EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 March 2021
EMA/275323/2021
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Tecentriq

International non-proprietary name: atezolizumab

Procedure No. EMEA/H/C/004143/II/0033

Marketing authorisation holder (MAH): Roche Registration GmbH

Note

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

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List of abbreviations

1L	first-line
2L	second-line
2L+	second-line and beyond
ADA	anti-drug antibody, also called anti-therapeutic antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
CCOD	clinical cutoff date
C_{max}	maximum concentration
C_{min}	minimum concentration
CSR	Clinical Study Report
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for the Research and Treatment of Cancer
HR	hazard ratio
IC	tumor-infiltrating immune cell
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
IxRS	Interactive Web/Voice Response System
MAD	multiple ascending dose
MAH	Marketing Authorization Holder
mUC	metastatic urothelial carcinoma
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
PFS	progression-free survival
PK	pharmacokinetic
popPK	population pharmacokinetic
q2w	every 2 weeks
q3w	every 3 weeks
q4w	every 4 weeks
QLQ-C30	Quality-of-Life Questionnaire Core
QLQ-LC13	Quality-of-Life Questionnaire Lung Cancer Module
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCLC	small cell lung cancer
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SILC	Symptoms in Lung Cancer
SmPC	Summary of Product Characteristics
TAI	treatment assignment information
TC	tumor cell
TNBC	triple-negative breast cancer
TPS	tumor proportion score
UC	urothelial carcinoma
USPI	U.S. Prescribing Information
WT	wild type

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 27 November 2019 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

Extension of indication to include the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours express PD-L1 for Tecentriq based on the results of the pivotal study GO29431 (IMpower110), comparing atezolizumab monotherapy to platinum-based chemotherapy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. The RMP version 12.0 has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0207/2019 on the granting of a (product-specific) waiver.

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 applicant received the following Scientific Advice on the clinical development relevant for the indication subject to the present application: EMEA/H/SA/2522/3/2014/II

1.2. Steps taken for the assessment of the product

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

Rapporteur: Sinan B. Sarac Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	27 November 2019
Start of procedure:	28 December 2019
CHMP Co-Rapporteur Assessment Report	21 February 2020
CHMP Rapporteur Assessment Report	21 February 2020
PRAC Rapporteur Assessment Report	27 February 2020
PRAC members comments	4 March 2020
Updated PRAC Rapporteur Assessment Report	5 March 2020
PRAC Outcome	12 March 2020
CHMP members comments	16 March 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 March 2020
Request for supplementary information (RSI)	26 March 2020
CHMP Rapporteur Assessment Report	22 December 2020
CHMP members comments	18 January 2021
Updated CHMP Rapporteur Assessment Report	21 January 2021
Request for supplementary information (RSI)	28 January 2021
CHMP Rapporteur Assessment Report	10 March 2021
CHMP members comments	15 March 2021
Updated CHMP Rapporteur Assessment Report	n/a
Opinion	25 March 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The MAH applied for the following indication:

"Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have a PD-L1 expression ≥ 50% tumour cells (TC) or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1)."

Epidemiology

Lung cancer remains the leading cause of cancer death worldwide, estimated to be responsible for nearly one in five cancer deaths globally (1.8 million deaths, 18% of the total; Globocan 2020). There were estimated to be 2.2 million new cases in 2020 (11.4% of the total). This disease is the most common cancer in men worldwide (1.4 million, 15% of the total cancers in men) and accounts for the highest absolute number of cancer deaths globally (1.2 million deaths, 24% of cancer deaths in men).

Biologic features

Non-small cell lung cancer (NSCLC) is the predominant subtype, accounting for approximately 85% of all cases. NSCLC can be divided into two major histologic types: non-squamous and squamous cell carcinoma. Non-squamous histology accounts for more than half of all NSCLC, whereas squamous histology accounts for approximately 30% (Brambilla et al, 2014 and Schrump DS et al. NSCLC; Principles and Practice of Oncology. 9th Edition. 2011).

Clinical presentation, diagnosis and stage/prognosis

More than half of the patients are diagnosed at an advanced stage of disease, which directly contributes to poor survival, as expressed by an untreated median OS of 4 months and a metastatic 5-year survival rate of <5% (Lindsey A. et al, 2016). Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor performance status (PS), and a history of unintentional weight loss. More than half of the patients with NSCLC are diagnosed with distant metastatic disease, which directly contributes to poor survival prospects.

Management

Platinum-based chemotherapy partnered with agents such as taxanes, vinorelbine, gemcitabine, or pemetrexed, with or without bevacizumab, remain standard 1L treatment options for patients with locally advanced or metastatic NSCLC whose tumours do not harbour EGFR mutations or ALK translocations (Hanna et al. 2017; Planchard et al. 2018). However, these regimens are associated with substantial toxicities and are generally poorly tolerated by elderly patients and those with poor performance status. Furthermore, the survival benefit conferred by cytotoxic chemotherapy has reached a plateau, with overall response rates of approximately 20% and 1-year survival ranging from 31% to 36% (Schiller et al. 2002), leaving considerable room for improvement.

Over the past 4 years, immune checkpoint inhibitors, such as PD-1/PD-L1-blocking antibodies, have emerged as effective alternatives to chemotherapy for many tumour types. In second-line and beyond (2L+) NSCLC, PD-1 and PD-L1 inhibitors demonstrated superiority over docetaxel as monotherapy. Subsequently, results from the KEYNOTE-024 study showed that pembrolizumab monotherapy is effective in the 1L setting for patients who express high levels of PD-L1 (Reck et al. 2016). On the basis of the KEYNOTE 024 study, pembrolizumab was approved in the United States and European Union as monotherapy for the 1L treatment of patients with NSCLC whose tumours express PD L1 (tumour proportion score [TPS] ≥50%) and do not harbour EGFR mutations or ALK rearrangement.

More recently, results from the KEYNOTE-042 study have shown that the benefit of pembrolizumab monotherapy can be extended to patients with low TPS scores (≥1%). However, the clinical benefit is driven by the subgroups of patients with high PD-L1 expression (TPS ≥50%; Mok et al. 2019), suggesting that the greater treatment benefit correlates with higher tumour PD-L1 expression.

Overall, additional treatment options are still needed for patients with advanced NSCLC. For patients with NSCLC, regardless of histology, who are considered ineligible for combination therapy, monotherapy with a checkpoint inhibitor is an attractive treatment option. In this regard, data from the Phase II BIRCH study showed clinically meaningful OS benefit with atezolizumab in PD-L1-selected patients in NSCLC, across lines of therapy (Peters et al. 2017). The Phase III IMpower110 study was designed to evaluate the efficacy and safety of atezolizumab monotherapy versus platinum-based chemotherapy in PD-L1 selected, chemotherapy-naïve patients with advanced NSCLC, regardless of histology.

2.1.2. About the product

Atezolizumab (TECENTRIQ) is a humanized IgG1 monoclonal antibody that targets human PD-L1 on tumor-infiltrating immune cells (ICs) and tumor cells (TCs). TECENTRIQ is globally approved for the treatment of patients with metastatic squamous and non-squamous non-small cell lung cancer (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 (SCLC), urothelial cancer (UC), and triple-negative breast cancer (TNBC).

The CHMP approved the following indication:

Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have a PD-L1 expression ≥ 50% tumour cells (TC) or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC.

Patients with first-line (1L) NSCLC should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test (see section 5.1).

The recommended dose of Tecentriq is:

- 840 mg administered intravenously every two weeks, or
- 1,200 mg administered intravenously every three weeks, or
- 1,680 mg administered intravenously every four weeks.

It is recommended that patients are treated with Tecentriq until disease progression or unmanageable toxicity.

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

Several interactions between the Marketing Authorization Holder (MAH) and the European Medicines Agency (EMA) have been held to discuss the atezolizumab development plan for the 1L treatment of NSCLC, including IMpower110.

The MAH received a written CHMP Scientific Advice on 22 January 2015 on the proposed clinical study design and Statistical Analysis Plan (SAP) of IMpower110. On 19 December 2016 and 20 December 2016, the MAH held meetings with the Rapporteur (Danish Health and Medicine Authority, DHMA, Denmark) and Co Rapporteur (Paul-Ehrlich-Institute, PEI, Germany) to discuss and obtain agreement on proposed changes to the statistical analyses in ongoing 1L and adjuvant NSCLC Phase III studies, including IMpower110. On 2 May 2019, the MAH held a meeting with the (Co-)Rapporteurs to discuss registrational clinical trials, including Study IMpower110, investigating atezolizumab in which PD-L1 status was determined with Ventana's investigational PD L1 (SP142) assay using an impacted

detection dispenser lot.

2.1.4. General comments on compliance with GCP

A request for GCP inspection was adopted by CHMP for the following study: GO29431 (IMpower110).

Sites were inspected in Switzerland and Greece between July and August 2020. The outcome of this triggered GCP inspection was that the Applicant was not able to demonstrate that the change of the primary analysis population, finally leading to a statistically significant result in the TC/IC 3 population, was not influenced by study knowledge. However, it is acknowledged that analyses of external data could have indeed resulted in the late change of the primary analysis population. The choice of the selected subgroup is supported by external data and is based on a strong biological rationale. Thus, it can be accepted that the presented Impower110 data in the sought TC3/IC3 population are plausible.

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

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: A summary of atezolizumab studies conducted in monotherapy settings

Atezolizumab Monotherapy Studies	Phase	Indication	N Enrolled/PK evaluable (Total 3239/3184)[d]	Design/Dose/Primary Clinical Endpoint
PCD4989g (GO27831)[a]	I	Multiple solid tumors	481/473	Dose-escalation/ up to 20 mg/kg q3w/ PK and safety
JO28944[a]	I	Multiple solid tumors	6/6	Dose-escalation/ 10 mg & 20 mg q3w/ PK and safety
IMvigor210 (GO29293)[a]	II	1L[c] & 2L+ mUC	438/427	1L, 2L+ cohorts/ 1200 mg q3w/ORR
IMvigor211 (GO29294)[a]	III	2L/3L mUC	467/455	2-arm study/ 1200 mg q3w vs. vinflunine, paclitaxel, or docetaxel/OS
FIR (GO28625)[a]	II	1L, 2L+ NSCLC	138/137	Single-arm study/ 1200 mg q3w/ORR
BIRCH (GO28754)[a]	II	1L, 2L+ NSCLC	667/654	Single-arm study/ 1200 mg q3w/ORR
POPLAR (GO28753)[a]	II	2L/3L NSCLC	144/142	2-arm study/ 1200 mg q3w vs docetaxel/ OS
OAK (GO28915)[b]	III	2L/3L NSCLC	613/606	2-arm study/ 1200 mg q3w vs. docetaxel/ OS
IMpower110 (GO29431)	III	1L NSCLC	285/284	1200 mg q3w vs. (Cisplatin/Carboplatin + Pemetrexed/Gemcitabine)/OS

1L=first-line; 2L=second-line; 2L +=second-line and beyond; CSR=clinical study report; MAA = Marketing Authorisation Application; mUC=metastatic urothelial carcinoma; NSCLC=non-small call lung cancer; ORR=overall response rate; q3w=every 3 weeks; OS=overall survival; PK=pharmacokinetic.

[a] MAA procedure number EMEA/H/C/4143 eCTD Sequence 0000.

[b] MAA procedure number EMEA/H/C/4143 eCTD Sequence 0002.

[c] Cisplatin-ineligible patients.

[d] For randomized studies (i.e., IMvigor211, POPLAR, OAK), number enrolled corresponds to the number of patients enrolled into the atezolizumab arm.

Sources: CSR PCD4989g, CSR JO28944, CSR IMvigor210, CSR IMvigor211, CSR BIRCH, CSR POPLAR, CSR FIR, CSR OAK and CSR IMpower110.

2.3.2. Pharmacokinetics

The clinical pharmacology properties of atezolizumab were originally characterized using previous studies where atezolizumab was administered as 1200 mg IV every three weeks (q3w) as monotherapy in patients with predominantly mUC and NSCLC. Previous assessments have determined that atezolizumab pharmacokinetics is linear over a dose range of 1 to 20 mg/kg. A target efficacy serum concentration of 6 µg/mL has been identified.

IMpower110

IMpower110 is a randomized, Phase III, multicenter, open-label study designed to evaluate the safety and efficacy of atezolizumab as monotherapy in PD-L1 selected patients with chemotherapy-naive Stage IV squamous or non-squamous NSCLC. The pharmacokinetics in IMpower110 was based on data from Arm A where atezolizumab was administered as 1200 mg IV q3w.

Bioanalytical methods

For IMpower110, a validated sandwich ELISA method was used to determine the concentration of atezolizumab in human serum samples. Validated ELISA methods were also used to detect anti-atezolizumab antibodies in human serum samples from IMpower110 and to confirm and determine the titer of detected anti-atezolizumab antibodies.

PD-L1 expression in tumour tissue was measured using a validated immunohistochemistry assay. Table 2 show the sampling schedule in IMpower110.

Table 2: Schedule of pharmacokinetic, biomarker and anti-therapeutic antibody assessments

Study Visit	Time	Patients Randomized to Chemotherapy	Patients Randomized to Atezolizumab
Screening	—	Biomarkers [a]	Biomarkers [a]
Cycle 1, Day 1	Prior to dosing (same day as treatment administration)	Biomarkers [b]	ATA Atezolizumab pharmacokinetics Biomarkers [b]
	30 (±10) minutes after end of atezolizumab infusion	—	Atezolizumab pharmacokinetics
Cycles 2, 3, 4, 8 and 16, Day 1	Prior to dosing (same day as treatment administration)	Biomarkers [b]	ATA Atezolizumab pharmacokinetics Biomarkers [b]
After Cycle 16, every eighth cycle, Day 1	Prior to dosing (same day as treatment administration)	Biomarkers [b]	ATA Atezolizumab pharmacokinetics Biomarkers [b]
At time of fresh biopsy (on-treatment, or at progression, including during follow-up)	At visit	Biomarkers [b]	Biomarkers [b]
Treatment discontinuation visit	At visit	Biomarkers [b]	ATA Atezolizumab pharmacokinetics Biomarkers [b]
120±30 days after last dose of atezolizumab	At visit	—	ATA Atezolizumab pharmacokinetics Biomarkers [b]
Any time point during the study (RCR consent required)		Optional RCR blood (DNA extraction) [b]	Optional RCR blood (DNA extraction) [b]

ATA=anti-therapeutic antibody; RCR=Roche Clinical Repository.

[a] Whole blood for biomarkers.

[b] Plasma and serum for biomarkers.

ADME properties of atezolizumab

Atezolizumab is administered as an IV infusion. There have been no clinical studies performed with other routes of administration. A popPK analysis indicates that V1 is 3.28 L and Vss is 6.91 L in the typical patient, and that the typical CL of atezolizumab was 0.200 L/day and the typical terminal t1/2 was 27 days. An NCA indicates that doses ≥ 1 mg/kg display dose proportional pharmacokinetics.

