patient exposure

After randomization the patients in the atezolizumab arm received atezolizumab 1200 mg by intravenous (IV) infusion on Day 1 every 3 weeks (q3w) for a total of 16 cycles. Patients in the BSC arm received no treatment during the randomized phase other than best supportive care and were continuously followed starting on Day 1 of each 21-day cycle (considered as observation period) for one year followed by survival follow-up. Cross over to the atezolizumab arm was not permitted.

To ensure the same frequency of study assessments between the treatment arms, including assessments for disease recurrence and safety, patients in the BSC arm were required to undergo medical contact q3w for assessments during the first year for symptom and adverse event (AE) assessment.

The median duration of treatment was longer in the atezolizumab arm of IMpower010 (10.4 months) where patients were treated in the adjuvant setting compared with Atezo Mono pooled populations (3.5 months each), where metastatic patients with disease present were treated until disease progression or loss of clinical benefit. The median number of atezolizumab doses administered was 16 in IMpower010 (maximum allowed per protocol) and was 6 in the Atezo Mono pooled populations.

Table 56: Study drug exposure for atezolizumab infusion

	IMPOWER010	Pooled Population	
	Atezolizumab (N=495)	Atezo Mono[1] (N=2616)	Atezo Mono[2] (N=3178)
Number of doses			
n	495	2616	3178
Mean (SD)	12.4 (5.4)	9.7 (9.5)	9.9 (9.8)
Median	16.0	6.0	6.0
Min - Max	1 - 16	1 - 64	1 - 64
Treatment duration (M)			
n	495	2616	3178
Mean (SD)	8.2 (3.9)	6.5 (7.5)	6.6 (7.5)
Median	10.4	3.5	3.5
Min - Max	0 - 16	0 - 53	0 - 53
Treatment duration (M)			
n	495	2616	3178
<= 3	80 (16.2%)	1219 (46.6%)	1469 (46.2%)
>3-6	53 (10.7%)	449 (17.2%)	545 (17.1%)
>6-12	349 (70.5%)	438 (16.7%)	513 (16.1%)
>12-18	13 (2.6%)	273 (10.4%)	341 (10.7%)
>18-24	0	167 (6.4%)	222 (7.0%)
>24	0	70 (2.7%)	88 (2.8%)

Atezo=Atezolizumab. Atezo Mono[1]: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR Arm A) + GO28754(BIRCH) +
GO28915(OAK Arm A) + GO29293(IMVIGOR210); Atezo Mono[2]: Atezo Mono[1] + GO29294(IMVIGOR211) + WO29074(IMMOTION150 RCC ATEZO MONO
ARM B prior to crossover).
Note: The safety population from IMpower010 reflects safety evaluable patients from the randomized phase(B&C vs atezolizumab) of the
study.
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: GO29527:21JAN2021, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015,
GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, WO29074:17OCT2016.

Table 57: Demographics and baseline characteristics (safety evaluable population)

	IMPOWER010		Pooled Population	
	Best Supportive Care (BSC) (N=495)	Atezolizumab (N=495)	Atezo Mono[1] (N=2616)	Atezo Mono[2] (N=3178)
Age (years)				
n	495	495	2616	3178
Mean (SD)	61.1 (9.2)	61.2 (8.5)	63.0 (11.0)	63.3 (10.8)
Median	62.0	62.0	64.0	64.0
Min - Max	26 - 84	33 - 83	20 - 92	20 - 92
Age Group (years)				
n	495	495	2616	3178
<65	299 (60.4%)	315 (63.6%)	1347 (51.5%)	1595 (50.2%)
>=65	196 (39.6%)	180 (36.4%)	1269 (48.5%)	1583 (49.8%)
Age Group (years)				
n	495	495	2616	3178
< 65	299 (60.4%)	315 (63.6%)	1347 (51.5%)	1595 (50.2%)
65 - 74	172 (34.7%)	160 (32.3%)	886 (33.9%)	1105 (34.8%)
75 - 84	24 (4.8%)	20 (4.0%)	365 (14.0%)	458 (14.4%)
>=85	0	0	18 (0.7%)	20 (0.6%)
Sex				
n	495	495	2616	3178
Female	162 (32.7%)	166 (33.5%)	1012 (38.7%)	1146 (36.1%)
Male	333 (67.3%)	329 (66.5%)	1604 (61.3%)	2032 (63.9%)
Race				
n	495	495	2616	3178
American Indian or Alaska Native	0	0	4 (0.2%)	4 (0.1%)
Asian	111 (22.4%)	126 (25.5%)	256 (9.8%)	320 (10.1%)
Black or African American	1 (0.2%)	5 (1.0%)	68 (2.6%)	73 (2.3%)
Native Hawaiian or other Pacific Islander	1 (0.2%)	1 (0.2%)	7 (0.3%)	7 (0.2%)
White	374 (75.6%)	354 (71.5%)	2115 (80.8%)	2533 (79.7%)
Other	0	0	118 (4.5%)	121 (3.8%)
Multiple	1 (0.2%)	0	6 (0.2%)	6 (0.2%)
Unknown	7 (1.4%)	9 (1.8%)	42 (1.6%)	114 (3.6%)
Pooled Race Group				
n	495	495	2616	3178
Asian	111 (22.4%)	126 (25.5%)	256 (9.8%)	320 (10.1%)
Black or African American	1 (0.2%)	5 (1.0%)	68 (2.6%)	73 (2.3%)
White	374 (75.6%)	354 (71.5%)	2115 (80.8%)	2533 (79.7%)
Other	9 (1.8%)	10 (2.0%)	177 (6.8%)	252 (7.9%)
Baseline Weight (kg)				
n	495	495	2574	3125
Mean (SD)	74.45 (15.80)	73.62 (16.53)	75.12 (18.27)	75.62 (18.08)
Median	73.00	71.50	73.54	74.00
Min - Max	43.1 - 140.0	39.6 - 132.5	34.3 - 175.8	34.3 - 175.8
Baseline ECOG Performance Score				
n	495	495	2610	3069
0	282 (57.0%)	269 (54.3%)	985 (37.7%)	1201 (39.1%)
1	212 (42.8%)	224 (45.3%)	1589 (60.9%)	1832 (59.7%)
2	1 (0.2%)	2 (0.4%)	36 (1.4%)	36 (1.2%)
Tobacco Use History				
n	495	495	2614	3072
Never	107 (21.6%)	112 (22.6%)	703 (26.9%)	842 (27.4%)
Current	86 (17.4%)	71 (14.3%)	287 (11.0%)	344 (11.2%)
Previous	302 (61.0%)	312 (63.0%)	1624 (62.1%)	1886 (61.4%)

Table 58: Safety summary (safety evaluable patients)

	IMPOWER010		Pooled Population	
	Best Supportive Care(BSC) (N=495)	Atezolizumab (N=495)	Atezo Mono[1] (N=2616)	Atezo Mono[2] (N=3178)
Total number of patients with at least one AE	350 (70.7%)	459 (92.7%)	2510 (95.9%)	3051 (96.0%)
Total number of events	1253	2742	27658	33370
Total number of patients with at least one				
Atezo-related AE	0	335 (67.7%)	1760 (67.3%)	2167 (68.2%)
Grade 3-4 AE	57 (11.5%)	108 (21.8%)	1200 (45.9%)	1482 (46.6%)
Atezo-related Grade 3-4 AE	0	53 (10.7%)	382 (14.6%)	496 (15.6%)
Grade 5 AE	3 (0.6%)	8 (1.6%)	87 (3.3%)	119 (3.7%)
Atezo-related Grade 5 AE	0	4 (0.8%)	7 (0.3%)	11 (0.3%)
Serious AE	42 (8.5%)	87 (17.6%)	1065 (40.7%)	1309 (41.2%)
Atezo-related serious AE	0	37 (7.5%)	266 (10.2%)	353 (11.1%)
AE leading to Atezo discontinuation	0	90 (18.2%)	182 (7.0%)	226 (7.1%)
AE leading to Atezo interruption	0	142 (28.7%)	717 (27.4%)	881 (27.7%)
Total number of patients with at least one AE of Special Interest	47 (9.5%)	256 (51.7%)	899 (34.4%)	1101 (34.6%)
Total number of events	70	510	1792	2199
Total number of patients with at least one				
Atezo-related AE of Special Interest	0	223 (45.1%)	644 (24.6%)	796 (25.0%)
Grade 3-4 AE of Special Interest	3 (0.6%)	39 (7.9%)	197 (7.5%)	247 (7.8%)
Atezo-related Grade 3-4 AE of Special Interest	0	31 (6.3%)	136 (5.2%)	173 (5.4%)
Grade 5 AE of Special Interest	0	2 (0.4%)	3 (0.1%)	5 (0.2%)
Atezo-related Grade 5 AE of Special Interest	0	2 (0.4%)	1 (<0.1%)	2 (<0.1%)
Serious AE of Special Interest	2 (0.4%)	21 (4.2%)	116 (4.4%)	152 (4.8%)
Atezo-related Serious AE of Special Interest	0	20 (4.0%)	96 (3.7%)	128 (4.0%)
AE of Special Interest leading to Atezo discontinuation	0	52 (10.5%)	49 (1.9%)	60 (1.9%)
AE of Special Interest leading to Atezo interruption	0	58 (11.7%)	171 (6.5%)	213 (6.7%)
AE of Special Interest Requiring the Use of Systemic Corticosteroids	4 (0.8%)	60 (12.1%)	197 (7.5%)	247 (7.8%)

Table 59: Adverse events with an incidence rate of at least 5% in any treatment arm by system organ class and preferred term (safety evaluable patients) (COD: 21 January 2021)

MedDRA System Organ Class MedDRA Preferred Term	Best Supportive Care(BSC) (N=495)	Atezolizumab (N=495)
Infections and infestations		
Nasopharyngitis	50 (10.1%)	33 (6.7%)
Upper respiratory tract infection	12 (2.4%)	35 (7.1%)
Respiratory, thoracic and mediastinal disorders		
Cough	46 (9.3%)	66 (13.3%)
Dyspnoea	32 (6.5%)	31 (6.3%)
General disorders and administration site conditions		
Pyrexia	11 (2.2%)	65 (13.1%)
Asthenia	14 (2.8%)	37 (7.5%)
Fatigue	11 (2.2%)	33 (6.7%)
Investigations		
Alanine aminotransferase increased	16 (3.2%)	53 (10.7%)
Aspartate aminotransferase increased	16 (3.2%)	53 (10.7%)
Blood creatinine increased	15 (3.0%)	29 (5.9%)
Gastrointestinal disorders		
Diarrhoea	9 (1.8%)	37 (7.5%)
Nausea	16 (3.2%)	30 (6.1%)
Musculoskeletal and connective tissue disorders		
Arthralgia	26 (5.3%)	52 (10.5%)
Nervous system disorders		
Headache	20 (4.0%)	28 (5.7%)
Skin and subcutaneous tissue disorders		
Pruritus	3 (0.6%)	51 (10.3%)
Rash	5 (1.0%)	48 (9.7%)
Blood and lymphatic system disorders		
Anaemia	30 (6.1%)	38 (7.7%)
Endocrine disorders		
Hypothyroidism	3 (0.6%)	55 (11.1%)
Hyperthyroidism	3 (0.6%)	32 (6.5%)

Table 60: Adverse events with a difference of at least 5% between treatment arms by preferred term (safety evaluable patients) (COD: 21 January 2021)

MedDRA Preferred Term	Best Supportive Care (BSC) (N=495)	Atezolizumab (N=495)
Arthralgia	26 (5.3%)	52 (10.5%)
Pyrexia	11 (2.2%)	65 (13.1%)
Alanine aminotransferase increased	16 (3.2%)	53 (10.7%)
Aspartate aminotransferase increased	16 (3.2%)	53 (10.7%)
Hypothyroidism	3 (0.6%)	55 (11.1%)
Pruritus	3 (0.6%)	51 (10.3%)
Rash	5 (1.0%)	48 (9.7%)
Diarrhoea	9 (1.8%)	37 (7.5%)
Hyperthyroidism	3 (0.6%)	32 (6.5%)

Table 61: Adverse events by preferred term with a difference of at least 5% in Impower010 and the pooled populations (safety evaluable patients)