Phamacokinetics in the target population

The descriptive statistics of the available, C_{max} (30 minutes following the end of the infusion) and C_{min} (pre-dose) serum concentrations of atezolizumab following 1200 mg q3w IV administration are summarized in Table 3. Of the 286 patients treated with atezolizumab, a total of 284 (99%) were evaluable for atezolizumab pharmacokinetics. Mean serum atezolizumab concentrations over time are shown in Figure . The PK results observed in IMpower110 are consistent with the known PK of atezolizumab.

Table 3 Summary Statistics for Atezolizumab Cmax and Cmin Following Multiple IV Doses of Atezolizumab 1200 mg, Administered Every 3 Weeks

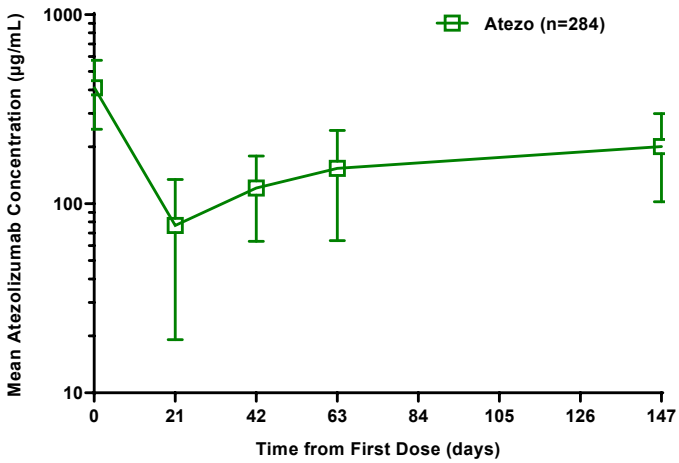
Atezo N=284									
Visit[1]	Nominal Time from First Dose (Day)	N	AM (µg/mL)	AM SD (µg/mL)	GM (µg/mL)	GM %CV	Min (µg/mL)	Median (µg/mL)	Max (µg/mL)
Cycle 1 Predose C1D1	0	262	NR	NR	NE	NR	NR	0.00	0.00
Cycle 1C_{max}/ C1D1	0.0625	270	411	163	274	614	0.0300	403	1510
Cycle 1 C_{min}/ Predose C2D1	21	256	76.7	57.6	56.4	175	0.0300	72.1	604
Cycle 2 C_{min}/ Predose C3D1	42	215	121	57.7	106	71.0	1.17	122	560
Cycle 3 C_{min}/ Predose C4D1	63	207	154	90.1	128	97.4	0.0678	144	844
Cycle 7 C_{min}/ Predose C8D1	147	145	201	98.6	178	54.5	24.5	191	670

AM = Arithmetic Mean; C_{max} = maximum serum concentration; C_{min} = minimum serum concentration; CV = coefficient of variation; GM = Geometric Mean; IV = intravenous; Max=maximum; Min = minimum; N = number of patients included in summary statistics; SD=standard deviation; NE = Not Evaluable; NR = Not Reported.

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

Data source: CSR IMpower110, Table 37.

Figure 1 Mean (±SD) Plot of Atezolizumab Concentrations versus Time Following Multiple IV Doses of Atezolizumab 1200 mg



Atezo=atezolizumab; SD=standard deviation.

Data source: CSR IMpower110, Figure 16.

Population PK analysis

Population PK analysis was performed using nonlinear mixed effect (NLME) modeling in NONMEM, V7.3. Perl-Speak-NONMEM V4.8.1 was used for model evaluation and covariate analysis. Dataset preparation; exploration and visualization of the data as well as descriptive statistics were performed using R® V3.4.3 in addition to CRAN packages.

The Phase I popPK model was subjected to an external evaluation using pharmacokinetic data collected in Phase III clinical Study GO29431 (IMpower110) to assess atezolizumab PK in NSCLC patients receiving intravenous administration of atezolizumab 1200 mg every three weeks (q3w) in monotherapy. Bayesian post-hoc estimation (MAXEVAL=0) in NONMEM with no fit of IMpower110 data.

The Phase I popPK model was built on Phase I data from 2 clinical studies: Study PCD4989g in patients with various solid tumors (including NSCLC, SCLC and mUC) and Study JO28944 in Japanese patients with advanced solid tumors. The Phase I popPK model had earlier been subject to external validations by prediction-corrected visual predictive check (pcVPC) for urothelial carcinoma, NSCLC, extensive stage-small cell lung cancer and triple negative breast cancer separately, using PK data collected in studies: IMvigor210 and IMvigor211 for UC; BIRCH, POPLAR, FIR, OAK, IMpower150 and IMpower130 for NSCLC; IMpower133 for ES-SCLC and IMpassion130 for TNBC.

Table 4: PK sampling for study GO29431 (IMpower110)

Study Visit	Time	Arm A
Cycle 1, Day 1	Pre-dose	Atezolizumab ADA Atezolizumab pharmacokinetics
	30 min (± 10 min) after end of atezolizumab infusion	Atezolizumab pharmacokinetics
Cycles 2, 3, 4, 8, and 16, Day 1	Pre-dose	Atezolizumab ADA Atezolizumab pharmacokinetics
Cycle 16, and every eighth cycle thereafter Day 1	Pre-dose (same day as treatment administration)	Atezolizumab ADA Atezolizumab pharmacokinetics
Treatment discontinuation visit [a]	At visit	Atezolizumab ADA Atezolizumab pharmacokinetics
120 ± 30 days after last dose of atezolizumab	At visit	Atezolizumab ADA Atezolizumab pharmacokinetics

ADA= anti-drug antibody.

PK data in IMpower110 were sparse with a limited number of peak samples (Cycle 1) and a large number of trough levels. The Phase I popPK model was used to derive individual PK parameter estimates based on 1306 atezolizumab serum concentrations from 283 patients. A total of 37 PK samples were excluded for various reasons.

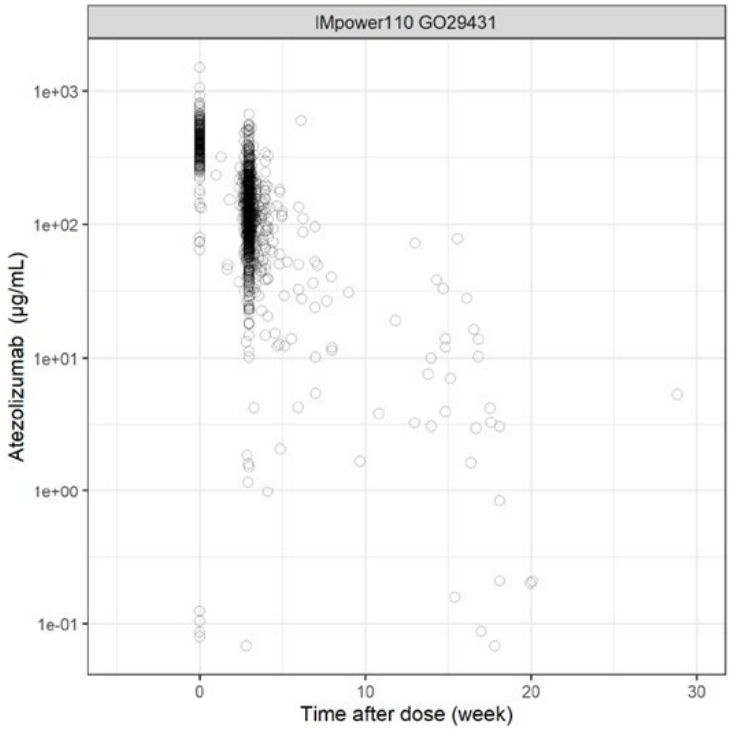


Figure 2: Graphical exploration of atezolizumab concentration data in Impower110

No patient had any covariate identified in the Phase I popPK model missing in the current dataset, except for 17 patients with missing ADA status which were imputed to the most frequent category, i.e., ADA negative.

Comparison to the PK population used to inform the Phase I popPK model for the covariates retained in the model (BW, albumin, ADA, tumor burden, sex), the current population in IMpower110 had: slightly lower weight (median 70 vs. 77 kg), higher tumor burden (median 80 vs. 63 mm), similar albumin (median 40 vs. 40 g/L), higher proportion of males (69% vs. 59%), and lower proportion of patients with positive ADA (23% vs. 29%).

Covariate effects (Phase 1 popPK model):

According to the Phase I popPK Model, the typical clearance (CL) (L/day) of atezolizumab for patient *i* was:

$$\mathrm{CL}_i = \left(0.200 \cdot \left(\frac{ALBU_i}{40}\right)^{-1.12} \cdot \left(\frac{BWT_i}{77}\right)^{0.808} \cdot \left(\frac{Tumor\ burden_i}{63}\right)^{0.125}\right) \cdot (1.159\ \ if\ ADA\ is\ positive)$$

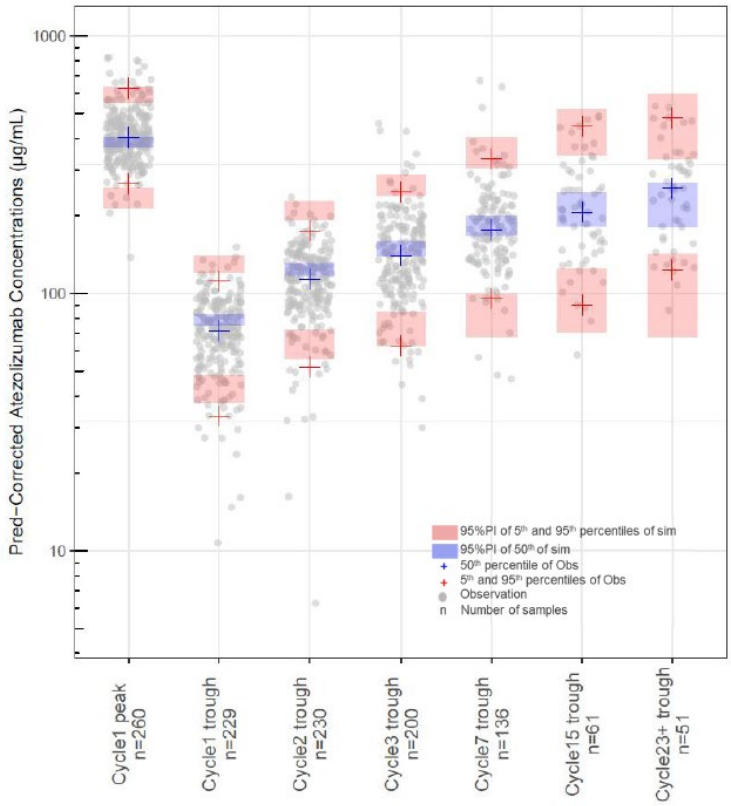
BWT = Body weight (kg); ALBU = Albumin (g/L); Tumor burden (mm); ADA = Post-baseline status of anti-drug (ATAG) antibodies, also called anti-therapeutic antibodies;
Post-baseline Negative ADA when at all post-dose samples after baseline or ADA signal not enhanced after baseline (treatment unaffected);
Post-baseline Positive ADA when treatment-induced or treatment enhanced;
Missing when all post-dose samples missing.

The typical volumes of distribution of the central compartment (V1) (L) and the peripheral compartment (V2) (L) of atezolizumab for patient *i* were:

$$V1_i = \left(3.28 \cdot \left(\frac{BWT_i}{77}\right)^{0.559} \cdot \left(\frac{ALBU_i}{40}\right)^{-0.350}\right) \cdot (0.871\ if\ female)$$

$$V2_i = 3.63 \cdot (0.728\ if\ female)$$

The performance of the Phase I popPK model to predict IMpower110 data was evaluated using diagnostic GoF plots and evaluated by external pcVPC based on 1000 replicates.



PI=prediction interval; VPC=visual prediction check.

Figure 3: Prediction-corrected VPC of peaks and troughs of atezolizumab (all patients, semi-log scale)

In the pcVPC (Figure 3) there is a trend toward over-prediction of atezolizumab exposure data for Cycle 1 and Cycle 2 Cmin with observations below the prediction intervals, while the Cmin at later cycles are better predicted. The GoF plots did not indicate any trends or misspecifications.

VPCs were performed by simulating 90% PIs of the concentration-time profiles over 50 weeks and concentration versus time-after-dose (Cycle 5 and later) profiles, across 100 replicates and compared to observed concentrations in Appendix 9. The observed concentrations are well within the model prediction intervals including the late data collected (45 weeks after treatment start).

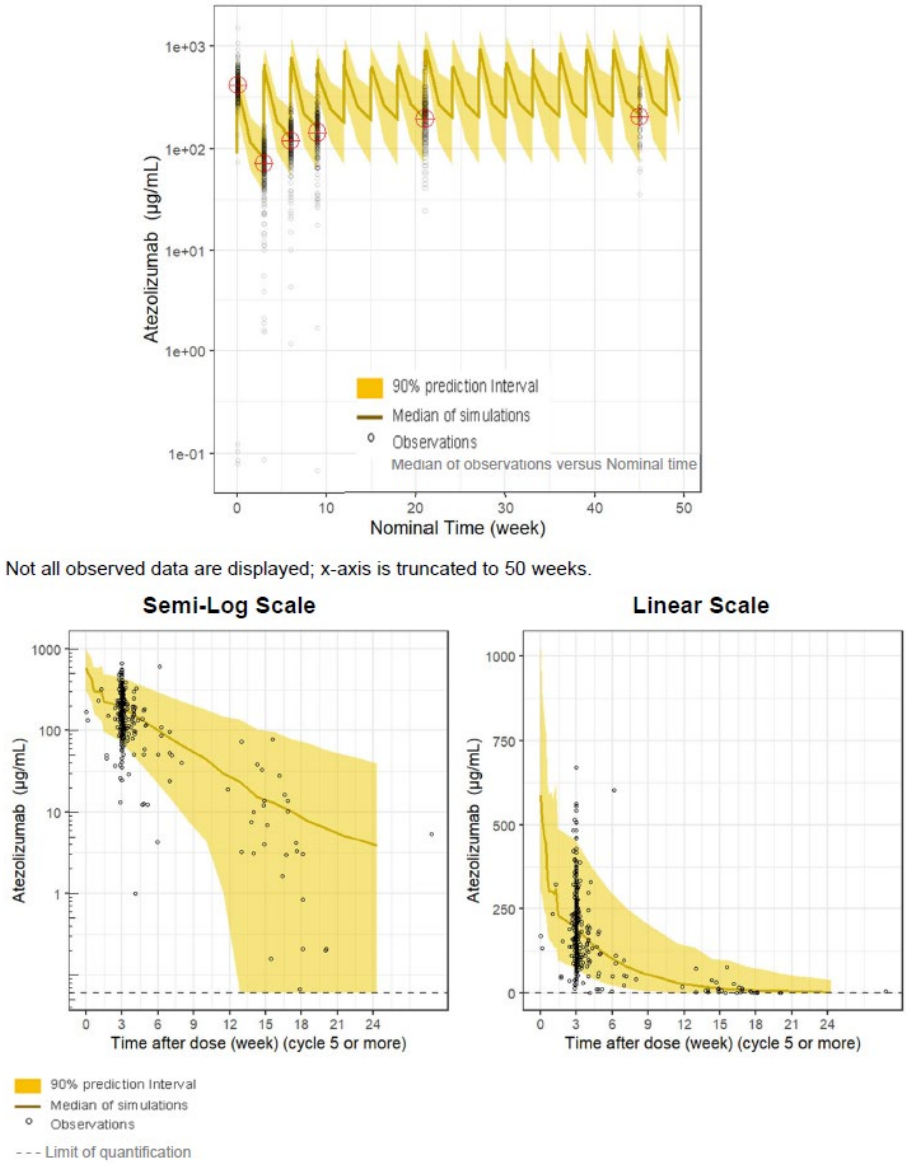


Figure 4: 90% prediction interval of the PK profile using the Phase I PopPK model with IMpower110 observed concentrations

Individual estimates of patient-level random effects were plotted vs. baseline covariates to assess whether the Phase I popPK model adequately captured covariate effects in IMpower110 patients. The explorative covariate analysis did not identify any unexpected covariate effects. The lack of trends indicated the relationships already enclosed in the model adequately described Impower100.