MedDRA Preferred Term	IMPOWER010	Pooled Population	
	Atezolizumab (N=495)	Atezo Mono[1] (N=2616)	Atezo Mono[2] (N=3178)
Fatigue	33 (6.7%)	959 (36.7%)	1142 (35.9%)
Decreased appetite	22 (4.4%)	665 (25.4%)	810 (25.5%)
Nausea	30 (6.1%)	623 (23.8%)	747 (23.5%)
Cough	66 (13.3%)	581 (22.2%)	660 (20.8%)
Dyspnoea	31 (6.3%)	564 (21.6%)	651 (20.5%)
Pyrexia	65 (13.1%)	502 (19.2%)	639 (20.1%)
Constipation	24 (4.8%)	508 (19.4%)	652 (20.5%)
Diarrhoea	37 (7.5%)	504 (19.3%)	624 (19.6%)
Arthralgia	52 (10.5%)	514 (19.6%)	588 (18.5%)
Anaemia	38 (7.7%)	381 (14.6%)	505 (15.9%)
Vomiting	20 (4.0%)	410 (15.7%)	477 (15.0%)
Back pain	17 (3.4%)	385 (14.7%)	489 (15.4%)
Asthenia	37 (7.5%)	359 (13.7%)	461 (14.5%)
Headache	28 (5.7%)	302 (11.5%)	352 (11.1%)
Oedema peripheral	16 (3.2%)	265 (10.1%)	332 (10.4%)
Urinary tract infection	14 (2.8%)	232 (8.9%)	338 (10.6%)
Weight decreased	8 (1.6%)	225 (8.6%)	277 (8.7%)
Abdominal pain	14 (2.8%)	206 (7.9%)	268 (8.4%)
Aspartate aminotransferase increased	53 (10.7%)	153 (5.8%)	180 (5.7%)
Pain	4 (0.8%)	170 (6.5%)	207 (6.5%)
Alanine aminotransferase increased	53 (10.7%)	141 (5.4%)	167 (5.3%)
Hypothyroidism	55 (11.1%)	107 (4.1%)	137 (4.3%)
Hyperthyroidism	32 (6.5%)	19 (0.7%)	27 (0.8%)

Table 62: Grade 3-4 adverse events with an incidence rate of at least 2% in Impower010 and the pooled populations (safety evaluable patients)

	IMPOWER010		Pooled Population	
MedDRA System Organ Class MedDRA Preferred Term	Best Supportive Care (BSC) (N=495)	Atezolizumab (N=495)	Atezo Mono[1] (N=2616)	Atezo Mono[2] (N=3178)
Infections and infestations				
Pneumonia	3 (0.6%)	7 (1.4%)	85 (3.2%)	95 (3.0%)
Urinary tract infection	1 (0.2%)	2 (0.4%)	44 (1.7%)	72 (2.3%)
Blood and lymphatic system disorders				
Anaemia	1 (0.2%)	2 (0.4%)	110 (4.2%)	160 (5.0%)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	2 (0.4%)	1 (0.2%)	103 (3.9%)	117 (3.7%)
General disorders and administration site conditions				
Fatigue	1 (0.2%)	2 (0.4%)	89 (3.4%)	109 (3.4%)
Metabolism and nutrition disorders				
Hyponatraemia	0	2 (0.4%)	80 (3.1%)	98 (3.1%)

Adverse events of special interest (AESI)

AESIs for atezolizumab were selected based on its mechanism of action.

Table 63: Overview of adverse events of special interest (safety-evaluable population) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=495)	Atezolizumab (N=495)
Total number of patients with at least one AE	47 (9.5%)	256 (51.7%)
Total number of events	70	510
Total number of patients with at least one		
AE with fatal outcome	0	2 (0.4%)
Related AE with fatal outcome	0	2 (0.4%)
Serious AE	2 (0.4%)	21 (4.2%)
Related Serious AE	0	20 (4.0%)
Grade 3-4 AE	3 (0.6%)	39 (7.9%)
Related Grade 3-4 AE	0	31 (6.3%)
Related AE	0	223 (45.1%)
AE leading to dose interruption of Atezolizumab	0	58 (11.7%)
AE leading to Atezolizumab discontinuation	0	52 (10.5%)
Medical concepts: patients with		
Identified risks for Atezolizumab		
Immune-Mediated Hepatitis (Diagnosis and Lab Abnormalities)	22 (4.4%)	86 (17.4%)
Immune-Mediated Hepatitis (Lab Abnormalities)	21 (4.2%)	81 (16.4%)
Immune-Mediated Rash	11 (2.2%)	91 (18.4%)
Immune-Mediated Hypothyroidism	3 (0.6%)	86 (17.4%)
Immune-Mediated Hyperthyroidism	4 (0.8%)	32 (6.5%)
Immune-Mediated Pneumonitis	3 (0.6%)	19 (3.8%)
Immune-Mediated Hepatitis (Diagnosis)	1 (0.2%)	7 (1.4%)
Infusion-Related Reactions	0	7 (1.4%)
Immune-Mediated Adrenal Insufficiency	0	6 (1.2%)
Immune-Mediated Colitis	1 (0.2%)	4 (0.8%)
Immune-Mediated Diabetes Mellitus	1 (0.2%)	4 (0.8%)
Immune-Mediated Myositis	1 (0.2%)	4 (0.8%)
Immune-Mediated Myositis (Myositis+Rhabdomyolysis)	1 (0.2%)	4 (0.8%)
Immune-Mediated Meningoencephalitis	0	4 (0.8%)
Immune-Mediated Pancreatitis	1 (0.2%)	2 (0.4%)
Immune-Mediated Encephalitis	0	2 (0.4%)
Immune-Mediated Meningitis	0	2 (0.4%)
Immune-Mediated Myocarditis	0	2 (0.4%)
Immune-Mediated Severe Cutaneous Reactions	0	2 (0.4%)
Immune-Mediated Guillain-Barre Syndrome	0	1 (0.2%)
Immune-Mediated Hypophysitis	0	1 (0.2%)
Immune-Mediated Nephritis	0	1 (0.2%)
Potential risks for Atezolizumab		
Autoimmune Hemolytic Anemia	0	2 (0.4%)
Immune-Mediated Ocular Inflammatory Toxicity	1 (0.2%)	1 (0.2%)
Immune-Mediated Vasculitis	1 (0.2%)	0

Table 64: Summary of AESIs for atezolizumab (Safety-evaluable population)

	IMPOWER010		Pooled Population	
	Best Supportive Care (BSC) (N=495)	Atezolizumab (N=495)	Atezo Mono[1] (N=2616)	Atezo Mono[2] (N=3178)
Total number of patients with at least one AE of Special Interest	47 (9.5%)	256 (51.7%)	899 (34.4%)	1101 (34.6%)
Total number of events	70	510	1792	2199
Total number of patients with at least one				
Atezo-related AE of Special Interest	0	223 (45.1%)	644 (24.6%)	796 (25.0%)
Grade 3-4 AE of Special Interest	3 (0.6%)	39 (7.9%)	197 (7.5%)	247 (7.8%)
Atezo-related Grade 3-4 AE of Special Interest	0	31 (6.3%)	136 (5.2%)	173 (5.4%)
Grade 5 AE of Special Interest	0	2 (0.4%)	3 (0.1%)	5 (0.2%)
Atezo-related Grade 5 AE of Special Interest	0	2 (0.4%)	1 (<0.1%)	2 (<0.1%)
Serious AE of Special Interest	2 (0.4%)	21 (4.2%)	116 (4.4%)	152 (4.8%)
Atezo-related Serious AE of Special Interest	0	20 (4.0%)	96 (3.7%)	128 (4.0%)
AE of Special Interest leading to Atezo discontinuation	0	52 (10.5%)	49 (1.9%)	60 (1.9%)
AE of Special Interest leading to Atezo interruption	0	58 (11.7%)	171 (6.5%)	213 (6.7%)
AE of Special Interest Requiring the Use of Systemic Corticosteroids	4 (0.8%)	60 (12.1%)	197 (7.5%)	247 (7.8%)
Identified Risks: patients with at least one				
Immune-Mediated Rash	11 (2.2%)	91 (18.4%)	496 (19.0%)	613 (19.3%)
Immune-Mediated Hepatitis (Diagnosis and Lab Abnormalities)	22 (4.4%)	86 (17.4%)	282 (10.8%)	343 (10.8%)
Immune-Mediated Hepatitis (Lab Abnormalities)	21 (4.2%)	81 (16.4%)	263 (10.1%)	315 (9.9%)
Immune-Mediated Hypothyroidism	3 (0.6%)	86 (17.4%)	128 (4.9%)	164 (5.2%)
Immune-Mediated Pneumonitis	3 (0.6%)	19 (3.8%)	83 (3.2%)	91 (2.9%)
Immune-Mediated Hepatitis (Diagnosis)	1 (0.2%)	7 (1.4%)	48 (1.8%)	62 (2.0%)
Immune-Mediated Hyperthyroidism	4 (0.8%)	32 (6.5%)	21 (0.8%)	30 (0.9%)
Infusion-Related Reactions	0	7 (1.4%)	25 (1.0%)	34 (1.1%)
Immune-Mediated Colitis	1 (0.2%)	4 (0.8%)	26 (1.0%)	34 (1.1%)
Immune-Mediated Severe Cutaneous Reactions	0	2 (0.4%)	15 (0.6%)	22 (0.7%)
Immune-Mediated Pancreatitis	1 (0.2%)	2 (0.4%)	11 (0.4%)	18 (0.6%)
Immune-Mediated Meningoencephalitis	0	4 (0.8%)	13 (0.5%)	14 (0.4%)
Immune-Mediated Adrenal Insufficiency	0	6 (1.2%)	11 (0.4%)	12 (0.4%)
Immune-Mediated Myositis (Myositis+Rhabdomyolysis)	1 (0.2%)	4 (0.8%)	10 (0.4%)	13 (0.4%)
Immune-Mediated Meningitis	0	2 (0.4%)	11 (0.4%)	12 (0.4%)
Immune-Mediated Diabetes Mellitus	1 (0.2%)	4 (0.8%)	7 (0.3%)	10 (0.3%)
Immune-Mediated Myositis	1 (0.2%)	4 (0.8%)	6 (0.2%)	8 (0.3%)
Identified Risks: patients with at least one				
Immune-Mediated Guillain-Barre Syndrome	0	1 (0.2%)	5 (0.2%)	5 (0.2%)
Rhabdomyolysis	0	0	4 (0.2%)	5 (0.2%)
Immune-Mediated Encephalitis	0	2 (0.4%)	2 (<0.1%)	2 (<0.1%)
Immune-Mediated Nephritis	0	1 (0.2%)	1 (<0.1%)	3 (<0.1%)
Immune-Mediated Hypophysitis	0	1 (0.2%)	2 (<0.1%)	2 (<0.1%)
Immune-Mediated Myasthenia Gravis	0	0	1 (<0.1%)	1 (<0.1%)
Immune-Mediated Myocarditis	0	2 (0.4%)	0	0
Potential Risks: patients with at least one				
Immune-Mediated Ocular Inflammatory Toxicity	1 (0.2%)	1 (0.2%)	14 (0.5%)	16 (0.5%)
Immune-Mediated Vasculitis	1 (0.2%)	0	6 (0.2%)	7 (0.2%)
Autoimmune Hemolytic Anemia	0	2 (0.4%)	4 (0.2%)	4 (0.1%)
Haemorphagocytic lymphohistiocytosis	0	0	0	1 (<0.1%)

Serious adverse event/deaths/other significant events

Serious adverse events

Table 65: Serious adverse events by system organ class and preferred term (safety evaluable patients) (COD: 21 January 2021)