Predicted exposure metrics

It has been described that atezolizumab CL tended to decrease over time, with a decrease in CL associated with best overall response, generating a confounded relationship between steady-state exposure and response. Therefore, exposure metrics were estimated with Cycle 1 PK data only, to minimize the confounding due to time-varying clearance in relation with the response.

The exposure metrics for atezolizumab were derived by prediction based on the individual PK parameters. Table 5 provides the summary of the individual exposure metrics at Cycle 1 and at steady-state, respectively, based on Cycle 1 PK data and the Phase I popPK model. Steady-state exposure was assessed at 10 cycles.

Table 5: Summary statistics (Geometric mean [CV%]) of atezolizumab exposure metrics at cycle 1 and steady state, half-life and accumulation ratio in IMpower110 predicted using the phase I PopPK model

IMpower110 (N=283)			
C_{max} (µg/mL)	C_{min} (µg/mL)	AUC_{0-21} (µg.day/mL)	$t_{1/2}$ beta (day)
397.1 [18.8]	72.9 [37.8]	2912 [21.6]	21.6 [35.3]
$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)	$AUC_{,ss}$ (µg.day/mL)	Accumulation ratio
563 [23.9]	153 [61.1]	5384 [38.2]	1.85 [19.8]

N = Number of patients; C_{max} = C_{max} at Cycle 1; C_{min} = C_{min} at Cycle 1; AUC_{0-21} = $AUC_{(0-21)}$ at Cycle 1; CV% = coefficient of variation; $C_{max,ss}$ = C_{max} at steady-state; $C_{min,ss}$ = C_{min} at steady-state; AUC_{ss} = AUC at steady-state; accumulation ratio is derived as the ratio between AUC and $AUC_{,ss}$; $t_{1/2}$ beta is the terminal half-life.

The geometric mean accumulation ratio based on AUC was close to 1.85-fold. Cmin and Cmax accumulated 1.42 and 2.10-fold (geometric means), respectively.

All PK data from IMpower110 (not just PK data from Cycle 1) were used to assess (external validation) the Phase I popPK model. Cycle 1 data was used only to derive individual exposure metrics. As a sensitivity analysis, exposure metrics were derived using all PK data with the Phase I popPK model. The results are given below in Table 6, for comparison to those previously reported in Table 5 of the popPK Report No. 1098051, which are based on Cycle 1 data only.

Table 6: Summary statistics (Geometric mean [CV%]) of atezolizumab exposure metrics at cycle 1 and steady state, half-life and accumulation ratio in IMpower110 predicted using the phase I PopPK model and all PK data

IMpower110 (N=283)			
C_{max} (µg/mL)	C_{min} (µg/mL)	AUC_{0-21} (µg.day/mL)	$t_{1/2}$ beta (day)
398.1 [19.5] *0.3%*	73.1 [37.7] *0.3%*	2928 [22.4] *0.6%*	22.1 [40.4]
$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)	$AUC_{,ss}$ (µg.day/mL)	Accumulation ratio
569 [24.7] *1.1%*	157 [61.9] *2.6%*	5486 [39.7] *1.9%*	1.87 [23.0]

N = Number of patients; C_{max} = C_{max} at Cycle 1; C_{min} = C_{min} at Cycle 1; AUC_{0-21} = $AUC_{(0-21)}$ at Cycle 1; CV% = coefficient of variation; $C_{max,ss}$ = C_{max} at steady-state; $C_{min,ss}$ = C_{min} at steady-state; AUC_{ss} = AUC at steady-state; accumulation ratio is derived as the ratio between AUC and $AUC_{,ss}$; $t_{1/2}$ beta is the terminal half-life.
Italic: difference from estimates with Cycle 1 data.

Both Cycle 1 and steady-state exposure metrics were similar to those estimated in other studies using atezolizumab monotherapy q3w in both second, third-line NSCLC or mUC, in combination therapy in first-line NSCLC and in small cell lung cancer. See Table 7.

Table 7: Summary statistics (Geometric mean [CV%]) of atezolizumab exposure metrics at cycle 1 and steady state predicted using PopPK model in NSCLC, mUC and SCLC studies

	Geometric Mean (Geometric Mean [CV%])			
Study (N)	**C_{max} (µg/mL)**	**C_{min} (µg/mL)**	**AUC (µg.day/mL)**	**$t_{1/2}$ beta (day)**
BIRCH (N=652)[3]	402 [20.6]	77.6 [34.9]	3039 [22.0]	21.5 [7.72] [a]
FIR (N=128) [3]	391 [19.6]	68.9 [44.4]	2855 [23.1]	19.6 [8.35] [a]
POPLAR (N=140)[3]	355 [17.9]	63.1 [34.0]	2599 [20.5]	19.8 [7.06] [a]
OAK (N=596) [4]	396 [22.8]	74.6 [43.3]	2978 [26.1]	22.2 [8.02] [a]
BIRCH cohort 1 (N=138) (1L)[3]	412 [21.3]	78.8 [36.8]	3113 [23.7]	21.2 [6.65] [a]
BIRCH cohort 2 (N=263) (2L)[3]	395 [20]	75.6 [35.6]	2979 [21.9]	21.2 [6.75] [a]
BIRCH cohort 3 (N=251) (3L)[3]	404 [20.7]	79 [33.1]	3061 [21]	21.9 [6.37] [a]
IMvigor210 N=117 [cohort 1] [5]	370 [17.8]	71.1 [32.9]	2850 [18.8]	22.5 [7.5] [a]
IMvigor210 N=306 [cohort 2] [5]	355 [17.8]	69.1 [28.9]	2728 [19.1]	21.7 [6.6] [a]
IMvigor211 (N= 455) [6]	367 [19.5]	64.6 [49.5]	2762 [20.4]	19.8 [7.2] [a]
IMpower150 (N=778) [7]	393 [20.7]	77.1 [32.6]	2980 [21.6]	22.9 [8.23]
IMpower150, Atezo+CP Arm (N=395) [7]	388 [21.2]	75.0 [35.7]	2930 [22.7]	22.3 [7.42]
IMpower150, Atezo+Bev+CP Arm (N=388) [7]	398 [20.2]	79.4 [29.0]	3030 [20.3]	23.5 [8.69]
IMpower133, Atezo+CE Arm (N = 192) [9]	391 [19.5] [b]	76.7 [28.0] [b]	2958 [19.6] [b]	21.9 [5.0] [b]
IMpower110, (N=283)	397 [18.8] [b]	72.9 [37.8] [b]	2912 [21.6] [b]	21.6 [35.3] [b]

	Geometric Mean (Geometric Mean [CV%])			
Study (N)	**$C_{max,ss}$ (µg/mL)**	**$C_{min,ss}$ (µg/mL)**	**$AUC_{,ss}$ (µg.day/mL)**	**Accumulation ratio**
BIRCH (N=652) [3]	582 [24.9]	170 [51.8]	5770 [35.4]	1.90 [17.9]
FIR (N=128) [3]	550 [25.8]	145 [64.7]	5199 [41.3]	1.82 [21.6]
POPLAR (N=140) [3]	492 [22.7]	129 [54.6]	4636 [35.4]	1.78 [19.1]
OAK (N=596) [4]	570 [27.9]	162 [61.2]	5573 [38.7]	1.87 [21.2]
BIRCH cohort 1 (N=138) (1L) [3]	597 [26.5]	174 [57.4]	5916 [38.1]	1.90 [18.4]
BIRCH cohort 2 (N=263) (2L) [3]	570 [25.1]	165 [55.1]	5630 [37.0]	1.89 [18.7]
BIRCH cohort 3 (N=251) (3L) [3]	586 [23.7]	174 [45.0]	5840 [32.1]	1.91 [16.7]
IMvigor210 N=117 [cohort 1] [5]	544 [22.3]	165 [48.4]	5528 [33.2]	1.94 [18.1]
IMvigor210 N=306 [cohort 2] [5]	513 [22.5]	150 [47.3]	5133 [32.9]	1.88 [17.5]
IMvigor211 (N= 455) [6]	520 [22.6]	142 [53.9]	5018 [34.0]	1.82 [19.0]
IMpower150 (N=778) [7]	578 [24.7]	176 [50.1]	5860 [34.8]	1.97 [18.7]
IMpower150, Atezo+CP Arm (N=395) [7]	567 [25.9]	169 [54.9]	5700 [37.0]	1.94 [19.1]
IMpower150, Atezo+Bev+CP Arm (N=388) [7]	590 [23.3]	184 [44.4]	6040 [32.0]	1.99 [18.2]
IMpower133, Atezo+CE Arm (N=192) [9]	561 [23.6] [b]	165 [41.1] [b]	5556 [30.6] [b]	1.87 [14.1] [b]
IMpower110, (N=283)	563 [23.9] [b]	153 [61.1] [b]	5384 [38.2] [b]	1.85 [19.8] [b]

N = Number of patients; C_{max} = C_{max} at Cycle 1; C_{min} = C_{min} at Cycle 1; AUC= $AUC_{(0-21)}$ at Cycle 1; CV = coefficient of variation; $C_{max,ss}$ = C_{max} at steady-state; $C_{min,ss}$ = C_{min} at steady-state; $AUC_{,ss}$ = AUC at steady-state; Accumulation ratio is derived as the ratio between AUC at Cycle 1 and $AUC_{,ss}$. t1/2 beta is the terminal half-life;

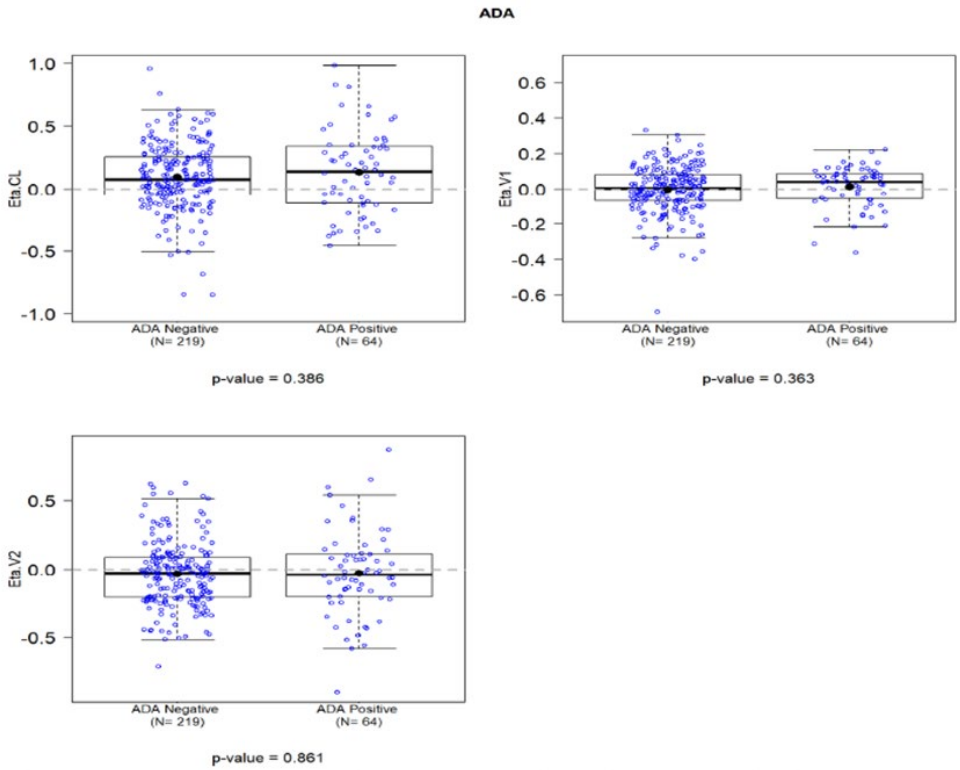
[a] For these studies harmonic mean and pseudo-standard deviation are reported; Atezo + CP= Atezolizumab + carboplatin + paclitaxel; Atezo + Bev + CP= Atezolizumab +bevacizumab + carboplatin + paclitaxel; Atezo Atezo+CE= Atezolizumab+carboplatin+etoposide

[b] For IMpower133 and IMpower110, individual PK parameters used for the predictions of exposures, were estimated on Cycle 1 PK data only while for the other studies, the individual PK parameters were estimated on all PK data.

Implications of ADA status in IMpower110

All atezolizumab ADA responses were treatment-induced ADA responses. In the IMpower110 PK population, 202 patients were ADA negative, 65 patients were ADA positive and 17 patients were missing ADA status. The 17 patients with missing ADA status were imputed to the most frequent category, i.e., ADA negative in the Pop PK analysis.

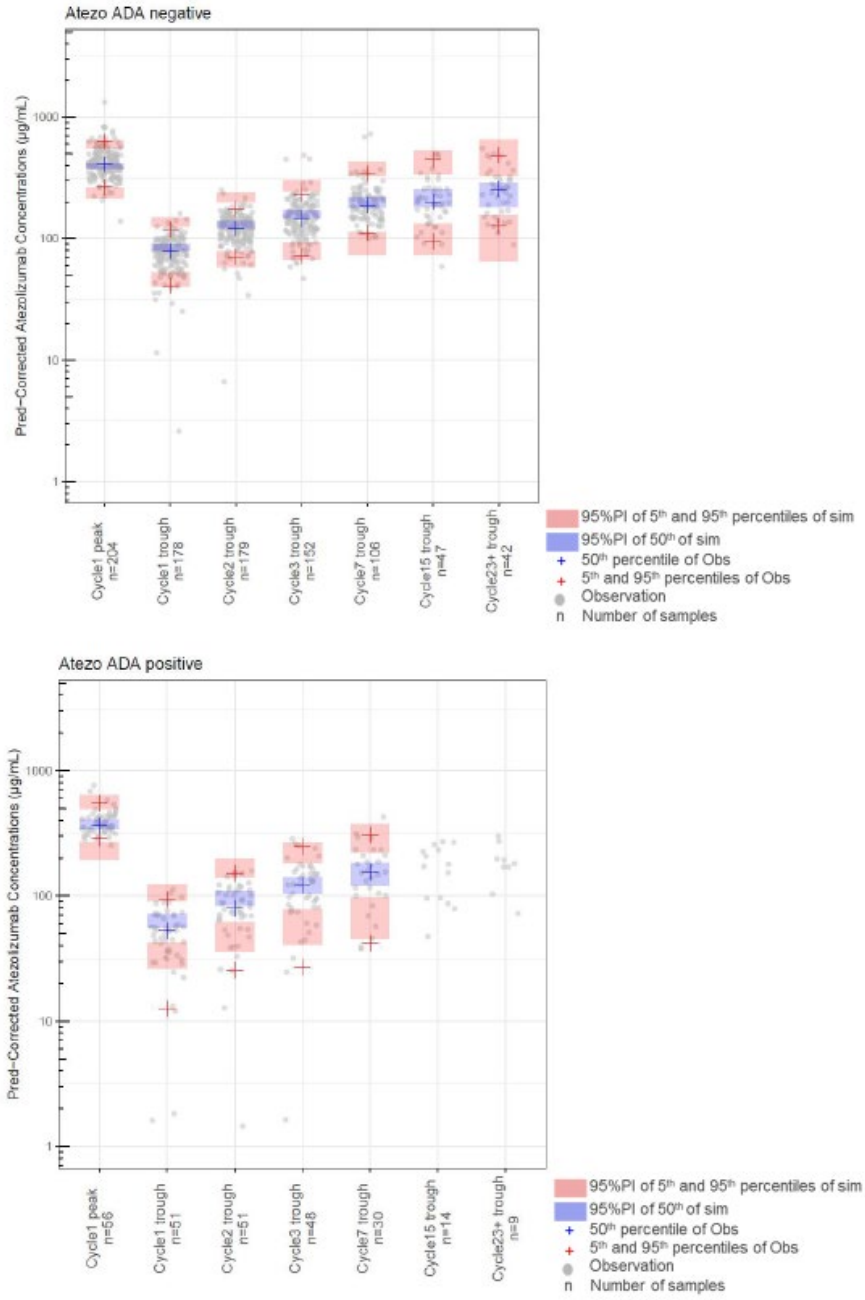
According to the Phase 1 popPK model, patients with positive ADA, clearance was estimated to be 16% higher than in patients with negative ADA. Appendix 14 show the correlation of random effects and ADA status.



Eta.CL = random effect on clearance; Eta.V1 = random effect on central volume of distribution; Eta.V2 = random effect on peripheral volume of distribution; N = number of patients.

Figure 5: Exploratory correlation between random effects and covariates for the Phase I population PK model of atezolizumab – Impower110

The fit of IMpower110 data stratified by ADA status was evaluated by pc-VPC (Appendix 7). For ADA positive patients, the number of PK concentrations was limited but the model was able to describe the atezolizumab median and 95th percentile for the long-term exposure, while there was a trend to over-predict the Cmin at early timepoints (Cycle 1 and Cycle 2).



PI=prediction interval; VPC=visual prediction check

Figure 6: Prediction-corrected VPC of peaks and troughs of atezolizumab by ADA status (Semi-log scale)

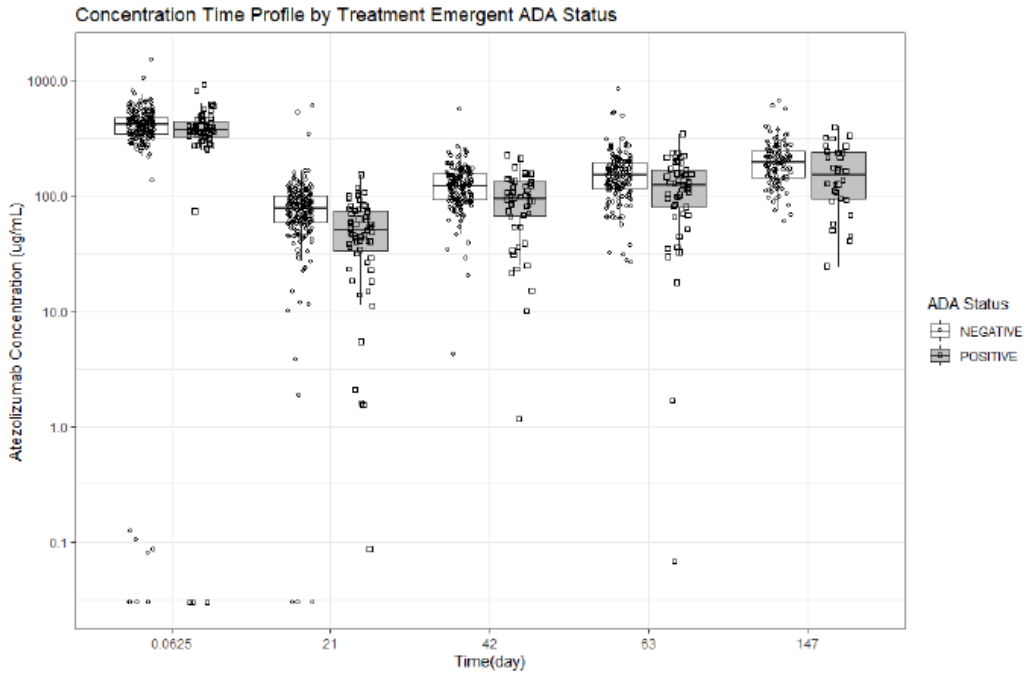
A statistical t-test showed that ADA positive patients (N=64) tend to experience lower atezolizumab exposure than ADA negative patients (N=219). Exposure by ADA status was presented in Table 8, for the geometric mean. There was a significant difference ($p<0.001$) between atezolizumab clearance in ADA positive patients and ADA negative patients. A similar difference between ADA positive and ADA negative patients was also observed for exposure metrics Cmin and AUC0-21 with lower exposure in ADA positive patients compared to ADA negative patients, less pronounced for Cmax.

Table 8 Summary Statistics (Geometric Mean [CV%]) and t-test on Atezolizumab Clearance and Exposure Metrics by ADA Status

Variable (unit)	ADA Negative N=219	ADA Positive N=64	p-value	Ratio 95%CI
Clearance (L/d)	0.206 [33.2]	0.292 [40.7]	4.87E-09	0.707 (0.635,0.786)
C_{max}, Cycle 1 (µg/mL)	401 [18.7]	384 [18.7]	1.07E-01	1.04 (0.991,1.1)
C_{min}, Cycle 1 (µg/mL)	78.5 [29.7]	56.6 [49.9]	1.3E-06	1.39 (1.22,1.57)
AUC_{0-21}, Cycle 1 (µg.day/mL)	3016 [19.3]	2583 [24.4]	8.24E-06	1.17 (1.09,1.25)

C_{min} = Individual model-predicted minimum atezolizumab concentration at Cycle 1;
C_{max}=Individual model-predicted maximum atezolizumab concentration at Cycle 1;
AUC_{0-21} = Area under the curve from 0 to 21 days at Cycle 1; CV = coefficient of variation;
CI=confidence interval, the 95% CI for difference/ratio and t–test.
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.
N= number of patients in each ADA status group in the popPK population.

However, the distributions of exposure in ADA-negative and ADA-positive patients overlaps (Figure 7), and the vast majority of patients had Cmin above the target exposure of 6 µg/mL, regardless of ADA status.



ADA=anti-drug antibody.
Data source: CSR IMpower110, Figure 19.

Figure 7: Box plots of Atezolizumab Concentrations versus Time by Treatment-Emergent ADA Status Following Multiple IV Doses of Atezolizumab

Examination of baseline characteristics by ADA status revealed several imbalances in known 1L NSCLC prognostic factors between the ADA-positive and ADA-negative patient subgroups. These imbalances between ADA subgroups were seen in both the ADA-evaluable population and the TC3 or IC3 WT ADA evaluable population. A greater imbalance in negative prognostic factors in the ADA-positive subgroup compared with the ADA-negative subgroup for both populations is noted, suggesting poorer prognosis for ADA-positive patients.

No formal E-R analysis was conducted for IMpower110. However, in unadjusted exploratory analyses, which did not take into account the imbalances in baseline characteristics between ADA subgroups, for both PFS and OS, the percentage of patients with events was numerically higher for ADA-positive patients, and the median time to event was shorter (Table 9). The proportion of responders was numerically lower in the ADA-positive subgroup compared with ADA-negative.

Table 9: Efficacy Results by Treatment-Emergent ADA status in the TC3 or IC3-WT population

	Atezolizumab Arm		Control
Efficacy Endpoint	**ADA– (N=75)**	**ADA+ (N=23)**	
OS			
Patients with event (%)	39 (52.0%)	17 (73.9%)	60 (65.2%)
Median time to event – months (95% CI)	27.1 (20.2, NE)	13.8 (4.9, 23.1)	14.7 (7.4, 17.7)
PFS: INV-assessed			
Patients with event (%)	42 (56.0%)	18 (78.3%)	57 (58.2%)
Median time to event – months (95% CI)	9.6 (7.7, 17.5)	4.5 (2.3, 8.2)	5.0 (4.2, 5.7)
Confirmed ORR			
Responders (%)	34 (45.3%)	7 (30.4%)	28 (28.6%)
95% CI for response rates	(33.79, 57.25)	(13.21, 52.92)	(19.9, 38.58)

Blue: OS data is per CCOD of 4FEB2020 and ADA status is per CCOD of 10SEP2018.
Yellow: PFS, and ORR by Atezolizumab ADA Status, Atezolizumab ADA Evaluable Patients in the TC3 or IC3-WT Population (primary analysis))

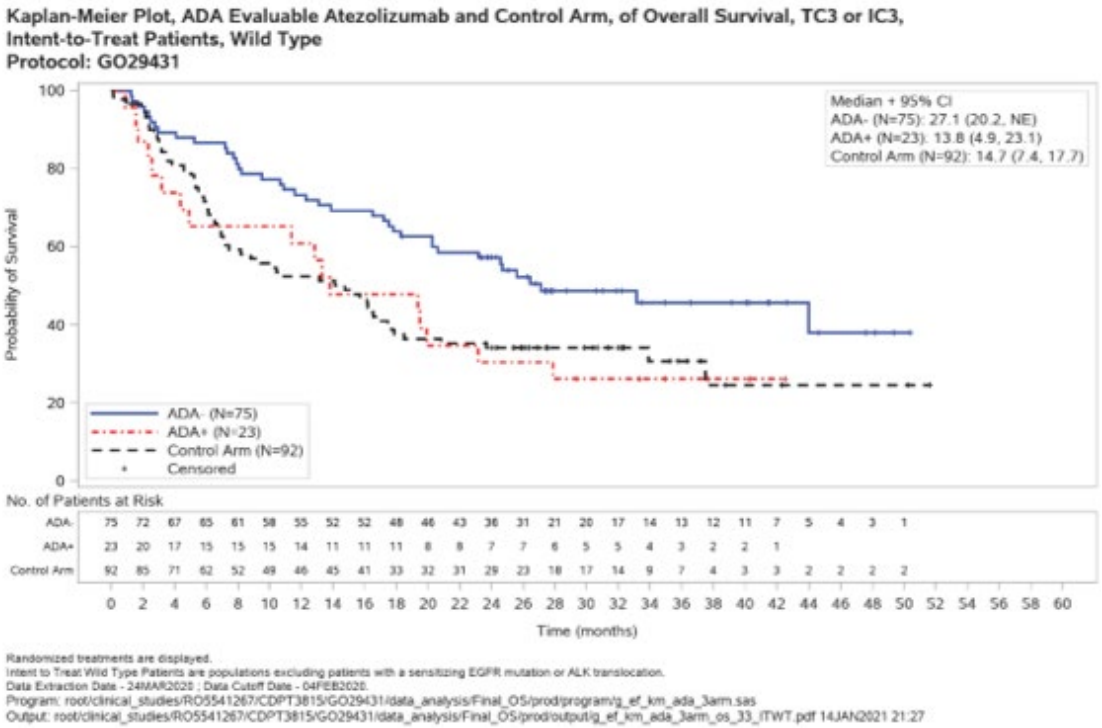


Figure 8: Kaplan-Meier plot of updated overall survival by treatment-emergent ADA status in the TC3 or IC3-WT population

Among ADA-evaluable patients in the safety evaluable population, ADA-negative and ADA-positive patients received atezolizumab for a median duration of 6.8 and 4.9 months, respectively. An overview of safety by ADA status is shown in Table 10. There was a difference in Grade 3-4 AE incidence by ADA status, with 28.8% ADA-negative and 40.0% ADA-positive patients reporting Grade 3-4 AEs. SAEs were

observed at a higher frequency in ADA-positive compared with ADA-negative patients (Table 10). These SAEs were observed in few patients and were not driven by any specific PT.

Table 10: Safety summary profile by atezolizumab ADA status (ADA-evaluable atezolizumab patients in safety evaluable population)

Protocol: GO29431

	ADA- (N=202)	ADA+ (N=65)
Total number of patients with at least one adverse event	182 (90.1%)	64 (98.5%)
Total number of events	1332	473
Total number of patients with at least one		
Treatment-related AE	128 (63.4%)	41 (63.1%)
Grade 3-4 AE	58 (28.7%)	26 (40.0%)
Treatment-related Grade 3-4 AE	23 (11.4%)	11 (16.9%)
Grade 5 AE	3 (1.5%)	2 (3.1%)
Serious Adverse Event	45 (22.3%)	25 (38.5%)
Treatment-Related Serious Adverse Event	15 (7.4%)	6 (9.2%)
AE leading to atezolizumab treatment withdrawal	10 (5.0%)	5 (7.7%)
AE leading to dose modification/interruption	51 (25.2%)	20 (30.8%)

Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.
Counts in "Grade 3-4 AE" are number of patients whose highest grades of AE are 3 or 4.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

2.3.3. Pharmacodynamics

Dose rationale

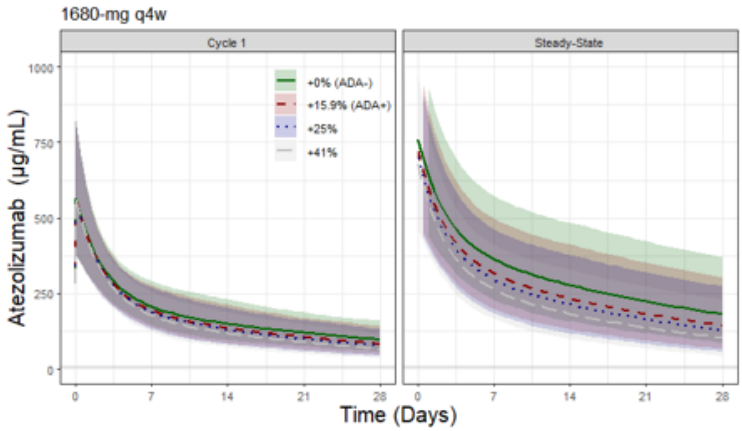
The following three dosing regimens are recommended for atezolizumab when administered as a monotherapy:

- Atezolizumab 840 mg every 2 weeks (q2w) administered intravenously; or
- Atezolizumab 1200 mg every three weeks (q3w) administered intravenously; or
- Atezolizumab 1680 mg every 4 weeks (q4w) administered intravenously.