MedDRA System Organ Class MedDRA Preferred Term	Best Supportive Care(BSC) (N=495)	Atezolizumab (N=495)
Total number of patients with at least one adverse event	42 (8.5%)	87 (17.6%)
Overall total number of events	56	125
Infections and infestations		
Total number of patients with at least one adverse event	11 (2.2%)	28 (5.7%)
Total number of events	11	32
Pneumonia	5 (1.0%)	8 (1.6%)
Sepsis	0	3 (0.6%)
Septic shock	1 (0.2%)	2 (0.4%)
Meningitis	0	2 (0.4%)
Respiratory tract infection	1 (0.2%)	1 (0.2%)
Urinary tract infection	0	2 (0.4%)
Abscess limb	0	1 (0.2%)
Appendicitis	1 (0.2%)	0
Biliary tract infection	1 (0.2%)	0
Bronchitis	0	1 (0.2%)
Cellulitis	0	1 (0.2%)
Device related infection	0	1 (0.2%)
Encephalitis	0	1 (0.2%)
Enterocolitis infectious	0	1 (0.2%)
Influenza	0	1 (0.2%)
Laryngitis	0	1 (0.2%)
Otitis media chronic	1 (0.2%)	0
Pleural infection	1 (0.2%)	0
Pneumonia pneumococcal	0	1 (0.2%)
Staphylococcal sepsis	0	1 (0.2%)
Tonsillitis	0	1 (0.2%)
Viral myocarditis	0	1 (0.2%)
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	3 (0.6%)	14 (2.8%)
Total number of events	3	17
Pneumonitis	0	4 (0.8%)
Interstitial lung disease	0	3 (0.6%)
Chronic obstructive pulmonary disease	0	2 (0.4%)
Pulmonary embolism	1 (0.2%)	1 (0.2%)
Respiratory failure	2 (0.4%)	0
Acute respiratory distress syndrome	0	1 (0.2%)
Acute respiratory failure	0	1 (0.2%)
Alveolitis	0	1 (0.2%)
Lung infiltration	0	1 (0.2%)
Pneumothorax	0	1 (0.2%)
Nervous system disorders		
Total number of patients with at least one adverse event	2 (0.4%)	12 (2.4%)
Total number of events	3	14
Neuropathy peripheral	0	2 (0.4%)
Axonal neuropathy	0	1 (0.2%)
Cerebellar infarction	1 (0.2%)	0
Cerebral haemorrhage	0	1 (0.2%)
Cerebral infarction	0	1 (0.2%)
Cerebrovascular accident	0	1 (0.2%)
Demyelinating polyneuropathy	0	1 (0.2%)
Encephalitis autoimmune	0	1 (0.2%)
Encephalopathy	0	1 (0.2%)
Intracranial haematoma	0	1 (0.2%)
Ischaemic stroke	0	1 (0.2%)
Loss of consciousness	0	1 (0.2%)
Paraesthesia	1 (0.2%)	0
Peripheral sensory neuropathy	1 (0.2%)	0
Syncope	0	1 (0.2%)
Cardiac disorders		
Total number of patients with at least one adverse event	4 (0.8%)	8 (1.6%)
Total number of events	4	8
Atrial fibrillation	0	2 (0.4%)
Myocardial infarction	1 (0.2%)	1 (0.2%)
Acute coronary syndrome	1 (0.2%)	0
Arrhythmia	0	1 (0.2%)
Cardiac arrest	0	1 (0.2%)
Cardiac failure acute	0	1 (0.2%)
Cardiac tamponade	1 (0.2%)	0
Myocarditis	0	1 (0.2%)
Pericardial effusion	1 (0.2%)	0
Supraventricular tachycardia	0	1 (0.2%)
General disorders and administration site conditions		
Total number of patients with at least one adverse event	3 (0.6%)	9 (1.8%)
Total number of events	3	9
Pyrexia	1 (0.2%)	6 (1.2%)
General physical health deterioration	1 (0.2%)	1 (0.2%)
Chest pain	1 (0.2%)	0
Multiple organ dysfunction syndrome	0	1 (0.2%)
Oedema peripheral	0	1 (0.2%)

MedDRA System Organ Class MedDRA Preferred Term	Best Supportive Care(BSC) (N=495)	Atezolizumab (N=495)
Gastrointestinal disorders		
Total number of patients with at least one adverse event	6 (1.2%)	4 (0.8%)
Total number of events	6	4
Abdominal pain	1 (0.2%)	1 (0.2%)
Large intestine polyp	2 (0.4%)	0
Abdominal hernia	1 (0.2%)	0
Diarrhoea	0	1 (0.2%)
Dyspepsia	0	1 (0.2%)
Food poisoning	1 (0.2%)	0
Gastritis	0	1 (0.2%)
Rectal haemorrhage	1 (0.2%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Total number of patients with at least one adverse event	6 (1.2%)	4 (0.8%)
Total number of events	6	4
Acute myeloid leukaemia	0	1 (0.2%)
Anal squamous cell carcinoma	1 (0.2%)	0
Colon cancer metastatic	1 (0.2%)	0
Langerhans' cell histiocytosis	1 (0.2%)	0
Pancreatic carcinoma	1 (0.2%)	0
Squamous cell carcinoma of head and neck	1 (0.2%)	0
Squamous cell carcinoma of skin	0	1 (0.2%)
Transitional cell carcinoma	0	1 (0.2%)
Urinary tract neoplasm	1 (0.2%)	0
Uterine leiomyoma	0	1 (0.2%)
Injury, poisoning and procedural complications		
Total number of patients with at least one adverse event	4 (0.8%)	5 (1.0%)
Total number of events	5	5
Radius fracture	2 (0.4%)	0
Comminuted fracture	1 (0.2%)	0
Foot fracture	0	1 (0.2%)
Infusion related reaction	0	1 (0.2%)
Pelvic fracture	0	1 (0.2%)
Prescribed overdose	1 (0.2%)	0
Traumatic fracture	0	1 (0.2%)
Ulna fracture	1 (0.2%)	0
Urethral stricture traumatic	0	1 (0.2%)
Hepatobiliary disorders		
Total number of patients with at least one adverse event	2 (0.4%)	5 (1.0%)
Total number of events	2	6
Drug-induced liver injury	0	2 (0.4%)
Hepatitis	0	2 (0.4%)
Bile duct stone	0	1 (0.2%)
Cholelithiasis	1 (0.2%)	0
Cholestasis	1 (0.2%)	0
Immune system disorders		
Total number of patients with at least one adverse event	1 (0.2%)	5 (1.0%)
Total number of events	1	5
Sarcoidosis	0	2 (0.4%)
Anaphylactic reaction	0	1 (0.2%)
Contrast media reaction	1 (0.2%)	0
Hypersensitivity	0	1 (0.2%)
Immune-mediated adverse reaction	0	1 (0.2%)
Investigations		
Total number of patients with at least one adverse event	1 (0.2%)	4 (0.8%)
Total number of events	1	4
Blood creatinine increased	0	1 (0.2%)
Colonoscopy	1 (0.2%)	0
Endoscopic retrograde cholangiopancreatography	0	1 (0.2%)
Platelet count decreased	0	1 (0.2%)
Weight decreased	0	1 (0.2%)
Endocrine disorders		
Total number of patients with at least one adverse event	0	4 (0.8%)
Total number of events	0	4
Adrenal insufficiency	0	1 (0.2%)
Hypopituitarism	0	1 (0.2%)
Inappropriate antidiuretic hormone secretion	0	1 (0.2%)
Secondary adrenocortical insufficiency	0	1 (0.2%)
Musculoskeletal and connective tissue disorders		
Total number of patients with at least one adverse event	1 (0.2%)	3 (0.6%)
Total number of events	1	3
Arthralgia	0	1 (0.2%)
Back pain	0	1 (0.2%)
Intervertebral disc degeneration	1 (0.2%)	0
Myalgia	0	1 (0.2%)

MedDRA System Organ Class MedDRA Preferred Term	Best Supportive Care(BSC) (N=495)	Atezolizumab (N=495)
Psychiatric disorders		
Total number of patients with at least one adverse event	3 (0.6%)	1 (0.2%)
Total number of events	4	1
Depression	2 (0.4%)	0
Dissociative disorder	1 (0.2%)	0
Hallucination, visual	0	1 (0.2%)
Skin and subcutaneous tissue disorders		
Total number of patients with at least one adverse event	0	3 (0.6%)
Total number of events	0	3
Psoriasis	0	2 (0.4%)
Drug eruption	0	1 (0.2%)
Eye disorders		
Total number of patients with at least one adverse event	2 (0.4%)	0
Total number of events	2	0
Retinal detachment	1 (0.2%)	0
Vitreous haemorrhage	1 (0.2%)	0
Renal and urinary disorders		
Total number of patients with at least one adverse event	0	2 (0.4%)
Total number of events	0	2
Acute kidney injury	0	1 (0.2%)
Urinary tract obstruction	0	1 (0.2%)
Reproductive system and breast disorders		
Total number of patients with at least one adverse event	1 (0.2%)	1 (0.2%)
Total number of events	1	1
Adnexal torsion	0	1 (0.2%)
Benign prostatic hyperplasia	1 (0.2%)	0
Vascular disorders		
Total number of patients with at least one adverse event	2 (0.4%)	0
Total number of events	3	0
Deep vein thrombosis	2 (0.4%)	0
Thrombophlebitis	1 (0.2%)	0
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event	0	1 (0.2%)
Total number of events	0	1
Anaemia	0	1 (0.2%)
Ear and labyrinth disorders		
Total number of patients with at least one adverse event	0	1 (0.2%)
Total number of events	0	1
Vertigo	0	1 (0.2%)
Metabolism and nutrition disorders		
Total number of patients with at least one adverse event	0	1 (0.2%)
Total number of events	0	1
Hyponatraemia	0	1 (0.2%)

Table 66: Serious adverse events in the infections and infestations system organ class (safety evaluable patients)

Protocol: GO29527

MedDRA System Organ Class MedDRA Preferred Term	IMPOWER010 Best Supportive Care (BSC) (N=495)	IMPOWER010 Atezolizumab (N=495)	Pooled Population Atezo Mono [1] (N=2616)	Pooled Population Atezo Mono [2] (N=3178)
Total number of patients with at least one adverse event	42 (8.5%)	87 (17.6%)	1065 (40.7%)	1309 (41.2%)
Overall total number of events	56	125	1822	2267
Infections and infestations				
Total number of patients with at least one adverse event	11 (2.2%)	28 (5.7%)	300 (11.5%)	370 (11.6%)
Total number of events	11	32	364	448
Pneumonia	5 (1.0%)	8 (1.6%)	101 (3.9%)	112 (3.5%)
Urinary tract infection	0	2 (0.4%)	40 (1.5%)	61 (1.9%)
Sepsis	0	3 (0.6%)	31 (1.2%)	41 (1.3%)
Lower respiratory tract infection	0	0	10 (0.4%)	15 (0.5%)
Respiratory tract infection	1 (0.2%)	1 (0.2%)	10 (0.4%)	12 (0.4%)
Cellulitis	0	1 (0.2%)	10 (0.4%)	10 (0.3%)
Septic shock	1 (0.2%)	2 (0.4%)	7 (0.3%)	11 (0.3%)
Urosepsis	0	0	8 (0.3%)	10 (0.3%)
Pyelonephritis	0	0	7 (0.3%)	10 (0.3%)
Bronchitis	0	1 (0.2%)	7 (0.3%)	7 (0.2%)
Bacteraemia	0	0	6 (0.2%)	6 (0.2%)
Meningitis	0	2 (0.4%)	5 (0.2%)	5 (0.2%)
Device related infection	0	1 (0.2%)	4 (0.2%)	6 (0.2%)

Table 67: Serious adverse events with an incidence rate of at least 2% in any treatment group by system organ class and preferred term (safety evaluable patients)

Protocol: GO29527

MedDRA System Organ Class MedDRA Preferred Term	IMPOWER010 Best Supportive Care (BSC) (N=495)	IMPOWER010 Atezolizumab (N=495)	Pooled Population Atezo Mono [1] (N=2616)	Pooled Population Atezo Mono [2] (N=3178)
Infections and infestations				
Pneumonia	5 (1.0%)	8 (1.6%)	101 (3.9%)	112 (3.5%)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	0	0	79 (3.0%)	89 (2.8%)
General disorders and administration site conditions				
Pyrexia	1 (0.2%)	6 (1.2%)	59 (2.3%)	79 (2.5%)

Deaths

Table 68: Deaths and causes of death (safety-evaluable population) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=495)	Atezolizumab (N=495)	All Patients (N=990)
All deaths			
n	90 (18.2%)	95 (19.2%)	185 (18.7%)
<=30 days from last study treatment/ safety visit	5 (1.0%)	4 (0.8%)	9 (0.9%)
>30 days from last study treatment/ safety visit	85 (17.2%)	91 (18.4%)	176 (17.8%)
Primary cause of death			
n	90	95	185
Adverse event	3 (0.6%)	8 (1.6%)	11 (1.1%)
Disease relapse	77 (15.6%)	63 (12.7%)	140 (14.1%)
Other	10 (2.0%)	24 (4.8%)	34 (3.4%)

Includes deaths occurring on or after the start of treatment in randomization period

Table 69: All deaths and primary cause of death (safety-evaluable population)

	IMPOWER010		Pooled Population	
	Best Supportive Care (BSC) (N=495)	Atezolizumab (N=495)	Atezo Mono[1] (N=2616)	Atezo Mono[2] (N=3178)
All death				
n	90 (18.2%)	95 (19.2%)	1545 (59.1%)	1898 (59.7%)
Primary cause of death				
ADVERSE EVENT	3 (0.6%)	8 (1.6%)	88 (3.4%)	120 (3.8%)
PROGRESSIVE DISEASE	77 (15.6%)	63 (12.7%)	1158 (44.3%)	1476 (46.4%)
OTHER	10 (2.0%)	24 (4.8%)	299 (11.4%)	302 (9.5%)
Other cause of death				
n	10	24	298	301
DEATH DURING FOLLOW-UP	0	0	269	269
DEAD	0	0	8	8
DEATH DUE TO UNKNOWN	0	2	4	4
DEATH DUE TO DEATH RECORDED AS PER PUBLIC RECORDS	2	4	0	0
DEATH DUE TO NOT KNOWN	0	0	3	3
DEATH DUE TO CARDIAC ARREST	0	2	1	1
DEATH DUE TO CEREBRAL INFARCTION	0	0	1	1
DEATH DUE TO DEATH DURING FOLLOW UP	0	0	1	1
DEATH DUE TO DEATH IN FOLLOW UP	0	0	1	1
DEATH DUE TO DEATH OCCURRED DURING FOLLOW UP AND REASON UNKNOWN.	0	0	1	1
DEATH DUE TO DEATH OCCURRED DURING FOLLOW-UP AND NO FURTHER DETAILS WERE PROVIDED IN SOURCE.	0	0	1	1
DEATH DUE TO EUTHANASIA	0	0	1	1
DEATH DUE TO FUNGAL PNEUMONIA DURING FOLLOW FOLLOW UP PERIOD	0	0	1	1
DEATH DUE TO ILEUS (PATIENT REFUSED TREATMENT)	0	0	1	1
DEATH DUE TO INTRACRANIAL BLEED	0	0	1	1
DEATH DUE TO MYOCARDIAL INFARCTION	1	1	0	0
DEATH DUE TO NOT FOLLOWED, PATIENT WENT BACK TO PAKISTAN. REASON OF DEATH UNKNOWN	0	0	1	1
DEATH DUE TO RENAL FAILURE	0	0	1	1
DEATH DUE TO UNKNOWN CAUSE OF DEATH - SUSPECTED THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) AND DISSEMINATED INTRAVASCULAR COAGULATION (DIC) MULTIPLE FACTORS AND CANNOT DETERMINE CAUSE OF DEATH	0	0	1	1
DEATH RECORDED AS PER PUBLIC RECORDS	0	0	1	1
DEATH	0	0	0	1
DEATH DUE TO ANOXIC ENCEPHALOPATHY NOT RELATED TO LUNG CANCER	0	1	0	0
DEATH DUE TO ASPIRATION IN PRESENCE OF PNEUMONIA	1	0	0	0
DEATH DUE TO COPD EXACERBATION	0	1	0	0
DEATH DUE TO COVID-19	0	1	0	0
DEATH DUE TO DEATH BY PUBLIC RECORDS WAS CONFIRMED, AUTOPSY WAS NOT DONE	0	1	0	0
DEATH DUE TO DISEASE PROGRESSION	1	0	0	0
DEATH DUE TO DUE TO PROGRESSION OF NEW SMALL CELL LUNG CANCER	0	1	0	0
DEATH DUE TO ELECTROLYTE DISTURBANCE	0	1	0	0
DEATH DUE TO EMPYEMA	0	1	0	0
DEATH DUE TO GASTROINTESTINAL HAEMORRHAGE SECONDARY TO DUODENAL ULCER	0	1	0	0
DEATH DUE TO ISCHEMIC HEART DISEASE (MEDICAL HISTORY)	0	1	0	0
DEATH DUE TO LEUKEMIA	0	1	0	0
DEATH DUE TO MIOCARDIAL INFARCTION	1	0	0	0
DEATH DUE TO PATIENT HAD A FALL ON 30 DEC 15 SUFFERING INTRACEREBRAL HAEMORRHAGE WITH INTRAVENTRICULAR HAEMORRHAGE. PATIENT PASSED AWAY 17 JAN 16	0	0	0	1
DEATH DUE TO PNEUMONIA	1	0	0	0
DEATH DUE TO PNEUMONIA RELATED TO SARS-COVID	0	1	0	0
DEATH DUE TO PROGRESSION OF BUCCAL FLOOR CANCER	0	1	0	0
DEATH DUE TO PULMONARY EMBOLISM	1	0	0	0
DEATH DUE TO RESPIRATORY FAILURE	1	0	0	0
DEATH DUE TO SEPSIS OF UNKNOWN ORIGIN	0	0	0	1
DEATH DUE TO SEPTIC SHOCK	1	0	0	0
DEATH DUE TO THE ?AUSE ISN'T KNOWN	0	1	0	0
DEATH DUE TO THROMBOEMBOLIA OF PULMONARY ARTERIA	0	1	0	0
DEATH DUE TO WE DON'T HAVE CORRECT INFORMATION KNOW	0	1	0	0

Table 70: Adverse events leading to death (safety-evaluable population) (COD: 21 January 2021)

MedDRA System Organ Class MedDRA Preferred Term	Best Supportive Care (BSC) (N=495)	Atezolizumab (N=495)
Total number of patients with at least one adverse event	3 (0.6%)	8 (1.6%)
Overall total number of events	4	8
Cardiac disorders		
Total number of patients with at least one adverse event	1 (0.2%)	3 (0.6%)
Total number of events	1	3
Arrhythmia	0	1 (0.2%)
Cardiac failure acute	0	1 (0.2%)
Cardiac tamponade	1 (0.2%)	0
Myocarditis	0	1 (0.2%)
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	1 (0.2%)	2 (0.4%)
Total number of events	1	2
Interstitial lung disease	0	1 (0.2%)
Pneumothorax	0	1 (0.2%)
Pulmonary embolism	1 (0.2%)	0
Infections and infestations		
Total number of patients with at least one adverse event	2 (0.4%)	0
Total number of events	2	0
Pneumonia	1 (0.2%)	0
Septic shock	1 (0.2%)	0
General disorders and administration site conditions		
Total number of patients with at least one adverse event	0	1 (0.2%)
Total number of events	0	1
Multiple organ dysfunction syndrome	0	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Total number of patients with at least one adverse event	0	1 (0.2%)
Total number of events	0	1
Acute myeloid leukaemia	0	1 (0.2%)
Nervous system disorders		
Total number of patients with at least one adverse event	0	1 (0.2%)
Total number of events	0	1
Cerebrovascular accident	0	1 (0.2%)

Other significant events/Identified risks

Identified risks are AESIs for which there is scientific evidence of a causal association between the risk and treatment with atezolizumab. AESIs that are considered identified risks for atezolizumab in IMpower010 are presented in Table 71.

Table 71: Summary of identified risks for atezolizumab (safety-evaluable population)

Medical Concept	Arm	All Grades	Grade 3-4	Grade 5	Resolved All Grades	AESIs Leading to Atezo withdrawal All Grades	AESIs Requiring Systemic Corticosteroids	AESIs Leading to Atezo Interruption	AESIs reported as Serious
Immune-Mediated Rash	Atezo N=495	91 (18.4%)	7 (1.4%)	0	73/91 (80.2%)	4 (0.8%)	17 (3.4%)	15 (3.0%)	1 (0.2%)
	BSC N=495	11 (2.2%)	0	0	11/11 (100.0%)	0	3 (0.6%)	0	0
Immune-Mediated Hypothyroidism	Atezo N=495	86 (17.4%)	0	0	47/86 (54.7%)	8 (1.6%)	7 (1.4%)	8 (1.6%)	0
	BSC N=495	3 (0.6%)	0	0	1/3 (33.3%)	0	0	0	0
Immune-Mediated Hepatitis (Diagnosis and Lab Abnormalities)	Atezo N=495	86 (17.4%)	20 (4.0%)	0	80/86 (93.0%)	13 (2.6%)	16 (3.2%)	15 (3.0%)	4 (0.8%)
	BSC N=495	22 (4.4%)	1 (0.2%)	0	18/22 (81.8%)	0	0	0	0
Immune-Mediated Hepatitis (Lab Abnormalities)	Atezo N=495	81 (16.4%)	16 (3.2%)	0	75/81 (92.6%)	10 (2.0%)	14 (2.8%)	14 (2.8%)	0
	BSC N=495	21 (4.2%)	1 (0.2%)	0	18/21 (85.7%)	0	0	0	0
Immune-Mediated Hyperthyroidism	Atezo N=495	32 (6.5%)	2 (0.4%)	0	19/32 (59.4%)	4 (0.8%)	4 (0.8%)	14 (2.8%)	0
	BSC N=495	4 (0.8%)	0	0	2/4 (50.0%)	0	0	0	0
Immune-Mediated Pneumonitis	Atezo N=495	19 (3.8%)	4 (0.8%)	1 (0.2%)	16/19 (84.2%)	11 (2.2%)	12 (2.4%)	4 (0.8%)	8 (1.6%)
	BSC N=495	3 (0.6%)	0	0	2/3 (66.7%)	0	1 (0.2%)	0	0
Immune-Mediated Hepatitis (Diagnosis)	Atezo N=495	7 (1.4%)	4 (0.8%)	0	6/7 (85.7%)	3 (0.6%)	3 (0.6%)	2 (0.4%)	4 (0.8%)
	BSC N=495	1 (0.2%)	0	0	0/1 (0.0%)	0	0	0	0
Infusion-Related Reactions	Atezo N=495	7 (1.4%)	1 (0.2%)	0	7/7 (100.0%)	2 (0.4%)	0	3 (0.6%)	1 (0.2%)
	BSC N=495	0	0	0	0/0 (0.0%)	0	0	0	0
Immune-Mediated Adrenal Insufficiency	Atezo N=495	6 (1.2%)	2 (0.4%)	0	4/6 (66.7%)	3 (0.6%)	5 (1.0%)	1 (0.2%)	2 (0.4%)
	BSC N=495	0	0	0	0/0 (0.0%)	0	0	0	0
Immune-Mediated Colitis	Atezo N=495	4 (0.8%)	2 (0.4%)	0	2/4 (50.0%)	2 (0.4%)	3 (0.6%)	0	0
	BSC N=495	1 (0.2%)	0	0	0/1 (0.0%)	0	0	0	0
Immune-Mediated Diabetes Mellitus	Atezo N=495	4 (0.8%)	0	0	0/4 (0.0%)	0	0	0	0
	BSC N=495	1 (0.2%)	0	0	0/1 (0.0%)	0	0	0	0
Immune-Mediated Meningoencephalitis	Atezo N=495	4 (0.8%)	3 (0.6%)	0	4/4 (100.0%)	4 (0.8%)	4 (0.8%)	0	4 (0.8%)
	BSC N=495	0	0	0	0/0 (0.0%)	0	0	0	0
Immune-Mediated Myositis	Atezo N=495	4 (0.8%)	0	0	3/4 (75.0%)	1 (0.2%)	0	0	0
	BSC N=495	1 (0.2%)	0	0	0/1 (0.0%)	0	0	0	0
Immune-Mediated) Myositis(Myositis+ Rhabdomyolysis	Atezo N=495	4 (0.8%)	0	0	3/4 (75.0%)	1 (0.2%)	0	0	0
	BSC N=495	1 (0.2%)	0	0	0/1 (0.0%)	0	0	0	0
Immune-Mediated Encephalitis	Atezo N=495	2 (0.4%)	2 (0.4%)	0	2/2 (100.0%)	2 (0.4%)	2 (0.4%)	0	2 (0.4%)
	BSC N=495	0	0	0	0/0 (0.0%)	0	0	0	0
Immune-Mediated Meningitis	Atezo N=495	2 (0.4%)	1 (0.2%)	0	2/2 (100.0%)	2 (0.4%)	2 (0.4%)	0	2 (0.4%)
	BSC N=495	0	0	0	0/0 (0.0%)	0	0	0	0
Immune-Mediated Myocarditis	Atezo N=495	2 (0.4%)	0	1 (0.2%)	1/2 (50.0%)	1 (0.2%)	2 (0.4%)	1 (0.2%)	1 (0.2%)
	BSC N=495	0	0	0	0/0 (0.0%)	0	0	0	0
Immune-Mediated Pancreatitis	Atezo N=495	2 (0.4%)	1 (0.2%)	0	2/2 (100.0%)	0	0	0	0
	BSC N=495	1 (0.2%)	1 (0.2%)	0	1/1 (100.0%)	0	0	0	0
Immune-Mediated Severe Cutaneous Reactions	Atezo N=495	2 (0.4%)	0	0	0/2 (0.0%)	0	1 (0.2%)	0	0
	BSC N=495	0	0	0	0/0 (0.0%)	0	0	0	0
Immune-Mediated Guillain-Barre Syndrome	Atezo N=495	1 (0.2%)	1 (0.2%)	0	0/1 (0.0%)	0	1 (0.2%)	0	1 (0.2%)
	BSC N=495	0	0	0	0/0 (0.0%)	0	0	0	0
Immune-Mediated Hypophysitis	Atezo N=495	1 (0.2%)	0	0	0/1 (0.0%)	0	1 (0.2%)	0	0
	BSC N=495	0	0	0	0/0 (0.0%)	0	0	0	0
Immune-Mediated Nephritis	Atezo N=495	1 (0.2%)	0	0	0/1 (0.0%)	1 (0.2%)	1 (0.2%)	0	0
	BSC N=495	0	0	0	0/0 (0.0%)	0	0	0	0

ADA and safety

Descriptive analyses were performed at the trial level evaluating demographics, pharmacokinetics (PK), efficacy, and safety by treatment-emergent ADA-positive and ADA-negative subgroups, and the results are reported in the CSR.