The rationale for the 1200 mg q3w regimen was based on data from nonclinical studies and clinical data from the Phase I Study GO27831 (PCD4989g).

The rationale for the 840 mg q2w and 1680 mg q4w dosing regimens is based on PK modeling and simulation, exposure-response assessments, and safety analyses. The two dose regimens have been approved for the 2L NSCLC and mUC monotherapy indications. Data from all evaluated dose levels using a q3w dosing frequency, showed no clinically meaningful exposure-efficacy or exposure-safety relationship.

IMpower110 evaluated atezolizumab administered at a fixed dose of 1200 mg by intravenous infusion q3w as monotherapy in chemotherapy-naïve patients with Stage IV NSCLC. As the pharmacokinetics of atezolizumab in IMpower110 are consistent with observations from other studies using the 1200 mg q3w regimen (IMvigor210 and IMvigor211 for UC; BIRCH, POPLAR, FIR, OAK, IMpower150 and IMpower130 for NSCLC; IMpower133 for ES-SCLC), these results are also applicable to chemotherapy-naïve patients with Stage IV NSCLC.



Lines: geometric means, areas: 90% prediction intervals (500 patients); Horizontal grey line: 6 µg/mL target concentration

Figure 9: Superimposed simulated atezolizumab exposure profiles for 1680 mg (Geometric mean and 90%PI, 500 patients) for ADA-negative and ADA-positive patients assuming 16%, 25% or 41% increase in CL in ADA-positive patients

Table 11: Simulated atezolizumab Cmin (Geometric mean [90%PI], 500 patients) at cycle 1 and at steady-state for the 1680 mg q4w dosing regimen for ADA-negative and ADA-positive patients assuming 16%, 25% or 41% increase in CL in ADA-positive patients

	Cycle 1 [µg/mL]	Steady-State [µg/mL]
ADA negative	97 [58; 159]	182 [87; 369]
ADA positive +16%	83 [47; 141]	144 [67; 303]
ADA positive +25%	76 [43; 132]	127 [58; 274]
ADA positive +41%	66 [35; 116]	103 [45; 231]

2.3.4. Discussion on clinical pharmacology

IMpower110 evaluated the pharmacokinetics of atezolizumab monotherapy administered at a fixed dose of 1200 mg q3w given intravenously in chemotherapy-naïve patients with Stage IV NSCLC. The predicted exposure metrics in IMpower110 following 1200 mg q3w at Cycle 1 and at steady-state were within the range of exposures observed in other studies with monotherapy and a similar dosing frequency. The Applicant also seeks approval for a lower and a higher dose regimen, 840 mg q2w and 1680 mg q4w. Based on PK modelling data, the 840 mg q2w or 1680 mg q4w atezolizumab monotherapy regimens are expected to have comparable efficacy and safety with the 1200 mg q3w regimen in chemotherapy-naïve patients with Stage IV NSCLC. These alternative dose regimens for monotherapy are already approved for 2L NSCLC and mUC indications based on simulation studies only.

The time-stationary Pop PK model used to predict the Impower110 metrics was based on Phase 1 data and did not capture the confounding effect of time varying CL observed for PD-L1 inhibitors (for atezolizumab a reduction of 22% from baseline clearance) or the Ctrough after first dose in ADA-positive patients, Exposure metrics derived using Cycle 1 data only or based on all PK data gave comparable exposure estimates. The stationary Pop PK model is capable of describing all Impower110 data, including the long-term treatment data, even though clearance decrease over time.

Without correction of prognostic factors, post-hoc CL in ADA-positive patients is 41% faster in IMpower110 compared to ADA-negative patients. A sensitivity analysis including a faster clearance of 41% indicated that all exposures within a 90% CI would fall above MEC at Cycle 1 and at steady-state. Thus indicating that Cmin is adequate with a less frequent dosing in the ADA-positive subgroup of patients which typically accounts for 30% of the study population across atezolizumab indications. The

impact of ADAs on CL adjusted for the effects of baseline covariates in the Phase I popPK model was 18.5%.

Results of unadjusted exploratory analyses (Kaplan Meier Plot), which did not adjust for imbalances in baseline characteristics between ADA subgroups, showed that the subset of TC3/IC3 patients who were ADA positive appeared to have less efficacy (effect on overall survival) as compared to TC3/IC3 patients who tested negative for treatment emergent ADA. Moreover, comparison of the ADA positive vs. control in unadjusted analyses showed no meaningful differences between the two populations. However, the limited patient numbers in the TC3/IC3 subgroup is acknowledged. The incidences of ADAs and the impact on efficacy have been adequately reflected in the SmPC in the context of variation EMEA/H/C/004143/II/0030.

2.3.5. Conclusions on clinical pharmacology

Overall atezolizumab PK is sufficiently described. Based on PK modelling data, the 840 mg q2w or 1680 mg q4w atezolizumab monotherapy regimens are expected to have comparable efficacy and safety with the 1200 mg q3w regimen in chemotherapy-naïve patients with Stage IV NSCLC.

Exploratory analyses did not exclude possible attenuation of efficacy benefit in patients who developed ADA compared to patients who did not develop ADA.

2.4. Clinical efficacy

2.4.1. Dose response study

Please see section 2.3.3 Pharmacodynamics.

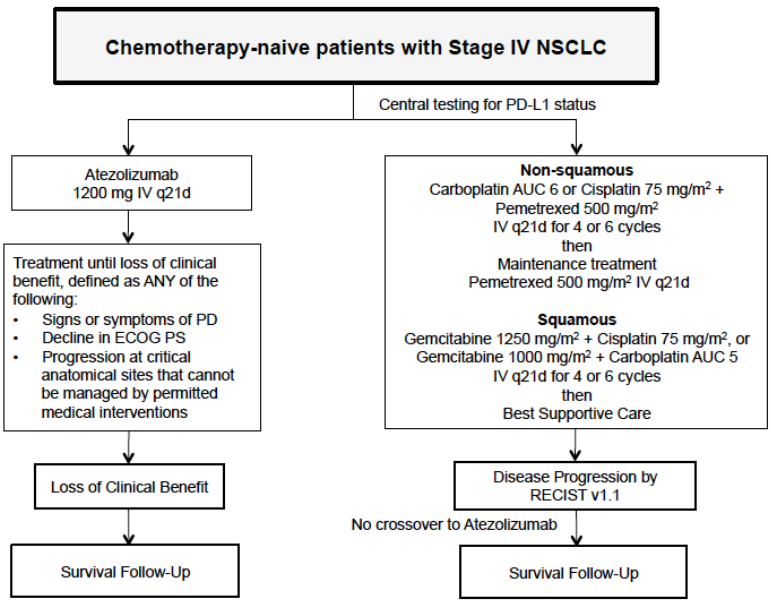
2.4.2. Main study

IMpower110: A phase III, open-label, randomized study of atezolizumab (anti-PD-L1 antibody) compared with platinum agent (cisplatin or carboplatin) in combination with either pemetrexed or gemcitabine for PD-L1-selected, chemotherapy-naive patients with stage IV non-squamous or squamous non-small cell lung cancer.

IMpower110 is a randomized, phase III, global, multicenter, open-label study designed to evaluate the safety and efficacy of atezolizumab compared with chemotherapy consisting of a platinum agent (cisplatin or carboplatin per investigator discretion) combined with either pemetrexed (non-squamous disease) or gemcitabine (squamous disease), chemotherapy-naïve patients with Stage IV NSCLC. Patients had PD-L1 expression ≥ 1% TC (PD-L1 stained ≥ 1% of tumour cells) or ≥ 1% IC (PD-L1 stained tumour-infiltrating immune cells covering ≥ 1% of the tumour area) based on the VENTANA PD-L1 (SP142) Assay.

Table 12: Summary of studies contributing to efficacy evaluation

Study Number	Study Design	Population	Number of Patients Enrolled	Dose, Route, and Regimen	Primary Efficacy Endpoint	Timing of Primary/Interim Analysis (Clinical Cutoff Date)
Pivotal Study						
GO29431 (IMpower110)	Phase III, global, randomized, open-label study	PD-L1-selected (TC1/2/3 or IC1/2/3), chemotherapy-naïve patients with Stage IV squamous or non-squamous NSCLC excluding patients with a sensitizing EGFR mutation or ALK translocation Patients were stratified by sex (male vs. female), ECOG Performance Status (0 vs. 1), histology (non-squamous vs. squamous), and PD-L1 tumor expression by IHC (TC1/2/3 and any IC vs. TC0 and IC1/2/3)	Total: N=572 Atezolizumab: n=285 Chemotherapy: n=287	**Atezolizumab:** 1200mg IV q3w **Chemotherapy:** Induction Period: Non-squamous: Pemetrexed (500mg/m^2 IV) in combination with cisplatin (75 mg/m^2 IV) or carboplatin (AUC 6 IV] q3w for 4-6 cycles Squamous: gemcitabine (1250 mg/m^2 IV) on day 1 and 8 + cisplatin on day 1 (75 mg/m^2 IV) or gemcitabine (1000 mg/m^2 IV) on day 1 and 8 + carboplatin on day 1 (AUC 5 IV) q3w for 4-6 cycles Maintenance Period: Non-squamous: Pemetrexed (500mg/m^2 IV q3w) until PD Squamous: Best supportive care	OS	**The interim analysis** of OS was planned for when an approximately 45% event-patient ratio and approximately 96 deaths were observed in the TC3 or IC3-WT population (10 September 2018)



AUC = area under the concentration–time curve; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IV = intravenous; NSCLC = non–small cell lung cancer; PD-L1 = programmed death–ligand 1; q21d = every 21 days; RECIST = Response Evaluation Criteria in Solid Tumors. Note: Gemcitabine is given on Days 1 and 8.

Figure 10: **Overview of Study Design for IMpower110**

Methods

Study participants

Key study eligibility criteria

Patients were enrolled in the study if the following key inclusion criteria were met:

- Age ≥ 18 years
- ECOG Performance Status of 0 or 1
- Histologically or cytologically confirmed, Stage IV non-squamous or squamous NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system, 7th edition)
    - Patients with tumors of mixed histology had to be classified as non-squamous or squamous based on the major histological component.
- No prior treatment for Stage IV non-squamous or squamous NSCLC
    - Patients known to have a sensitizing mutation in the EGFR gene or an ALK fusion oncogene are excluded from the study.
    - Patients with non-squamous NSCLC who had an unknown EGFR or ALK status were required to be tested at prescreening/screening. Patients with squamous NSCLC who had an unknown EGFR or ALK status were not required to be tested at prescreening/screening.
    - EGFR and/or ALK could be assessed locally or at a central lab. Additional tissue was required for central testing of EGFR and/or ALK.
- Patients who had received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months from randomization since the last chemotherapy, radiotherapy, or chemoradiotherapy cycle.
- Patients with a history of treated asymptomatic central nervous system (CNS) metastases were eligible, provided they met all of the following criteria:
    - Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla, or spinal cord)
    - No ongoing requirement for corticosteroids as therapy for CNS disease
    - No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomization
    - No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

        Patients with new asymptomatic CNS metastases detected at the screening scan must have received radiation therapy and/or surgery for CNS metastases. Following treatment, these patients could then be eligible without the need for an additional brain scan prior to randomization, if all other criteria were met.

- Tumor PD-L1 expression (TC1/2/3 or IC1/2/3; corresponding to ≥ 1% PD-L1 expressing TCs and ≥ 1% of tumor area occupied by PD-L1 expressing ICs), as determined by an IHC assay performed by a central laboratory on previously obtained archival tumor tissue or tissue obtained from a biopsy at screening.
- Measurable disease, as defined by RECIST v1.1
    - Previously irradiated lesions could only be considered measurable disease if disease progression had been unequivocally documented at that site since radiation and the previously irradiated lesion was not the only site of measurable disease

Key exclusion criteria are shown below:

- Known sensitizing mutation in the EGFR gene or ALK fusion oncogene
- Active or untreated CNS metastases as determined by computed tomography (CT) or MRI evaluation during screening and prior radiographic assessments
- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥ 2 weeks prior to randomization
- Leptomeningeal disease
- Malignancies other than NSCLC within 5 years prior to randomization, 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 (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)

Treatments

Atezolizumab treatment: atezolizumab 1200 mg iv (21-day cycles)

Chemotherapy treatment:

- Non-Squamous disease: pemetrexed 500 mg/m2 + platinum-based chemotherapy (cisplatin 75 mg/m2 or carboplatin AUC 6) (induction: four to six 21-day cycles); followed by pemetrexed 500 mg/m2 (maintenance: 21-day cycles)
- Squamous disease: gemcitabine 1250 mg/m2 + platinum-based chemotherapy (cisplatin 75 mg/m2 or carboplatin AUC 6) (induction: four to six 21-day cycles); followed by best supportive care

The intended number of cycles planned for the platinum-based induction chemotherapy (i.e., four or six cycles) was specified by the investigator prior to study randomization. Chemotherapy treatment continued until disease progression, unacceptable toxicity, or death. Given the toxicities associated with platinum-based chemotherapies (e.g., neutropenia, anemia) and the requirement for pre-medications, this was an open-label study. No crossover was allowed from the control arm (platinum-based chemotherapy) to the experimental arm (atezolizumab).

Patients who were treated with atezolizumab and who demonstrated evidence of clinical benefit were permitted to continue atezolizumab treatment after evidence of PD based on RECIST v1.1 criteria. Atezolizumab treatment continued as long as patients were experiencing clinical benefit as assessed by the investigator (i.e., in the absence of unacceptable toxicity or symptomatic deterioration attributed to

disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results [if available], and clinical status) or until unacceptable toxicity or death.