Serum samples were collected from patients before, during and after atezolizumab treatment to characterize atezolizumab ADA baseline prevalence and atezolizumab PK and ADA incidence post-treatment.

Safety by ADA subgroup analyses are based on ADA-evaluable patients, defined as patients with at least one post-baseline atezolizumab ADA result, in the safety evaluable population (i.e., treated patients).

Table 72: Exposure to atezolizumab by treatment-emergent ADA status (ADA-evaluable atezolizumab patients in safety-evaluable population) (COD: 21 January 2021)

	ADA - (N=335)	ADA + (N=152)
Treatment duration (months)		
n	335	152
Mean (SD)	8.7 (3.5)	7.6 (4.3)
Median	10.4	10.4
Min - Max	0 - 14	0 - 16
Dose intensity (%)		
n	335	152
Mean (SD)	99.3 (4.0)	98.2 (8.5)
Median	100.0	100.0
Min - Max	50 - 100	40 - 100
Total cumulative dose (mg)		
n	335	152
Mean (SD)	15790.5 (5871.1)	13745.4 (7073.1)
Median	19200.0	19200.0
Min - Max	1200 - 19200	1200 - 19200
Number of doses/cycles received		
n	335	152
Mean (SD)	13.2 (4.9)	11.5 (5.9)
Median	16.0	16.0
Min - Max	1 - 16	1 - 16
Number of doses/cycles		
0 to < 8	66 (19.7%)	51 (33.6%)
>= 8 to < 16	33 (9.9%)	14 (9.2%)
>= 16	236 (70.4%)	87 (57.2%)

Table 73: Safety summary profile by treatment-emergent ADA status (ADA-evaluable atezolizumab patients in safety-evaluable population) (COD: 21 January 2021)

	ADA - (N=335)	ADA + (N=152)
Total number of patients with at least one AE	315 (94.0%)	137 (90.1%)
Total number of events	1951	766
Total number of patients with at least one		
AE with fatal outcome	5 (1.5%)	2 (1.3%)
Related AE with fatal outcome	2 (0.6%)	2 (1.3%)
Serious AE	53 (15.8%)	30 (19.7%)
Related Serious AE	17 (5.1%)	19 (12.5%)
Grade 3-4 AE	63 (18.8%)	41 (27.0%)
Related Grade 3-4 AE	29 (8.7%)	22 (14.5%)
Related AE	223 (66.6%)	107 (70.4%)
AE leading to dose interruption of Atezolizumab	94 (28.1%)	47 (30.9%)
AE leading to Atezolizumab discontinuation	48 (14.3%)	37 (24.3%)

Table 74: Serious adverse events by preferred term occurring in >1 patient in either subgroup, randomised ADA evaluable (ITT population) (COD: 21 January 2021)

MedDRA System Organ Class MedDRA Preferred Term	ADA - (N=335)	ADA + (N=152)
Total number of patients with at least one adverse event	53 (15.8%)	30 (19.7%)
Overall total number of events	68	50
Pneumonia	6 (1.8%)	2 (1.3%)
Sepsis	1 (0.3%)	2 (1.3%)
Meningitis	2 (0.6%)	0
Septic shock	0	2 (1.3%)
Pneumonitis	1 (0.3%)	3 (2.0%)
Interstitial lung disease	2 (0.6%)	1 (0.7%)
Chronic obstructive pulmonary disease	2 (0.6%)	0
Atrial fibrillation	2 (0.6%)	0
Pyrexia	3 (0.9%)	2 (1.3%)
Hepatitis	0	2 (1.3%)
Sarcoidosis	0	2 (1.3%)
Psoriasis	0	2 (1.3%)

Table 75: Selected adverse events by MedDRA preferred term, highest NCI CTCAE grade and treatment-emergent ADA status (ADA-evaluable atezolizumab patients in safety-evaluable population)

		Atezolizumab Treated Patients	
		ADA-Negative	ADA-Positive
MedDRA Preferred Term	Grade	N=335	N=152
Infusion-related reaction	Any	4 (1.2%)	3 (2.0%)
	1	1 (0.3%)	0
	2	3 (0.9%)	2 (1.3%)
	3	0	1 (0.7%)
Hypersensitivity	Any	1 (0.3%)	3 (2.0%)
	1	1 (0.3%)	2 (1.3%)
	3	0	1 (0.7%)
Anaphylactic reaction	Any	1 (0.3%)	0
	4	1 (0.3%)	0

Adverse drug reactions

The SmPC section 4.8 was updated using the Atezolizumab mono pool including 4349 patients from the following studies: GO29527, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, WO29074 and WO29636.

Table 76: Summary of adverse reactions occurring in patients treated with atezolizumab monotherapy

Atezolizumab monotherapy		**Incidence % (All Grades) N=4349**
Infections and infestations		
Very common	urinary tract infection	499 (11.5%)
Blood and lymphatic system disorders		
Common	thrombocytopenia	158 (3.6%)
Immune system disorders		
Common	infusion-related reaction	71 (1.6%)
Endocrine disorders		
Common	hypothyroidism, hyperthyroidism	331 (7.6%), 93 (2.1%)
Uncommon	diabetes mellitus, adrenal insufficiency	20 (0.5%), 21 (0.5%)
Rare	hypophysitis	4 (<0.1%)
Metabolism and nutrition disorders		
Very common	decreased appetite	926 (21.3%)

Atezolizumab monotherapy		Incidence % (All Grades) N=4349
Common	hypokalaemia, hyponatraemia, hyperglycaemia	168 (3.9%), 196 (4.5%), 142 (3.3%)
Nervous system disorders		
Very Common	headache	447 (10.3%)
Uncommon	Guillain-Barré syndrome, meningoencephalitis	6 (0.1%), 18 (0.4%)
Rare	myasthenic syndrome	1 (<0.1%)
Eye disorders		
Rare	uveitis	3 (<0.1%)
Cardiac disorders		
Rare	myocarditis	3 (<0.1%)
Vascular disorders		
Common	hypotension	116 (2.7%)
Respiratory, thoracic, and mediastinal disorders		
Very common	dyspnoea, cough	750 (17.2%), 808 (18.6%)
Common	pneumonitis, hypoxia, nasopharyngitis	130 (3.0%), 80 (1.8%), 386 (8.9%)
Gastrointestinal disorders		
Very common	nausea, vomiting, diarrhoea	871 (20.0%), 545 (12.5%), 782 (18.0%)
Common	colitis, abdominal pain, dysphagia, oropharyngeal pain	50 (1.1%), 320 (7.4%), 93 (2.1%), 166 (3.8%)
Uncommon	pancreatitis	32 (0.7%)
Hepatobiliary disorders		
Common	AST increased, ALT increased, hepatitis	282 (6.5%), 275 (6.3%), 75 (1.7%)
Skin and subcutaneous tissue disorders		
Very common	rash, pruritus	841 (19.3%), 573 (13.2%)
Common	dry skin	235 (5.4%)
Uncommon	severe cutaneous adverse reactions, psoriasis	28 (0.6%), 28 (0.6%)
Rare	pemphigoid	1 (<0.1%)
Musculoskeletal and connective tissue disorders		
Very common	arthralgia, back pain	726 (16.7%), 558 (12.8%)
Common	musculoskeletal pain	379 (8.7%)
Uncommon	myositis	20 (0.5%)
Renal and urinary disorders		
Common	blood creatinine increased	250 (5.7%)
Uncommon	nephritis	10 (0.2%)
Not known	cystitis noninfective	
General disorders and administration site conditions		
Very common	pyrexia, fatigue, asthenia	826 (19.0%), 1308 (30.1%), 574 (13.2%)
Common	influenza like illness, chills	219 (5.0%), 247 (5.7%)

Laboratory findings

Overall, few patients 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. The frequency of clinically relevant shift was similar between the arms except for a higher (≥2%) incidence of increased ALT, increased AST, and low lymphocyte count in the atezolizumab arm; see Table 77.

Table 77: Summary of clinically relevant laboratory shifts from baseline in laboratory safety parameters (safety population) (COD: 21 January 2021)

Laboratory Test	Direction of Abnormality	Best Supportive Care (BSC) (N=495)	Atezolizumab (N=495)
Chemistry			
Albumin	Low	1/482 (0.2%)	0/489
Alkaline Phosphatase	High	0/483	1/490 (0.2%)
SGPT/ALT	High	2/484 (0.4%)	16/490 (3.3%)
SGOT/AST	High	0/484	12/490 (2.4%)
Calcium	Low	1/481 (0.2%)	10/489 (2.0%)
	High	4/483 (0.8%)	1/489 (0.2%)
Creatinine	High	1/484 (0.2%)	1/490 (0.2%)
Glucose	Low	0/482	0/489
	High	13/476 (2.7%)	13/482 (2.7%)
Magnesium	Low	0/479	0/483
	High	3/476 (0.6%)	2/484 (0.4%)
Phosphate	Low	7/478 (1.5%)	4/482 (0.8%)
Potassium	Low	1/484 (0.2%)	5/489 (1.0%)
	High	13/481 (2.7%)	17/487 (3.5%)
Sodium	Low	7/482 (1.5%)	13/490 (2.7%)
	High	0/483	1/490 (0.2%)
Bilirubin	High	1/484 (0.2%)	2/489 (0.4%)
Coagulation			
Prothrombin Intl. Normalized Ratio	High	0/ 19	0/375
Activated Partial Thromboplastin Time	High	0/ 19	1/373 (0.3%)
Hematology			
Hemoglobin	Low	3/483 (0.6%)	3/490 (0.6%)
	High	0/483	0/490
Lymphocytes	Low	4/483 (0.8%)	16/490 (3.3%)
	High	0/483	0/490
Neutrophils	Low	3/483 (0.6%)	9/490 (1.8%)
Platelets	Low	0/483	1/490 (0.2%)
Leukocytes	Low	0/483	7/490 (1.4%)
	High	0/483	0/490

Baseline is the patient's last observation prior to initiation of study drug.
For each laboratory test, patients with at least 1 post-baseline assessment are included in the analysis.
For each cell, the denominator is the number of patients with baseline values with NCI-CTCAE Grade 0-2 in the specified direction of abnormality.
Patients with missing baseline values are counted as Grade 0-2 at baseline.

Blood samples for thyroid function assessment were collected routinely (every 4 cycles) for only patients in the atezolizumab arm; in the BSC arm, samples were collected only when clinically indicated.

Overall, the majority of patients (79.0%) on atezolizumab maintained normal thyroid stimulating hormone (TSH) levels during the study (Table 78).