Table 4: Summary of exposure to atezolizumab for patients in the atezolizumab arm treated beyond PD (safety-evaluable population)

Study Drug Exposure After Disease Progression, Overall, Atezolizumab, Reported Disease Progression, Intent-to-Treat Patients
Protocol: GO29431

	Atezo Treated on or after First PD (N=77)
Treatment duration (months)	
n	77
Mean (SD)	2.8 (3.7)
Median	1.4
Min - Max	0 - 17
Treatment duration (months)	
n	77
0 to <= 3 months	58 (75.3%)
> 3 to <= 6 months	8 (10.4%)
> 6 to <= 12 months	8 (10.4%)
> 12 months	3 (3.9%)
Total cumulative dose (mg)	
n	77
Mean (SD)	5797.4 (6218.4)
Median	3600.0
Min - Max	1200 - 28800
Dose intensity (%)	
n	77
Mean (SD)	97.6 (6.0)
Median	100.0
Min - Max	71 - 105
Number of doses/cycles	
n	77
Mean (SD)	4.8 (5.2)
Median	3.0
Min - Max	1 - 24
Number of doses/cycles	
n	77
0 to <= 3	42 (54.5%)
> 3 to <= 6	18 (23.4%)
> 6 to <= 12	10 (13.0%)
> 12	7 (9.1%)

Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Dose intensity is the number of doses actually received divided by the expected number of doses.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Objectives

Primary Efficacy Objective

The primary efficacy objective for this study was to evaluate the efficacy of atezolizumab compared with platinum-based chemotherapy consisting of a platinum agent (cisplatin or carboplatin) in combination with either pemetrexed (non-squamous disease) or gemcitabine (squamous disease) in chemotherapy-naïve patients with Stage IV NSCLC, as measured by OS.

Secondary Efficacy Objectives

The secondary objectives for this study were as follows:

- To evaluate the efficacy of atezolizumab compared with platinum-based chemotherapy as measured by investigator-assessed PFS according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- To evaluate the efficacy of atezolizumab compared with platinum-based chemotherapy as measured by objective response rate (ORR) according to RECIST v1.1 assessed by investigator

- To evaluate the efficacy of atezolizumab as measured by investigator-assessed duration of response (DOR) according to RECIST v1.1
- To evaluate the efficacy of atezolizumab compared with platinum-based chemotherapy as measured by OS and investigator-assessed PFS according to RECIST v1.1 in patients with PD-L1 expression defined by the SP263 IHC assay
- To evaluate the efficacy of atezolizumab compared with platinum-based chemotherapy as measured by OS and investigator-assessed PFS according to RECIST v1.1 in patients with blood tumor mutational burden (bTMB)
- To evaluate the OS rate at 1- and 2-year landmark timepoints in each treatment arm
- To determine the impact of atezolizumab compared with platinum-based chemotherapy as measured by time to deterioration (TTD) and change from baseline (i.e., improvement or deterioration based on presenting symptomatology) in each of the patient-reported lung cancer symptom (cough, dyspnea, chest pain) score as assessed by the Symptoms in Lung Cancer (SILC) scale
- To determine the impact of atezolizumab compared with platinum-based chemotherapy as measured by TTD in patient-reported lung cancer symptoms of cough, dyspnea (multi-item subscale), and chest pain as measured by the European Organisation for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core (QLQ-C30) and supplementary Quality-of-Life Questionnaire Lung Cancer Module (QLQ-LC13)

Outcomes/endpoints

The primary efficacy outcome measure was OS and was analyzed in three PD-L1-selected populations: the TC3 or IC3-WT subpopulation, the TC2/3 or IC2/3-WT subpopulation and the TC1/2/3 or IC1/2/3-WT population.

As per the pre-specified analysis hierarchy and α spending algorithm, OS in the TC3 or IC3-WT population was tested first and, if this test was significant, the testing continued to the TC2/3 or IC2/3-WT population and then to the TC1/2/3 or IC1/2/3-WT population.

Table 14 Key Efficacy Endpoint Definitions in IMpower110

Endpoint	Definition
OS	Time from randomization to death from any cause
PFS-INV	Time from randomization to first documented PD, as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurred first
ORR	Proportion of patients with an objective response (either CR or PR), as determined by the investigator using RECIST v1.1
DOR	Time from first documented objective response (CR or PR) to documented PD, as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurred first

CR=complete response; DOR=duration of response; ORR=objective response rate; OS=overall survival; PD=progressive disease; PFS-INV=investigator-assessed progression-free survival; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors

Sample size

A total enrolment of approximately 555 patients was planned for this study such that approximately 64% of those enrolled would be PD-L1 TC2/3 or IC2/3 patients.

Comparisons with respect to the primary endpoint of OS between treatment arms will be tested in a hierarchical fashion for the following populations: TC3 or IC3-wild type (WT), TC2/3 or IC2/3-WT, and TC1/2/3 or IC1/2/3-WT. Estimates of the number of events required to demonstrate efficacy in terms of OS are based on the following assumptions:

- 1:1 randomization ratio
- One interim analysis of OS in the TC3 or IC3-WT, TC2/3 or IC2/3-WT, and TC1/2/3 or IC1/2/3-WT populations
- Two-sided significance level of 0.05
- 99% power to detect a HR of 0.45 for OS in the TC3 or IC3-WT subpopulation
- 85% power to detect a HR of 0.65 for OS in the TC2/3 or IC2/3-WT subpopulation, and
- 77% power to detect a HR of 0.75 for OS in the TC1/2/3 or IC1/2/3-WT population
- Median survival of 14 months in the control arm (platinum-based chemotherapy)
- Event times exponentially distributed
- Dropout rate assumed for all treatment arms of 5% per 24 months
- 37% prevalence rate for TC3 or IC3 and 59% prevalence rate for TC2/3 or IC2/3 within the TC1/2/3 or IC1/2/3 population

Randomisation

Patients with non-squamous disease were to be randomized 1:1 to receive either atezolizumab alone or pemetrexed in combination with cisplatin or carboplatin. Patients with squamous disease were to be randomized 1:1 to receive either atezolizumab alone or gemcitabine in combination with cisplatin or carboplatin. A permuted-block randomization was applied to ensure a balanced assignment to each treatment arm for the following stratification factors: Sex (male vs. female), ECOG performance status (0 vs. 1), Histology (non-squamous vs. squamous), and PD-L1 tumour expression status (TC1/2/3 and any IC vs. TC0 and IC1/2/3).

Blinding (masking)

This was an open-label study.

Statistical methods

Efficacy Analysis Populations

The randomized population or intent-to-treat (ITT) population is defined as all randomized patients, regardless of receipt of the assigned treatment. The primary efficacy endpoint, OS, will be analyzed in three PD-L1 selected populations, the TC3 or IC3-WT subpopulation, the TC2/3 or IC2/3-WT subpopulation and the TC1/2/3 or IC1/2/3-WT population. Unless otherwise indicated, the secondary efficacy endpoints will be analyzed in TC1/2/3 or IC1/2/3-WT, TC2/3 or IC2/3-WT, and/or TC3 or IC3-WT.

For efficacy analyses, patients will be grouped per the treatment that was assigned at the time of randomization regardless whether they received any assigned study drug.

PD-L1 testing used to select the target population

PD-L1 expression on TC (tumour cells) or IC (immune cells) were assessed using prospectively stained tumour specimens evaluated by external central laboratories using the VENTANA PD-L1 (SP142) IHC assay, according to a scoring algorithm measuring PD-L1 on TCs and ICs. On 19 December 2017 and 2 August 2018, Ventana Medical Systems globally recalled multiple detection kits used for ICH laboratory testing due to the leaking and sticking of reagent dispensers, which could impact staining results. Impacted lots were deployed during the course of the IMpower110 study (as a component of the investigational PD-L1 [SP142] assay) and were used to determine the PD-L1 status of a total of 103 enrolled patients (18% of all randomized patients). Available samples from enrolled patients impacted by recalled dispensers from IMpower110 were re-tested. The primary analysis populations were defined by the original PD-L1 results derived from the PD-L1 tissue slide stained at enrolment.

Table 5: Concordance – cross tabulation of PD-L1 expression: retest results compared with original testing result

		Number (%) of Patients						
		Re-Test PD-L1 Status Result						
		TC3 or IC3 (N=20)	TC2/3 or IC2/3 excluding TC3 or IC3 (N=12)	TC1/2/3 or IC1/2/3 excluding TC2/3 or IC2/3 (N=25)	TC0 and IC0 (N=14)	Not Evaluable (N=10)	Not Tested (N=22)	Total (N=103)
Original PD-L1 Status Result	TC3 or IC3	16 (80.0%)	3 (25.0%)	0	0	1 (10.0%)	2 (9.1%)	22 (21.4%)
	TC2/3 or IC2/3 excluding TC3 or IC3	4 (20.0%)	5 (41.7%)	1 (4.0%)	2 (14.3%)	2 (20.0%)	3 (13.6%)	17 (16.5%)
	TC1/2/3 or IC1/2/3 excluding TC2/3 or IC2/3	0	4 (33.3%)	24 (96.0%)	12 (85.7%)	7 (70.0%)	17 (77.3%)	64 (62.1%)
	Total	20	12	25	14	10	22	103

IC=immune cell; PD-L1=programmed-dealth ligand 1; TC=tumor cell

Source: t_pdl1_rt_cat_IMP_10Sep2018_29431

Primary endpoint

Overall survival (OS)

The primary efficacy analysis is the comparison of OS between the two treatment arms (atezolizumab arm and chemotherapy control arm). Treatment comparisons will be based on the stratified log-rank test.

For the TC3 or IC3-WT subpopulation and the TC2/3 or IC2/3-WT subpopulation, the stratification factors will be those that were used during randomization. For the TC1/2/3 or IC1/2/3-WT population, the stratification factors will be those that were used during randomization and PD-L1 tumor expression status [TC1/2/3 and any IC vs. TC0 and IC1/2/3]).

Due to the potential risk of over-stratification, if at least 1 stratum has less than 10 OS events, the stratification factor which contains the level with the smallest number of patients will be removed from the stratified analyses. The removal of the stratification factor will continue until there is no stratum with less than 10 OS events in the analysis population. Results from an unstratified analysis will also be provided.

The HR will be estimated with a stratified Cox regression model with the same stratification variables that are used in the stratified log-rank test at the interim and final analyses. The unstratified HR will also be presented.

The Kaplan-Meier methodology will be used to estimate the median OS for each treatment arm and construct survival curves for the visual description of the difference between the treatment arms. The Brookmeyer-Crowley methodology will be used to construct the 95%CI for the median OS for each treatment arm.

Censoring rules: Data for patients, who are not reported as having died at the time of the analysis, will be censored at the date when they were last known to be alive. Patients who do not have any post-baseline information will be censored at the date of randomization plus 1 day.

Sensitivity analysis of OS for NPT was based on the time interval during, which patients received NPT until the event or censoring time was discounted at 10%, 20%, and 30% for both arms to investigate how the OS results would have looked if the NPT was not available.

Secondary endpoints

Progression free survival based on the investigators' assessment (PFS-INV)

PFS-INV will be analyzed through use of the same methods described for the OS analysis.

Censoring rules: Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day.

Objective response (partial response [PR] plus complete response [CR]) as determined by the investigator (ORR)

ORR is defined as the proportion of patients who had an objective response (CR or PR). Patients not meeting these criteria, including patients without any post-baseline tumor assessments, will be considered non-responders.

The analysis of ORR will be performed for patients in the secondary efficacy analysis populations who have measurable disease at baseline.

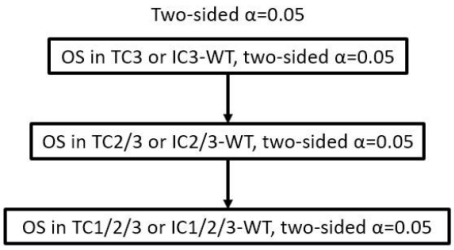
The confirmation of response in accordance with RECIST v.1.1 is not required, but for the exploratory purpose, rate of confirmed response may be reported as needed.

An estimate of ORR and its 95%CI will be calculated using the Clopper-Pearson method for each treatment arm. The 95%CIs for the difference in ORRs between the two arms will be computed using the normal approximation to the binomial distribution.

The ORR will be compared between the two arms using the stratified Cochran-Mantel-Haenszel test, stratified by the same factors used in the primary OS analysis.

Type I error control and interim analyses

The hierarchy of alpha spending is specified in Figure 11.



IC=tumor-infiltrating immune cell; OS=overall survival; TC=tumor cell; WT=wild type (i.e., excluding patients with a sensitizing epidermal growth factor receptor [*EGFR*] mutation or anaplastic lymphoma kinase [*ALK*] translocation).

Figure 11: Type I error control plan

The Sponsor plans to conduct one interim efficacy analysis for the primary endpoint of OS in the TC3 or IC3-WT, the TC2/3 or IC2/3-WT, and the TC1/2/3 or IC1/2/3-WT populations, respectively. With a lack of the final PD-L1 prevalence, to ensure the data maturity and have sufficient event-patient ratio for the evaluation of the OS benefit, an interim analysis of OS in the TC3 or IC3-WT population will be conducted when both of the following criteria have been met:

- An approximately 45% event-patient ratio has been observed in the TC3 or IC3-WT subpopulation
- Approximately 96 deaths have occurred in the TC3 or IC3-WTsubpopulation

It is expected that approximately 154 OS events would have occurred in the TC2/3 or IC2/3-WT population at the time of the interim analysis of OS in the TC3 or IC3-WT subpopulation. If the OS interim analysis in the TC3 or IC3-WT population is claimed as statistically significant, the OS analysis in the TC2/3 or IC2/3-WT population will be tested under the overall type I error of 0.05.

If there are significantly fewer than 154 OS events (i.e., <135 events) in the TC2/3 or IC2/3-WT population at the time of TC3 or IC3-WT OS interim analysis, a nominal two-sided alpha of 0.0001 (negligible impact on overall type I error rate) will be spent on the OS interim analysis in the TC2/3 or IC2/3-WT population. The next interim and final OS analysis in the TC2/3 or IC2/3-WT population will be conducted when approximately 154 and 216 events are observed, respectively. The interim and final analyses of OS in TC1/2/3 or IC1/2/3-WT would be conducted at the same time as those for the TC2/3 or IC2/3-WT population.

Boundaries will be adjusted based on observed number of OS events by using the Lan-DeMets approximation to the Pocock boundary.

Changes to the SAP

The first version (v1) of the SAP was issued on 18 April 2017 and was amended two times (v2 and v3). The key changes to the SAP are summarized below.

SAP Amendment 1, Version 2 (19 December 2018)

The following main changes were made in the SAP:

- Earlier interim analysis
- Crossing boundaries of interim and final analyses was determined by the Lan-DeMets approximation to the Pocock boundaries
- Potentially merged stratification factors in stratified analyses based on number of events in strata

In addition, exploratory analyses of tissue Tumor Mutational Burden and T-effector gene expression were removed given the correlation between blood TMB (already a secondary endpoint) and tissue TMB, and the limited biomarker value of T-effector gene expression observed in other 1L NSCLC studies in the atezolizumab clinical program.