Table 78: Thyroid stimulating hormone (safety evaluable population) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=495)			Atezolizumab (N=495)		
	Post-Baseline Status			Post-Baseline Status		
Status at Baseline	Low	Normal	High	Low	Normal	High
Low	2 (0.4%)	4 (0.8%)	0	28 (5.7%)	25 (5.1%)	10 (2.0%)
Normal	1 (0.2%)	21 (4.2%)	3 (0.6%)	72 (14.5%)	391 (79.0%)	90 (18.2%)
High	0	0	0	5 (1.0%)	18 (3.6%)	15 (3.0%)
Missing	1 (0.2%)	2 (0.4%)	1 (0.2%)	1 (0.2%)	4 (0.8%)	0

Safety in special populations

Table 79: Overview of safety by age (safety evaluable population) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=495)		Atezolizumab (N=495)	
	<65 (N=299)	>=65 (N=196)	<65 (N=315)	>=65 (N=180)
Total number of patients with at least one AE	206 (68.9%)	144 (73.5%)	288 (91.4%)	171 (95.0%)
Total number of events	710	543	1759	983
Total number of patients with at least one				
Related AE	0	0	204 (64.8%)	131 (72.8%)
Grade 3-4 AE	37 (12.4%)	20 (10.2%)	62 (19.7%)	46 (25.6%)
Related Grade 3-4 AE	0	0	31 (9.8%)	22 (12.2%)
Grade 5 AE	2 (0.7%)	1 (0.5%)	4 (1.3%)	4 (2.2%)
Related Grade 5 AE	0	0	1 (0.3%)	3 (1.7%)
Serious AE	25 (8.4%)	17 (8.7%)	43 (13.7%)	44 (24.4%)
Related serious AE	0	0	17 (5.4%)	20 (11.1%)
AE leading to dose interruption of Atezolizumab	0	0	85 (27.0%)	57 (31.7%)
AE leading to Atezolizumab discontinuation	0	0	55 (17.5%)	35 (19.4%)

Table 80: Overall summary of adverse events, randomised safety evaluable patients, by age group (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=495)			Atezolizumab (N=495)		
	<65 (N=299)	65-74 (N=172)	75-84 (N=24)	<65 (N=315)	65-74 (N=160)	75-84 (N=20)
Total number of patients with at least one AE	206 (68.9%)	128 (74.4%)	16 (66.7%)	288 (91.4%)	154 (96.3%)	17 (85.0%)
Total number of events	710	490	53	1759	858	125
Total number of patients with at least one						
Related AE	0	0	0	204 (64.8%)	119 (74.4%)	12 (60.0%)
Grade 3-4 AE	37 (12.4%)	15 (8.7%)	5 (20.8%)	62 (19.7%)	41 (25.6%)	5 (25.0%)
Related Grade 3-4 AE	0	0	0	31 (9.8%)	20 (12.5%)	2 (10.0%)
Grade 5 AE	2 (0.7%)	1 (0.6%)	0	4 (1.3%)	3 (1.9%)	1 (5.0%)
Related Grade 5 AE	0	0	0	1 (0.3%)	2 (1.3%)	1 (5.0%)
Serious AE	25 (8.4%)	14 (8.1%)	3 (12.5%)	43 (13.7%)	40 (25.0%)	4 (20.0%)
Related serious AE	0	0	0	17 (5.4%)	19 (11.9%)	1 (5.0%)
AE leading to dose interruption of Atezolizumab	0	0	0	85 (27.0%)	50 (31.3%)	7 (35.0%)
AE leading to Atezolizumab discontinuation	0	0	0	55 (17.5%)	29 (18.1%)	6 (30.0%)

Table 81: Overview of adverse events, by age group (Atezolizumab mono treated patients) (COD: 21 January 2021)

	Atezo Mono[1] (N=2616)				
	< 65 (N=1347)	>=65 (N=1269)	65 - 74 (N=886)	75 - 84 (N=365)	>=85 (N=18)
Total number of patients with at least one AE	1289 (95.7%)	1221 (96.2%)	847 (95.6%)	356 (97.5%)	18 (100%)
Total number of events	13610	14048	9802	4088	158
Total number of patients with at least one					
Atezo-related AE	873 (64.8%)	887 (69.9%)	622 (70.2%)	252 (69.0%)	13 (72.2%)
Grade 3-4 AE	606 (45.0%)	594 (46.8%)	409 (46.2%)	175 (47.9%)	10 (55.6%)
Atezo-related Grade 3-4 AE	179 (13.3%)	203 (16.0%)	137 (15.5%)	63 (17.3%)	3 (16.7%)
Grade 5 AE	46 (3.4%)	41 (3.2%)	28 (3.2%)	13 (3.6%)	0
Atezo-related Grade 5 AE	4 (0.3%)	3 (0.2%)	3 (0.3%)	0	0
Serious AE	542 (40.2%)	523 (41.2%)	357 (40.3%)	155 (42.5%)	11 (61.1%)
Atezo-related serious AE	133 (9.9%)	133 (10.5%)	101 (11.4%)	30 (8.2%)	2 (11.1%)
AE leading to Atezo discontinuation	97 (7.2%)	85 (6.7%)	52 (5.9%)	32 (8.8%)	1 (5.6%)
AE leading to Atezo interruption	349 (25.9%)	368 (29.0%)	258 (29.1%)	103 (28.2%)	7 (38.9%)

Table 82: Adverse events with an incidence rate of at least 5% in any treatment arm by system organ class and preferred term by age group (Safety evaluable population) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=495)			Atezolizumab (N=495)		
MedDRA System Organ Class MedDRA Preferred Term	<65 (N=299)	65-74 (N=172)	75-84 (N=24)	<65 (N=315)	65-74 (N=160)	75-84 (N=20)
Infections and infestations						
Nasopharyngitis	29 (9.7%)	21 (12.2%)	0	22 (7.0%)	11 (6.9%)	0
Upper respiratory tract infection	5 (1.7%)	7 (4.1%)	0	24 (7.6%)	10 (6.3%)	1 (5.0%)
Respiratory, thoracic and mediastinal disorders						
Cough	22 (7.4%)	21 (12.2%)	3 (12.5%)	40 (12.7%)	22 (13.8%)	4 (20.0%)
Dyspnoea	15 (5.0%)	15 (8.7%)	2 (8.3%)	12 (3.8%)	17 (10.6%)	2 (10.0%)
General disorders and administration site conditions						
Pyrexia	5 (1.7%)	4 (2.3%)	2 (8.3%)	38 (12.1%)	24 (15.0%)	3 (15.0%)
Asthenia	9 (3.0%)	5 (2.9%)	0	18 (5.7%)	18 (11.3%)	1 (5.0%)
Fatigue	8 (2.7%)	1 (0.6%)	2 (8.3%)	22 (7.0%)	9 (5.6%)	2 (10.0%)
Investigations						
Alanine aminotransferase increased	14 (4.7%)	2 (1.2%)	0	42 (13.3%)	9 (5.6%)	2 (10.0%)
Aspartate aminotransferase increased	11 (3.7%)	5 (2.9%)	0	38 (12.1%)	11 (6.9%)	4 (20.0%)
Blood creatinine increased	7 (2.3%)	7 (4.1%)	1 (4.2%)	17 (5.4%)	12 (7.5%)	0
Gastrointestinal disorders						
Diarrhoea	6 (2.0%)	3 (1.7%)	0	25 (7.9%)	12 (7.5%)	0
Nausea	8 (2.7%)	6 (3.5%)	2 (8.3%)	19 (6.0%)	8 (5.0%)	3 (15.0%)
Musculoskeletal and connective tissue disorders						
Arthralgia	15 (5.0%)	11 (6.4%)	0	32 (10.2%)	18 (11.3%)	2 (10.0%)
Nervous system disorders						
Headache	9 (3.0%)	9 (5.2%)	2 (8.3%)	20 (6.3%)	6 (3.8%)	2 (10.0%)
Skin and subcutaneous tissue disorders						
Pruritus	1 (0.3%)	2 (1.2%)	0	31 (9.8%)	17 (10.6%)	3 (15.0%)
Rash	2 (0.7%)	3 (1.7%)	0	30 (9.5%)	16 (10.0%)	2 (10.0%)
Blood and lymphatic system disorders						
Anaemia	19 (6.4%)	10 (5.8%)	1 (4.2%)	24 (7.6%)	11 (6.9%)	3 (15.0%)
Endocrine disorders						
Hypothyroidism	2 (0.7%)	0	1 (4.2%)	36 (11.4%)	18 (11.3%)	1 (5.0%)
Hyperthyroidism	1 (0.3%)	2 (1.2%)	0	24 (7.6%)	6 (3.8%)	2 (10.0%)

No patients are age 85 or above.
Investigator text for AEs was coded using MedDRA version 23.1.
Includes adverse events occurring on or after the start of treatment in randomization period.
Percentages were based on N in the column headings.
Multiple occurrences of the same AE in one individual were counted only once.

Safety related to drug-drug interactions and other interactions

No safety data regarding drug-drug interaction have been submitted in this application.

Discontinuation due to adverse events

At the CCOD, in the Safety Evaluable population, 35% of patients in the atezolizumab arm had discontinued treatment, most commonly due to adverse events (19%, Table 6). In the BSC arm, 25% of patients had discontinued treatment (observation period), mainly due to disease relapse (18%).

Table 83: Summary of treatment disposition (safety evaluable population) (COD: 21 January 2021)

	Best Supportive Care (BSC) (N=495)	Atezolizumab (N=495)
Treatment Status		
Completed	373 (75.4%)	323 (65.3%)
Withdrawn from treatment	122 (24.6%)	172 (34.7%)
Withdrawn from Treatment Reason		
ADVERSE EVENT	5 (1.0%)	92 (18.6%)
DISEASE RELAPSE	90 (18.2%)	55 (11.1%)
LOST TO FOLLOW-UP	1 (0.2%)	0
OTHER	2 (0.4%)	0
PHYSICIAN DECISION	3 (0.6%)	1 (0.2%)
PROTOCOL DEVIATION	3 (0.6%)	2 (0.4%)
WITHDRAWAL BY SUBJECT	18 (3.6%)	22 (4.4%)

Table 84: Adverse events leading to atezolizumab discontinuation by system organ class and preferred term (safety evaluable population) (COD: 21 January 2021)

MedDRA System Organ Class MedDRA Preferred Term	Atezolizumab (N=495)
Total number of patients with at least one adverse event	90 (18.2%)
Overall total number of events	115
Respiratory, thoracic and mediastinal disorders	
Total number of patients with at least one adverse event	15 (3.0%)
Total number of events	17
Pneumonitis	7 (1.4%)
Interstitial lung disease	3 (0.6%)
Acute respiratory distress syndrome	1 (0.2%)
Alveolitis	1 (0.2%)
Chronic respiratory failure	1 (0.2%)
Dyspnoea	1 (0.2%)
Lung disorder	1 (0.2%)
Oropharyngeal pain	1 (0.2%)
Pneumothorax	1 (0.2%)
Endocrine disorders	
Total number of patients with at least one adverse event	14 (2.8%)
Total number of events	14
Hypothyroidism	7 (1.4%)
Hyperthyroidism	4 (0.8%)
Adrenal insufficiency	3 (0.6%)
Investigations	
Total number of patients with at least one adverse event	10 (2.0%)
Total number of events	23
Aspartate aminotransferase increased	7 (1.4%)
Alanine aminotransferase increased	5 (1.0%)
Blood creatinine increased	3 (0.6%)
Blood thyroid stimulating hormone increased	1 (0.2%)
Gamma-glutamyltransferase increased	1 (0.2%)
Lymphocyte count decreased	1 (0.2%)
Neutrophil count decreased	1 (0.2%)
Platelet count decreased	1 (0.2%)
White blood cell count decreased	1 (0.2%)
Musculoskeletal and connective tissue disorders	
Total number of patients with at least one adverse event	7 (1.4%)
Total number of events	7
Arthralgia	4 (0.8%)
Arthritis	1 (0.2%)
Myalgia	1 (0.2%)
Myositis	1 (0.2%)

General disorders and administration site conditions	
Total number of patients with at least one adverse event	6 (1.2%)
Total number of events	8
Pyrexia	3 (0.6%)
Asthenia	2 (0.4%)
Gait disturbance	1 (0.2%)
General physical health deterioration	1 (0.2%)
Malaise	1 (0.2%)
Hepatobiliary disorders	
Total number of patients with at least one adverse event	6 (1.2%)
Total number of events	6
Hepatic function abnormal	3 (0.6%)
Drug-induced liver injury	2 (0.4%)
Hepatitis	1 (0.2%)
Nervous system disorders	
Total number of patients with at least one adverse event	6 (1.2%)
Total number of events	6
Peripheral sensory neuropathy	2 (0.4%)
Cerebrovascular accident	1 (0.2%)
Encephalitis autoimmune	1 (0.2%)
Intracranial haematoma	1 (0.2%)
Neuropathy peripheral	1 (0.2%)
Cardiac disorders	
Total number of patients with at least one adverse event	5 (1.0%)
Total number of events	5
Arrhythmia	1 (0.2%)
Atrial fibrillation	1 (0.2%)
Cardiac failure	1 (0.2%)
Myocarditis	1 (0.2%)
Ventricular extrasystoles	1 (0.2%)
Gastrointestinal disorders	
Total number of patients with at least one adverse event	5 (1.0%)
Total number of events	5
Colitis	2 (0.4%)
Diarrhoea	1 (0.2%)
Dyspepsia	1 (0.2%)
Vomiting	1 (0.2%)