SAP Amendment 2, Version 3 (2 April 2019)

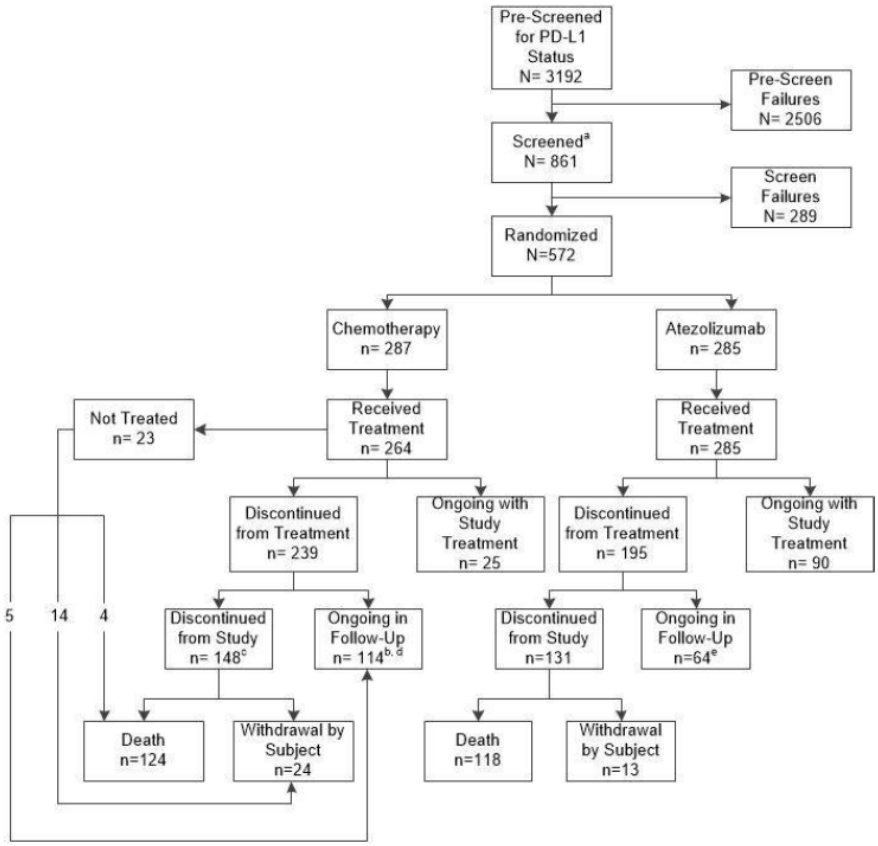
The following major changes were made in the SAP:

- The TC3 or IC3 population, excluding patients with a sensitizing EGFR mutation or ALK translocation (i.e., TC3 or IC3-WT), have been added as the first test in the hierarchy
- The timing of the efficacy analysis was updated to be when the pre-specified criteria were met for the TC3 or IC3-WT population

In addition, the cut-offs were clarified to include ≥1%, ≥25%, and ≥50% of tumor cells for the PD-L1 SP263 IHC assay and include ≥10, ≥16, and ≥20 mutations for the bTMB assay.

Results

Participant flow



[a] Pre-screening for PD-L1 status was not required prior to patients entering screening. Therefore, total number of screened patients includes patients that were not pre-screened for PD-L1 status or that were re-screened.

[b] Includes 5 patients who did not receive treatment.

[c] Includes 18 patients who did not receive treatment.

[d] Includes one patient that at the time of CCOD had survival follow up status lost to follow-up.

[e] Includes two patients that at the time of CCOD had survival follow up status lost to follow-up.

Figure 1: Patient disposition

Table 6: Patient disposition from study, ITT patients

Protocol: GO29431

	Chemotherapy (N=287)	Atezolizumab (N=285)	All Patients (N=572)
Received Treatment	264 (92.0%)	285 (100.0%)	549 (96.0%)
On-Study Status	139 (48.4%)	154 (54.0%)	293 (51.2%)
Alive: On Treatment	25 (8.7%)	90 (31.6%)	115 (20.1%)
Alive: In Follow-Up	113 (39.4%)	62 (21.8%)	175 (30.6%)
Survival Status Unknown at CCOD [a]	1 (0.3%)	2 (0.7%)	3 (0.5%)
Discontinued Study	148 (51.6%)	131 (46.0%)	279 (48.8%)
Death	124 (43.2%)	118 (41.4%)	242 (42.3%)
Withdrawal By Subject	24 (8.4%)	13 (4.6%)	37 (6.5%)

Data Extraction Date = 31AUG2018 ; Data Cutoff Date = 10SEP2018.

[a] Date of death (prior to CCOD) confirmed retrospectively by public records

Program:
root/clinical_studies/RO5541267/CDPT3815/GO29431/data_analysis/IA_10SEP2018/prod/program/t_ds.sas
Output:
root/clinical_studies/RO5541267/CDPT3815/GO29431/data_analysis/IA_10SEP2018/prod/output/t_ds_IT.out
18OCT2019 20:57

Recruitment

The IMpower110 study was fully recruited in approximately 31 months from 21 July 2015 to 21 February 2018. Median follow-up time for the targeted population (TC3/IC3-WT) was 16.5 months with atezolizumab monotherapy and 15.5 months with chemotherapy at data cut-off 10 September 2018.

Patients were recruited from 144 centers across 19 countries. The majority of centers each recruited between 1-4 patients; the 5 highest enrolling sites each recruited between 16-19 patients. The number of patients randomized per region and country, followed by the number of centers (in brackets), is summarized below in descending order.

- Europe and Middle East: Romania 54 (7), Poland 51 (5), Russia 50 (11), Italy 46 (12), Serbia 42 (5), Turkey 36 (6), Spain 35 (15), Greece 32 (12), France 27 (10), Ukraine 26 (8), Hungary 26 (4), Great Britain 13 (3), Germany 8 (2)
- Asia-Pacific: Japan 51 (16), Thailand 14 (4), Republic of Korea 11 (3), China 3 (1)
- South America: Brazil 31 (11)
- North America: United States of America 16 (9)

Conduct of the study

Protocol changes

The first version of the protocol was issued on 23 December 2014. There were also country specific protocol amendments issued for South Korea, Brazil, and China.

The key changes made to the protocol deemed important for the study conduct are summarized below:

Protocol Amendment 1, Version 2 (24 April 2015)

- Reporting for serious AEs and AESIs was extended to 90 days after last dose of study treatment or until initiation of a new anti-cancer therapy, whichever occurred first.

Protocol Amendment 2, Version 3 (5 October 2015; key changes listed)

- The study inclusion criteria were modified to allow for patients with treated, asymptomatic cerebellar metastases to be enrolled provided specific criteria were met.

- The exclusion criteria for history of autoimmune disease was broadened to allow for patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) to be permitted provided that they met the specific conditions.

- The exclusion criterion specifying that patients with a history of allergic reaction to IV contrast that requires steroid pretreatment should have baseline and subsequent tumor assessments performed via MRI was removed because this was in conflict with Section 4.5.5. Patients with contraindications to contrast could have assessments done with non-contrast CT or MRI.

- Systemic immune activation (SIA) was identified as a potential risk of atezolizumab when given in combination with other immunomodulating agents. The management recommendations regarding early identification and management of SIA were added.

Protocol Amendment 3, Version 4 (16 December 2015)

- Clarified that a wash-out period of at least 4 weeks or five half-lives, whichever was longer, of any systemic immunostimulatory agent was required prior to randomization.

Protocol Amendment 4, Version 5 (29 June 2016; key changes listed)

- Expanded the patient population to include patients with squamous NSCLC, who was randomized to receive either atezolizumab or chemotherapy consisting of a platinum agent (carboplatin or cisplatin per investigator discretion) combined with gemcitabine (in contrast to patients with non-squamous NSCLC, who received either atezolizumab or chemotherapy consisting of a platinum agent combined with pemetrexed).

- Revised the cutoff for PD-L1 expression in TCs and ICs to allow for inclusion of patients with TC1/2/3 or IC1/2/3 instead of TC3 of IC3.

- Added a co-primary endpoint of OS in addition to PFS endpoint.

- Made modifications to the statistical testing procedures.

- Stratification factors were modified to include sex (male vs. female), ECOG Performance Status (0 vs. 1), histology (non-squamous vs. squamous), and tumor tissue PD-L1 expression by IHC (TC1/2/3 and any IC vs. TC0 and IC1/2/3).

- The timing of the primary PFS analysis and the definition of end of study were updated. The primary efficacy analysis was performed when approximately 368 investigator-assessed PFS events have occurred in patients enrolled during the global enrollment phase or after the last patient has been enrolled, whichever occurred later. The study ended when approximately 425 deaths have occurred among patients enrolled during the global enrollment phase or when approximately 112 OS events have occurred in the China subpopulation, whichever occurred later.

Protocol Amendment 5, Version 6 (14 March 2017; key changes listed)

- Excluded patients with a known sensitizing EGFR mutation or ALK translocation from the study.

  This change in eligibility was made to further identify patients with NSCLC who may derive the most benefit from treatment with atezolizumab. In Study GO28915 (OAK), which investigated atezolizumab versus docetaxel as second- or third-line treatment in patients with advanced NSCLC, there was no difference in the magnitude of benefit observed in OS for atezolizumab versus docetaxel among patients with an EGFR mutation. Consistent results were observed with two PD-1 inhibitors, nivolumab and pembrolizumab in the CheckMate057 (Borghaei et al. 2015) and KEYNOTE-010 (Herbst et al. 2016) studies, respectively.

- Changed investigator-assessed PFS to a secondary endpoint and maintained OS as the primary endpoint.

> OS remains the primary endpoint since it is a well-established and robust endpoint that is generally accepted as the most objective measure of clinical benefit, and available data suggest that OS may be a more sensitive endpoint for cancer immunotherapy than PFS. For example, in Studies GO28753 (POPLAR) and GO28915 (OAK), OS in the TC1/2/3 or IC1/2/3 subgroup (subgroups based on TC and IC PD-L1 expression), was significantly improved with atezolizumab compared with docetaxel, whereas PFS was similar in the two arms. In Study GO28754 (BIRCH), the median OS observed in PD-L1-selected patients (TC2/3 or IC2/3) with advanced NSCLC who received 1L treatment with atezolizumab was favorable compared with data from platinum-based chemotherapy regimens, whereas PFS was consistent with data from platinum-based chemotherapy regimens. Because of this change, the additional PFS censoring rule for U.S. registrational purposes was removed.

- The secondary objective and outcome measure regarding independent review facility (IRF)-assessed PFS according to RECIST v1.1 have been removed.

- Made modifications to the statistical testing procedure for the primary efficacy endpoint (OS)

> The OS analysis was amended to test hierarchically in the TC2/3 or IC2/3 subpopulation and the TC1/2/3 or IC1/2/3 population, with both populations excluding patients with a sensitizing EGFR mutation or ALK translocation, at both the interim and final analysis. Evolving evidence indicates a strong treatment effect on OS in both the TC2/3 or IC2/3 subgroup and the TC1/2/3 or IC1/2/3 subgroup, with a stronger effect on the TC2/3 or IC2/3 subgroup compared with the TC1/2/3 or IC1/2/3 subgroup. In Study GO28915 (OAK), an improvement in OS was observed in the atezolizumab arm compared with the docetaxel arm in the TC2/3 or IC2/3 subgroup (HR=0.67; median OS, 16.3 vs. 10.8 months). In the TC1/2/3 or IC1/2/3 population, median OS was 15.7 months for atezolizumab versus 10.3 months for docetaxel (HR=0.74) (Barlesi et al. 2016). The total sample size and the timing of the interim and final OS analyses have been adjusted to account for the updated statistical testing procedure.

- Modified the OS interim analysis to be evaluated by the iDMC to minimize the Sponsor's access to population-level efficacy data summaries in this open-label study and ensured that any future modifications to the trial were not based on the OS interim analysis.

- The sample size was changed from 570 to 555 patients.

- The sensitivity analyses that accounted for missing data and evaluated the impact of discontinuation caused by toxicity was removed.

- Sensitivity analyses on the impact of non-protocol-specified anti-cancer therapy and the proportional hazards assumption on OS were added.

Protocol Amendment 6, Version 7 (16 April 2018; key changes listed)

- Modified the number of OS events required in the TC2/3 or tumor-infiltrating IC2/3-WT subgroup due to lower PD-L1 prevalence of TC2/3 or IC2/3-WT than the previous protocol assumption.

- Secondary endpoints to evaluate OS and PFS in patients with PD-L1 expression defined by the SP263 IHC assay and in patients with bTMB, including bTMB ≥10, and bTMB ≥16 were added. Exploratory endpoints of OS and PFS in patients with PD-L1 expression defined by the 22C3 PD-L1 IHC assay, T-effector gene expression, and/or high tumor mutational burden were specified.

Protocol Amendment 7, Version 8 (29 August 2018; key changes listed)

- Modified the timing of the interim efficacy analysis, as data external to this trial suggest that an earlier analysis can demonstrate OS benefit.

- Included the newly identified risk and associated management guidelines of immune-related nephritis for atezolizumab.

Protocol Amendment 8, Version 9 (14 March 2019; key changes listed)

-The TC3 or IC3 population excluding patients with a sensitizing EGFR mutation or ALK translocation (i.e.; TC3 or IC3-WT) was added as the first testing hierarchy. The ongoing blinded tracking of PD-L1 prevalence indicated that the prevalence of the TC3 or IC3 subgroup was higher than expected. Data from the atezolizumab 1L NSCLC Phase III Studies GO29436 and GO29437 and the second-line NSCLC Phase III Study GO28915 had shown that the TC3 or IC3 subgroup appears to derive the biggest clinical benefit. With these emerging data, this study could have adequate power for testing OS in the TC3 or IC3-WT population.

- The timing of the interim efficacy analysis was changed to be conducted when the prespecified criteria was met for the TC3 or IC3-WT population. This change was based on two factors: 1) the TC3 or IC3-WT was now the first primary patient population (see above), and 2) data external to this study suggested that the proposed event-patient ratio may be sufficient to evaluate OS benefit in this patient population, which could minimize the potential confounding effect due to the use of subsequent therapies.

- It was clarified that the Lan-DeMets approximation to the Pocock boundaries was used to determine the stopping boundaries.

- The secondary endpoints for OS and investigator-assessed PFS in patients defined by the SP263 IHC assay were being updated to include the validated PD-L1 tumor expression cutoff of ≥25% (in addition to ≥1% and ≥50%) in order to evaluate this additional PD-L1 expression level with respect to efficacy.