Infections and infestations	
Total number of patients with at least one adverse event	5 (1.0%)
Total number of events	5
Meningitis	2 (0.4%)
Encephalitis	1 (0.2%)
Pneumonia	1 (0.2%)
Viral myocarditis	1 (0.2%)
Skin and subcutaneous tissue disorders	
Total number of patients with at least one adverse event	5 (1.0%)
Total number of events	5
Dermatitis acneiform	1 (0.2%)
Erythema	1 (0.2%)
Psoriasis	1 (0.2%)
Rash	1 (0.2%)
Rash maculo-papular	1 (0.2%)
Immune system disorders	
Total number of patients with at least one adverse event	4 (0.8%)
Total number of events	4
Sarcoidosis	2 (0.4%)
Hypersensitivity	1 (0.2%)
Immune-mediated adverse reaction	1 (0.2%)
Injury, poisoning and procedural complications	
Total number of patients with at least one adverse event	3 (0.6%)
Total number of events	3
Infusion related reaction	2 (0.4%)
Traumatic fracture	1 (0.2%)
Renal and urinary disorders	
Total number of patients with at least one adverse event	2 (0.4%)
Total number of events	2
Acute kidney injury	1 (0.2%)
Autoimmune nephritis	1 (0.2%)
Eye disorders	
Total number of patients with at least one adverse event	1 (0.2%)
Total number of events	1
Glaucoma	1 (0.2%)
Metabolism and nutrition disorders	
Total number of patients with at least one adverse event	1 (0.2%)
Total number of events	1
Hypercreatininaemia	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Total number of patients with at least one adverse event	1 (0.2%)
Total number of events	1
Renal neoplasm	1 (0.2%)
Product issues	
Total number of patients with at least one adverse event	1 (0.2%)
Total number of events	1
Device dislocation	1 (0.2%)
Psychiatric disorders	
Total number of patients with at least one adverse event	1 (0.2%)
Total number of events	1
Psychopathic personality	1 (0.2%)

Table 85: Adverse events leading to treatment discontinuation by highest NCI CTCAE grade bys system organ class and preferred term (safety evaluable population) (COD: 21 January 2021)

MedDRA System Organ Class MedDRA Preferred Term	Grade	Atezolizumab (N=495)
- Any adverse events -	- Any Grade -	90 (18.2%)
	Grade 1-2	43 (8.7%)
	1	10 (2.0%)
	2	33 (6.7%)
	Grade 3-4	43 (8.7%)
	3	39 (7.9%)
	4	4 (0.8%)
	Grade 5	4 (0.8%)

Post marketing experience

Atezolizumab is globally approved for the treatment of patients with metastatic squamous and non-squamous NSCLC after prior chemotherapy, as well as first-line (1L) treatment of metastatic non-squamous NSCLC in combination with chemotherapy either with or without bevacizumab. Atezolizumab is also globally approved for the treatment of a variety of other cancers, including small cell lung cancer, urothelial cancer (UC), triple-negative breast cancer, melanoma, and hepatocellular carcinoma.

Since the International Birth Date (18 May 2016) through 17 May 2020, an estimated cumulative total of 106,316 patients have received atezolizumab from marketing experience (United States n=54,910; European Union n=25,768; Japan n=9,543; Rest of the World n=16,095).

No new or unexpected safety findings were identified in the post marketing setting for atezolizumab used as a monotherapy (Periodic Benefit Risk Evaluation Report).

2.5.1. Discussion on clinical safety

The randomized safety evaluable population from Study GO29527 (IMpower010) is defined as all randomized patients who received at least one dose of atezolizumab (n=495) and all randomized patients who were randomized to the control arm (n=495) and did not receive any dose of atezolizumab but who had at least one post baseline safety assessment (e.g., adverse events, laboratory tests, vital signs), regardless of their assigned treatment at randomization (atezolizumab/BSC). During the randomization phase, patients randomized to the atezolizumab arm received 1200 mg atezolizumab by IV infusion on Day 1 of every 21-day cycle.

The median follow-up of this study was 32.2 months. The median duration of study treatment in IMpower010 was 10.4 months and the number of median doses were 16.

Single-agent atezolizumab regardless of tumour type has been evaluated in a total of 3178 patients, referred to as the pooled population. All patients had advanced disease.

In the safety dataset of IMpower010 (N=990), common AEs were reported for ≥10% of patients including cough (13.3%), pyrexia (13.1%), hypothyroidism (11.1%), aspartate aminotransferase increased/alanine aminotransferase increased (10.7% for both) and arthralgia (10.5%). In the pooled populations the most common AEs were fatigue, decreased appetite, nausea, dyspnoea, pyrexia and constipation which is as expected in a patient population with advanced disease. The proportion of patients with **Grade 3-4 AEs** in the atezo arm (21.8%) was higher than the BSC arm (11.5%). The most common Grade 3-4 AEs by PT (›1% of patients in either arm) were (BSC arm vs. atezo arm, respectively): pneumonia (0.6% vs. 1.4%), increased ALT (0.2% vs. 1.6%), increased AST (0% vs. 1.4%), rash (0% vs. 1%) and hypertension (0.4% vs. 1%).

Adverse events of special interest (**AESI**) for atezo were selected based on its mechanism of action. The total number of AESI was 51.7%. However the majority of AEs were of Grade 1-2. At the time of CCOD of January 2021, the proportion of unresolved AESI were overall comparable between the atezo arm of IMpower010 and the atezo pooled populations (16% vs. 15.3%, respectively). The majority of ongoing AESIs were low-grade immune-mediated endocrinopathies. At CCOD, three patients had unresolved Grade 3 AESIS (AST increased, pneumonitis and immune-mediated Guillain-Barre Syndrome). AESI requiring the use of systemic corticosteroids was seen in 12.1% compared with 7.5% and 7.8% in the Atezo pooled population, respectively. The majority of the AESI for which atezo arm patients of IMpower010 received corticosteroids were Grade 1-2 in severity. It is possible that patients being treated in the adjuvant setting, being relatively healthier, may be more susceptible to developing immune-mediated AEs. This is consistent with what has been observed in adjuvant studies of other immune checkpoint inhibitors. **Grade 3-4 AESI and serious AESI** were seen in 7.9% and 4.2% in the Atezo

arm, respectively. This was consistent with what was seen in the pooled population (7.8% and 4.8%, respectively). Grade 5 AE with fatal outcome was seen in 2 patients (0.4%). This was higher than the incidences reported in the pooled population (5 patients, 0.2%). When comparing incidences of imAEs between the experimental arm of IMpower010 and the pooled atezolizumab population, a relatively higher rates of uncommon, but clinically relevant immune-related events are notable, such as immune-related adrenal insufficiency (1.2% vs. 0.4%), myositis (0.8% vs. 0.3%), diabetes mellitus (0.8% vs. 0.3%), meningoencephalitis (0.8% vs 0.4%), encephalitis (0.4% vs <0.1%), myocarditis (0.4% vs. 0%) and autoimmune haemolytic anaemia (0.4% vs. 0.1%). However, when available, all time to onset values observed in the serious AESIs of IMpower010 were within the data range of the atezo Mono pooled populations, except for a longer time to onset for immune mediated adrenal insufficiency. The majority of the patients with a serious AESI (19 of 21) in the atezo arm of IMpower010 had resolution of serious AESIs at the time of the clinical data cut-off date, although two serious AESIs remained unresolved, which included one event of pneumonitis and one event of Guillain Barre syndrome. The MAH will submit updated analyses of immune-related AESIs with the final DFS analysis.

The proportion of patients with at least one SAE was 17.6% in the Atezo arm compared with 8.5% in the BSC arm vs. 41.2% in the pooled population. The most common SAE was infections/infestations in 5.7% of the patients treated with atezolizumab (11.6% in the pooled population). The most frequent infection in the atezo arm was pneumonia in 1.6% (vs. 3.9% and 3.5%) of the patients. Patients in the BSC arm did not receive any treatment during the randomization phase, whereas patients in the study arm continued to receive atezo on Day 1 of every 21-day cycle. Therefore, the number of SAEs is expectedly higher in the atezo arm. Across both arms, most patients with SAEs had their SAEs resolved (83.9%) or resolving at the time (6.9%), unresolved (6.9%) and resolved with sequelae (4.6%) at the clinical data cut-off date.

The proportion of deaths were well balanced between the 2 arms of IMpower010 (19.2% in the Atezo arm vs. 18.2% in the BSC arm) with the majority of deaths occurring ›30 days from last study treatment/safety visit (18.4% and 17.2%, respectively). The most common primary cause of death was disease relapse (12.7% vs. 15,6%). AEs was the cause in 8 (1.6%) and 3 (0.6%) patients. 4 patients in the BSC arm and 8 patients in the atezo arm died of unknown/limited death information, respectively. It is not optimal that the causes of death are unclear in an adjuvant study where the ultimate purpose is an improvement of OS. However, the numbers are small and unlikely to change the overall conclusions. The higher rate of 0.8% (4 patients) with atezolizumab related Grade 5 AEs (compared to 0.3% in the metastatic setting) are of special concern in a setting where most patients are treated without adjuvant immunotherapy with a curative intention. After reassessment, these were myocarditis, interstitial lung disease (ILD), multiple organ dysfunction syndrome, and acute myeloid leukemia (AML) (n=1 each). In conclusion, all of the related AEs with fatal outcome were single event occurrences and therefore no trends in terms of a safety signal were noted. This has been reflected in the SmPC.

Laboratory findings: the laboratory test shifts to NCI-CTCAE Grade 3-4 Post-Baseline and those were low. The most frequent was high potassium (3.5%), high SGPT/ALT (3.3%), low sodium (2.7%), high glucose (2.7%) and high SGOT/AST (2.4%) in the Atezo arm. This was generally lower in the BSC arm (2.7%-0.2%) which was as expected.

The incidence of **AEs leading to discontinuation** of atezolizumab was 18.2% (including 10.5% of AESI leading to discontinuation) and higher than the discontinuation rate in the metastatic setting (7.1%). The most frequent AEs were pneumonitis (1.4%), hypothyroidism (1.4%), aspartate aminotransferase increased (1.4%), hyperthyroidism (0.8%) and arthralgia (0.8%). From the 18.2% of patients who discontinued atezolizumab due to AEs, 0.8% were due to Grade 5 AEs, 8.7% were due to Grade 3-4 AEs, and 8.7% were due to Grade 1-2 AEs.

2.5.2. Conclusions on clinical safety

The safety data of atezolizumab in Study IMpower010 were generally consistent with the established safety profile of anti-PD/PD-L1 agents and no new ADRs were observed; however, higher rates of discontinuations due to AEs and higher incidences of imAEs were observed in Study IMpower010 compared with the pooled atezolizumab monotherapy safety data. Higher frequencies of uncommon, but clinically relevant imAEs are of concern in the adjuvant setting. The most common primary cause of death was disease relapse. The rate of 0.8% of treatment-related deaths due to AEs is highlighted in the SmPC.

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 21.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 21.2 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Immune-related adverse reactions (including but not limited to): hepatitis, pneumonitis, colitis, pancreatitis, endocrinopathies (diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency and hypophysitis), neuropathies (Guillain-Barré syndrome, and myasthenic syndrome / myasthenia gravis), meningoencephalitis, myocarditis, nephritis, myositis and severe cutaneous adverse reactions (SCARs) Infusion-related reactions
Important potential risks	Attenuated efficacy or reduced tolerability in patients with anti-drug antibodies Embryo-fetal toxicity
Missing information	Long term use

No changes to the list of safety concerns were made as a result of the data submitted for this new indication.

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				
MO39171 (TAIL): Single-Arm Long-Term Safety and Efficacy Study of atezolizumab in previously treated NSCLC Patients Ongoing	To evaluate the long-term safety of atezolizumab on the bases of the following endpoints: The incidence of all serious adverse events (SAEs) related to atezolizumab treatment and the incidence of immune-related adverse events (irAEs) related to atezolizumab treatment	Long-term use	Final CSR	January 2023
MO29983: (SAUL): An Open-Label, Single Arm, Multicenter, Safety Study of atezolizumab in Locally Advanced or Metastatic Urothelial or Non-Urothelial Carcinoma of the Urinary Tract Ongoing	To evaluate the safety of atezolizumab based on the following endpoints: Nature, severity, duration, frequency and timing of adverse events (AEs) and changes in vital signs, physical findings, and clinical laboratory results during and following atezolizumab administration.	Long-term use	Final CSR	Q1 2023

No changes to the pharmacovigilance plan were made as a result of the data submitted for this new indication.

Risk minimisation measures

Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
Immune-related adverse reactions (including but not limited to): hepatitis, pneumonitis, colitis, pancreatitis, endocrinopathies (diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, and hypophysitis), neuropathies (Guillain-Barre Syndrome and myasthenia gravis), meningoencephalitis, myocarditis, nephritis, myositis, severe cutaneous adverse reactions	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects **Additional risk minimization measures:** • Patient alert cards (All Immune-related adverse reactions excluding Severe Cutaneous Adverse Reactions (SCARS)**:** • SCARS**:** DHPC: To inform healthcare professionals that immune-related severe cutaneous adverse reactions (SCARs) which were previously known to be potentially associated with use of Tecentriq (atezolizumab), are now considered to be an identified risk.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** SCARs: Metrics on the distribution and receipt of the DHPC will be taken to assess the effectiveness of this risk minimization activity.
Infusion-Related Reactions	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Section 4.8 Undesirable effects **Additional risk minimization measures:** Patient alert cards	None
Attenuated efficacy or reduced tolerability in patients with anti-drug antibodies	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.8 Undesirable effects **No additional risk minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Embryo-fetal toxicity	Routine risk minimization measures: Proposed measures are described in the E.U. SmPC under the following sections: Section 4.6 Fertility, pregnancy and lactation Section 5.3 Preclinical safety data **No additional risk minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Long-term use	**Routine risk minimization measures:** Proposed text in E.U. SmPC: None **No Additional risk minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Studies: • MO29983

Safety concern	Risk minimization measures	Pharmacovigilance activities
		• MO39171

The existing risk minimisation measures remains sufficient to minimise the risks of the product in the new indication.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

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:

No significant changes impacting the readability of the package leaflet are made. In particular, key safety messages are not affected by this variation. The additional text follows the same structure and use similar descriptions and terminology as used in the approved package leaflet.

The target group of users will be similar between the approved indication (metastatic NSCLC) and the applied indication (NSCLC following resection), with no significant age difference.

Moreover, the posology proposed in this application is the same as for the approved monotherapy indications for Tecentriq.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The Applicant is seeking an extension of indication as follows:

"Early-stage non-small cell lung cancer (NSCLC)

Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR mutant or ALK positive NSCLC (see section 5.1 for selection criteria)."

3.1.2. Available therapies and unmet medical need

With the development of cancer immunotherapy in advanced NSCLC, anti-PD-L1/PD-1 inhibitors such as atezolizumab, nivolumab, pembrolizumab, and durvalumab may improve the modest survival benefit of platinum-based chemotherapy alone in the adjuvant setting as they have when combined and/or sequentially administered with platinum-based chemotherapy in the recurrent or advanced settings.

There are currently no approved cancer immunotherapies for the adjuvant treatment of resectable, early-stage NSCLC, and it is agreed, that there is an unmet medical need for treatment options that improve the survival and reduces the relapse rates of these patients. Improvement of the adjuvant treatment after radical surgery is a relevant area of focus. The recent approval of osimertinib in early-stage EGFR-mutated NSCLC (EMEA/H/C/004124/II/0039/G) should be considered.

3.1.3. Main clinical studies

The main clinical study GO29527 (IMpower010) is a Phase III, open-label, randomized study to investigate the efficacy and safety of atezolizumab (anti-PD-L1 antibody) compared with best supportive care following adjuvant cisplatin-based chemotherapy in patients with completely resected stage IB-IIIA Non-Small Cell Lung Cancer.

The submitted data are an interim analysis with a CCOD of May 2021, with ~32 months median FU.

The primary endpoint of this trial was to evaluate the efficacy of atezolizumab monotherapy compared with BSC as measured by DFS as assessed by the investigator in:

- the PD-L1 ≥1% positive (defined as ≥ 1% TC by the SP263 IHC assay) NSCLC Stage II-IIIA subpopulation
- all randomized patients with Stage II-IIIA NSCLC, any degree of PD-L1 status
- the ITT population; Stage IB (tumour size ≥ 4 cm)-IIIA, any degree of PD-L1 status.

Overall survival was a secondary endpoint.

3.2. Favourable effects

The first two primary endpoints were met as DFS in the PD-L1 ≥1% stage II-IIIA subgroup and in the all randomised stage II-IIIA any PD-L1 status subgroup were statistically significant. Statistical significance for OS was however not reached, HR=0.77 (95%CI: 0.51- 1.17).

In the completely resected stage II-IIIA (7th edition AJCC) NSCLC patients with PD-L1 expression of ≥50% and without EGFR or ALK mutations (n=209; 106 in the atezo arm and 103 in the BSC arm), the stratified HR for DFS was 0.49 (0.29-0.81), with 24 (22.6%) events in the atezolizumab arm and 45 (43.7%) events in the BSC arm. Median DFS was not established (NE) (95% CI: NE-NE) in the atezolizumab arm and 37.3 (95% CI: 30.1-NE) months in the BSC arm. The stratified HR for OS was 0.39 (0.18-0.82) with 10 (9.5%) events in the atezolizumab arm and 24 (23%) events in the BSC arm. The median OS was NE in both arms.

The efficacy data support a favourable benefit risk balance for the PD-L1 high expression subgroup. This is based on the large effect size of the treatment effect of DFS and further supported by OS data.

3.3. Uncertainties and limitations about favourable effects

The sample size constituting the indication group (n=209; 106 and 103 in each arm) is relatively small considering the magnitude of the investigated patient group (n=1005).

The data are immature regarding DFS. This hampers the interpretation of data and the clinical meaningfulness of the effects. The MAH is recommended to submit the final DFS analysis from Study GO29527.

Overall, OS data are considered immature to draw reliable conclusions (event rates 9.5% and 23% in the atezolizumab and BSC arms, respectively), especially regarding the effect sizes in subgroups. The MAH is recommended to provide interim and final analysis of OS as soon as available.

Patients with stage IB (7th edition AJCC), PD-L1 expression of <50% or ALK and EGFR driver mutations showed in the subgroup analyses non or detrimental effect of adjuvant atezolizumab. Additionally, a proven effective adjuvant treatment with osimertinib for the EGFR mutated patients is available. These patients groups were excluded from the indication.

3.4. Unfavourable effects

- Nearly all patients in the atezolizumab arm (92.7%) had at least one AE compared to 70.7% in the BSC arm. In Atezo Mono 1 and 2 groups it was 95.9% and 96.0%, respectively. The most common AEs in Impower010 were cough (13.3%), pyrexia (13,1%), hypothyroidism (11.1%), aspartate aminotransferase increased/alanine aminotransferase increased (10.7% for both), arthralgia (10.5%) and anaemia (7.7%).

- The proportion of patients with Grade 3-4 AEs in the atezolizumab arm (21.8%) was higher than in the BSC arm (11.5%). The most common were (BSC arm vs. atezolizumab arm, respectively): pneumonia (0.6% vs. 1.4%), increased ALT (0.2% vs. 1.6%), increased AST (0% vs. 1.4%), rash (0% vs. 1%) and hypertension (0.4% vs. 1%).

- The proportion of patients with at least one SAE was 17.6% in the Atezo arm compared with 8.5% in the BSC arm vs. 41.2% in the pooled atezolizumab monotherapy population. The most common type of SAE were infections.

- The incidence of AEs leading to discontinuation of study treatment atezolizumab was 18.2% (including 10.5% of AESI leading to discontinuation) and higher than the discontinuation rate in the metastatic setting (7.1%).

- The proportion of deaths were well balanced between the 2 arms (19.2% in the Atezo arm vs. 18.2% in the BSC arm) and was mostly due to disease relapse and AEs. 4 patients (0.8%) treated with atezolizumab presented Grade 5 AEs (compared to 0.3% in the metastatic setting).

3.5. Uncertainties and limitations about unfavourable effects

Twice as many patients in the Atezo arm in Impower010 died compared to the BSC arm of "other" causes. After reassessment these were myocarditis, interstitial lung disease (ILD), multiple organ dysfunction syndrome, and acute myeloid leukemia (AML) (n=1 each). In conclusion, all of the related AEs with fatal outcome were single event occurrences and therefore no trends in terms of a safety signal were noted. However, the MAH has been asked to reflect this in the SmPC. The AEs with fatal outcome have been reflected in the SmPC.

3.6. Effects Table

Table 86: Effects Table for Impower010 (atezolizumab monotherapy as adjuvant treatment of NSCLC) (data cut-off: 21 Jan 2021)

Effect	Short description	Unit	Treatment Atezolizumab N=106	Control BSC N=103	Uncertainties/ Strength of evidence
Favourable Effects Primary endpoint					
DFS	PD-L1 ≥50 % positive, EGFR and ALK excluded	Months	NE (NE-NE)	37.3 (30.1-NE)	Stratified HR=0.49 (0.29-0.81) Target population
OS	PD-L1 ≥50 % positive, EGFR and ALK excluded	Months	NE (NE-NE)	NE (NE-NE)	Stratified HR=0.39 (0.18-0.82) Target population
Effect	**Short description**	**Unit**	**Treatment Atezolizumab N=495**	**Control BSC N=495**	**Uncertainties/ Strength of evidence**
Unfavourable Effects in the ITT population of IMpower010, N=990					
TEAEs	AE	%	92.7%	70.7%	NA
Grade 3-4	AE (ADR)	%	21.8%	11.5%	NA
SAEs	AE (ADR)	%	17.6%	8.5%	NA
AEs leading to discount.	AE (ADR)	%	18.2%	0.0%	NE
Cough	ADR	%	13.3%	9.3%	NA
Pyrexia	ADR	%	13.1%	2.2%	NA
Hypo-thyreoi-dism	ADR	%	11.1%	0.6%	NA
ALAT/ASAT increased	ADR	%	10.7%	3.2%	NA
Arthralgia	ADR	%	10.5%	5.3%	NA
Pruritus	ADR	%	10.3%	0.6%	NA

Abbreviations:
DFS: disease free survival, OS: overall survival, NA = not available, NE: not evaluable, HR: hazard ratio, CI: confidence interval, AE: adverse event, ADR: adverse drug reaction, SAE = serious adverse events. TEAE = Treatment emergent adverse event
Notes: It is important to consider, that the primary endpoint do not represent the group of patients that the MAH is seeking an extension of indication for.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The data presented in the interim analysis (CCOD January 2021) to assess the efficacy and safety of one year of adjuvant treatment with atezolizumab as monotherapy following radical resection and platinum-based adjuvant chemotherapy for adult patients with NSCLC with PD-L1 expression of ≥1% were immature and did not support overall benefit in the proposed target population of the initially formulated indication statement. Lack of benefit and a potential detrimental effect was observed in patients with stage IB disease (7th edition AJCC) and in patients with PD-L1<50%, which was of concern. It was thus agreed with the MAH to restrict the indication to the subgroup of patients who seemed to drive the DFS benefit, i.e., patients with the stage II-IIIA (7th edition AJCC) completely resected NSCLC with high PD-L1 expression (≥50%), with no EGFR and ALK mutations. Within this rather small subgroup of patients (n=209; 106 and 103 patients in each arm), the data showed a beneficial effect of adjuvant treatment with atezolizumab with regards to both DFS and OS, although data were immature. The MAH is recommended to submit final DFS data and updated and final OS data post-approval. Final DFS and 2nd

IA of OS is due in August 2024. The approved indication reflects the study population, who derived benefit from adjuvant treatment in the IMpower010 study, as precisely as possible and the exact selected patient population has been described in section 5.1 of the SmPC. Regarding safety, the toxicity profile of atezolizumab is known and no new ADRs were observed

3.7.2. Balance of benefits and risks

The benefit/risk is considered positive for the following indication: *Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1 for selection criteria).*

The MAH has updated the SmPC with the safety profile regarding this adjuvant treatment and with the efficacy data for the patients encompassed by the final indication statement. The staging of the patients included in the indication is thoroughly described in section 5.1 of the SmPC.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of atezolizumab as an adjuvant treatment for patients with completely resected stage II-IIIA (7th edition AJCC) NSCLC and PD-L1 ⩾50% positive tumours not harbouring EGFR or ALK mutations is considered 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 and IIIB

C.I.6 (Extension of indication)
Extension of indication to include adjuvant treatment of non-small cell lung cancer (NSCLC) following resection and platinum-based chemotherapy for adult patients whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) for Tecentriq as monotherapy based on the results from the pivotal phase III Study GO29527 (IMpower010); as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. Minor editorial changes have been made throughout the SmPC. The Package Leaflet is updated in accordance. Version 21.2 of the RMP has also been submitted.

Amendments to the marketing authorisation

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'EMEA/H/C/004143/II/0064'

Attachments

1. SmPC, Package Leaflet (changes highlighted) as adopted by the CHMP on 22 April 2022.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 08 April 2022. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 08 April 2022. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.