- The secondary endpoints for OS and investigator-assessed PFS in patients defined by the bTMB assay were being updated to include the 20 mutations cutoff (in addition to 10 and 16 mutations), in order to evaluate this additional TMB level with respect to efficacy.

- The exploratory analysis of T-effector gene expression was removed given the limited biomarker value of T-effector gene expression observed in other 1L NSCLC studies in the atezolizumab clinical program.

- The exploratory analysis of tissue tumor mutational burden (tTMB) was removed, as evolving data indicated that tTMB and bTMB (secondary endpoint) results are correlated (Gandara et al. 2018), and the missing data rate is expected to be high since tTMB testing requires a significant amount of tissue.

- It was clarified that the primary safety analyses included all treated patients, defined as randomized patients who received any amount of study treatment, regardless of EGFR/ALK and PD-L1 status.

Baseline data

Table 7: Summary of baseline demographic characteristics (TC3 or IC3-WT population)

Patient Demographics, TC3 or IC3, Intent-to-Treat Patients, Wild Type
Protocol: GO29431

	Chemotherapy (N=98)	Atezolizumab (N=107)	All Patients (N=205)
Age (years)			
n	98	107	205
Mean (SD)	64.2 (9.0)	63.3 (9.1)	63.7 (9.0)
Median	66.0	63.0	65.0
Min - Max	33 - 87	33 - 79	33 - 87
Age group (years)			
n	98	107	205
< 65	43 (43.9%)	59 (55.1%)	102 (49.8%)
>= 65	55 (56.1%)	48 (44.9%)	103 (50.2%)
Age Group (years)			
n	98	107	205
< 65	43 (43.9%)	59 (55.1%)	102 (49.8%)
65 to 74	47 (48.0%)	33 (30.8%)	80 (39.0%)
75 to 84	7 (7.1%)	15 (14.0%)	22 (10.7%)
>= 85	1 (1.0%)	0	1 (0.5%)
Sex			
n	98	107	205
Male	64 (65.3%)	79 (73.8%)	143 (69.8%)
Female	34 (34.7%)	28 (26.2%)	62 (30.2%)
Race			
n	98	107	205
Asian	15 (15.3%)	20 (18.7%)	35 (17.1%)
White	82 (83.7%)	87 (81.3%)	169 (82.4%)
Unknown	1 (1.0%)	0	1 (0.5%)
Ethnicity			
n	98	107	205
Hispanic or Latino	5 (5.1%)	9 (8.4%)	14 (6.8%)
Not Hispanic or Latino	91 (92.9%)	98 (91.6%)	189 (92.2%)
Not reported	2 (2.0%)	0	2 (1.0%)
Weight (kg) at baseline			
n	92	107	199
Mean (SD)	67.93 (14.33)	69.43 (14.99)	68.74 (14.67)
Median	66.73	69.00	68.00
Min - Max	32.9 - 98.4	39.4 - 111.0	32.9 - 111.0
Baseline ECOG per eCRF			
n	98	107	205
0	38 (38.8%)	35 (32.7%)	73 (35.6%)
1	60 (61.2%)	72 (67.3%)	132 (64.4%)
ECOG PS from IxRS			
n	98	107	205
0	38 (38.8%)	33 (30.8%)	71 (34.6%)
1	60 (61.2%)	74 (69.2%)	134 (65.4%)
Tobacco Use History			
n	98	107	205
Never	15 (15.3%)	9 (8.4%)	24 (11.7%)
Current	29 (29.6%)	20 (18.7%)	49 (23.9%)
Previous	54 (55.1%)	78 (72.9%)	132 (64.4%)

Intent to Treat Wild Type Patients are populations excluding patients with a sensitizing EGFR mutation or ALK translocation.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Demographic characteristics for the IC2/3 or TC2/3-WT population were consistent with those presented here for the TC1/2/3 or IC1/2/3-WT and the TC3 or IC3-WT populations.

Table 8: Summary of baseline disease characteristics (TC3 or IC3-WT population)

Baseline Disease Characteristics, TC3 or IC3, Intent-to-Treat Patients, Wild Type
Protocol: GO29431

	Chemotherapy (N=98)	Atezolizumab (N=107)	All Patients (N=205)
Staging at Initial Diagnosis			
n	98	107	205
STAGE IA	2 (2.0%)	3 (2.8%)	5 (2.4%)
STAGE IB	5 (5.1%)	7 (6.5%)	12 (5.9%)
STAGE IIA	4 (4.1%)	10 (9.3%)	14 (6.8%)
STAGE IIB	6 (6.1%)	2 (1.9%)	8 (3.9%)
STAGE IIIA	4 (4.1%)	8 (7.5%)	12 (5.9%)
STAGE IIIB	2 (2.0%)	2 (1.9%)	4 (2.0%)
STAGE IV	75 (76.5%)	73 (68.2%)	148 (72.2%)
Unknown	0	2 (1.9%)	2 (1.0%)
Histology at Initial Diagnosis (eCRF)			
n	98	107	205
Squamous	23 (23.5%)	27 (25.2%)	50 (24.4%)
Non-squamous	75 (76.5%)	80 (74.8%)	155 (75.6%)
Histology in Non-Squamous			
n	74	79	153
Adenocarcinoma	69 (93.2%)	74 (93.7%)	143 (93.5%)
Adenocarcinoma with Neuroendocrine Features	1 (1.4%)	1 (1.3%)	2 (1.3%)
Adenosquamous	2 (2.7%)	1 (1.3%)	3 (2.0%)
Large Cell	1 (1.4%)	2 (2.5%)	3 (2.0%)
Undifferentiated	1 (1.4%)	1 (1.3%)	2 (1.3%)
Histology in Squamous			
n	22	26	48
Squamous	21 (95.5%)	23 (88.5%)	44 (91.7%)
Adenosquamous (Predominantly Squamous)	1 (4.5%)	1 (3.8%)	2 (4.2%)
Other Mixed Histology (Predominantly Squamous)	0	2 (7.7%)	2 (4.2%)
Metastatic Disease Status			
n	98	107	205
Locally Advanced Disease	0	1 (0.9%)	1 (0.5%)
Metastatic Disease	98 (100.0%)	106 (99.1%)	204 (99.5%)
No. of Metastatic Sites at Enrollment			
n	98	107	205
Mean (SD)	3.28 (1.42)	2.93 (1.27)	3.09 (1.35)
Median	3.00	3.00	3.00
Min - Max	1.0 - 9.0	1.0 - 7.0	1.0 - 9.0
Date of 1st Diag. of Metastatic Disease to Initial Dose Admin. (Months)			
n	98	105	203
Mean (SD)	1.73 (1.25)	2.93 (6.19)	2.35 (4.57)
Median	1.48	1.64	1.54
Min - Max	0.1 - 9.9	0.1 - 50.8	0.1 - 50.8
KRAS Mutation Status			
n	98	107	205
Positive	7 (7.1%)	3 (2.8%)	10 (4.9%)
Negative	6 (6.1%)	13 (12.1%)	19 (9.3%)
Unknown	85 (86.7%)	91 (85.0%)	176 (85.9%)
EML4-ALK Rearrangement Status in Non-Squamous			
n	75	80	155
No	75 (100.0%)	80 (100.0%)	155 (100.0%)
BL Target Tumor Sum Longest Diameter			
n	98	107	205
Mean (SD)	110.84 (60.37)	97.99 (67.54)	104.13 (64.38)
Median	109.50	82.00	92.00
Min - Max	15.0 - 265.0	11.0 - 390.0	11.0 - 390.0
PD-L1 Tumor Expression by IHC (Strat Factor from IxRS)			
n	98	107	205
TC1/2/3 and any IC	73 (74.5%)	82 (76.6%)	155 (75.6%)
TC0 and IC1/2/3	25 (25.5%)	25 (23.4%)	50 (24.4%)
Liver Metastases at Baseline			
n	98	107	205
Yes	17 (17.3%)	18 (16.8%)	35 (17.1%)
No	81 (82.7%)	89 (83.2%)	170 (82.9%)
Intended Cycles at Induction Tx Period			
n	98	0	98
4 Cycles	45 (45.9%)	0	45 (45.9%)
6 Cycles	53 (54.1%)	0	53 (54.1%)

EGFR mutation = Sensitizing EGFR mutations include all EGFR activating mutations in exons 18-21.
ALK positive = ALK translocation.
Intent to Treat Wild Type Patients are populations excluding patients with a sensitizing EGFR mutation or ALK translocation.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Table 19 Baseline Disease Characteristics

	TC3 or IC3 WT		TC1/2/3 or IC1/2/3-WT	
	Chemotherapy	Atezolizumab	Chemotherapy	Atezolizumab
Liver metastases at enrollment	98	107	277	277
Yes	17 (17.3%)	18 (16.8%)	40 (14.4%)	47 (17.0%)
No	81 (82.7%)	89 (83.2%)	237 (85.6%)	230 (83.0%)
Brain metastases at enrollment*	98	107	277	277
Yes	11 (11.2%)	11 (10.3%)	26 (9.4%)	27 (9.7%)

No	87 (88.8%)	96 (89.7%)	251 (90.6%)	250 (90.3%)
Histology at Initial Diagnosis (eCRF)	98	107	277	277
Squamous	23 (23.5%)	27 (25.2%)	84 (30.3%)	85 (30.7%)
Non-squamous	75 (76.5%)	80 (74.8%)	193 (69.7%)	192 (69.3%)

*% is calculated manually.

Table 20: Summary of patients who received pemetrexed (TC3 or IC3-WT population)

Patients receiving Pemetrexed, TC3 or IC3, Intent-to-Treat Patients, Wild Type
Protocol: GO29431

	Pemetrexed Patients (N=70)
Pemetrexed received as Maintenance	
n	70
Yes	39 (55.7%)
No	31 (44.3%)

Intent to Treat Wild Type Patients are populations excluding patients with a sensitizing EGFR mutation or ALK translocation.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Numbers analysed

The ITT population consisted of 572 patients with Stage IV non-squamous or squamous NSCLC randomized into the study (287 chemotherapy vs. 285 atezolizumab). The TC1/2/3 or IC1/2/3-WT population (n=554) excluded patients whose tumours harboured sensitizing *EGFR* mutations (14 patients) or *ALK* translocations (4 patients). The targeted population for the applied indication i.e. the TC3 or IC3-WT population comprised 205 randomized patients (98 chemotherapy vs. 107 atezolizumab).

Outcomes and estimation

Primary endpoint: Overall survival

Table 9: Overall survival (TC3 or IC3-WT population)

	Interim Analysis (CCOD 10 September 2018)		Updated Analysis** (CCOD 4 February 2020)	
Parameter	Chemotherapy	Atezolizumab	Chemotherapy	Atezolizumab
Primary Endpoint: Overall Survival				
	n = 98	n = 107	n = 98	n = 107
Patients with event (%)	57 (58.2%)	44 (41.1%)	64 (65.3%)	64 (59.8%)
Median duration of survival (95% CI) (months)	13.1 (7.4, 16.5)	20.2 (16.5, NE)	14.7 (7.4, 17.7)	20.2 (17.2, 27.9)
Stratified Hazard Ratio (95% CI)	0.595 (0.398, 0.890)		0.764 (0.536, 1.087)	
p-value (Stratified log-rank)	0.0106		0.1338*	
12-month OS rate	50.6%	64.9%	52.3%	66.1%
24-month OS rate	24.8%	45.5%	34.1%	47.1%

CCOD=clinical cutoff date; CI=confidence interval; DOR=duration of response; NE=Not estimable; OS=overall survival; INV-PFS=investigator assessed-progression free survival; WT=wild-type.
* p-value is descriptive only.
** exploratory analysis for the TC3 or IC3-WT Population at this cut-off date.

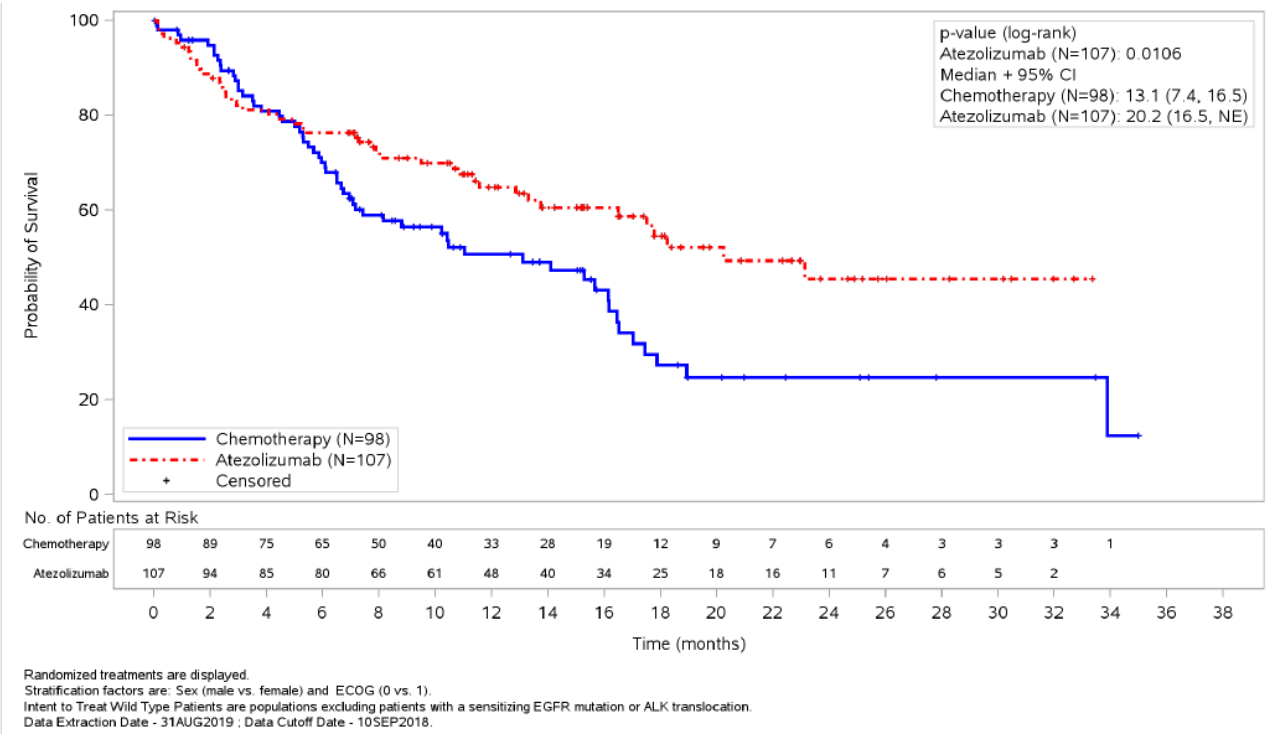


Figure 2: KM Plot of OS with Stratified Analysis (TC3 or IC3-WT Population) CCOD: 10 September 2018

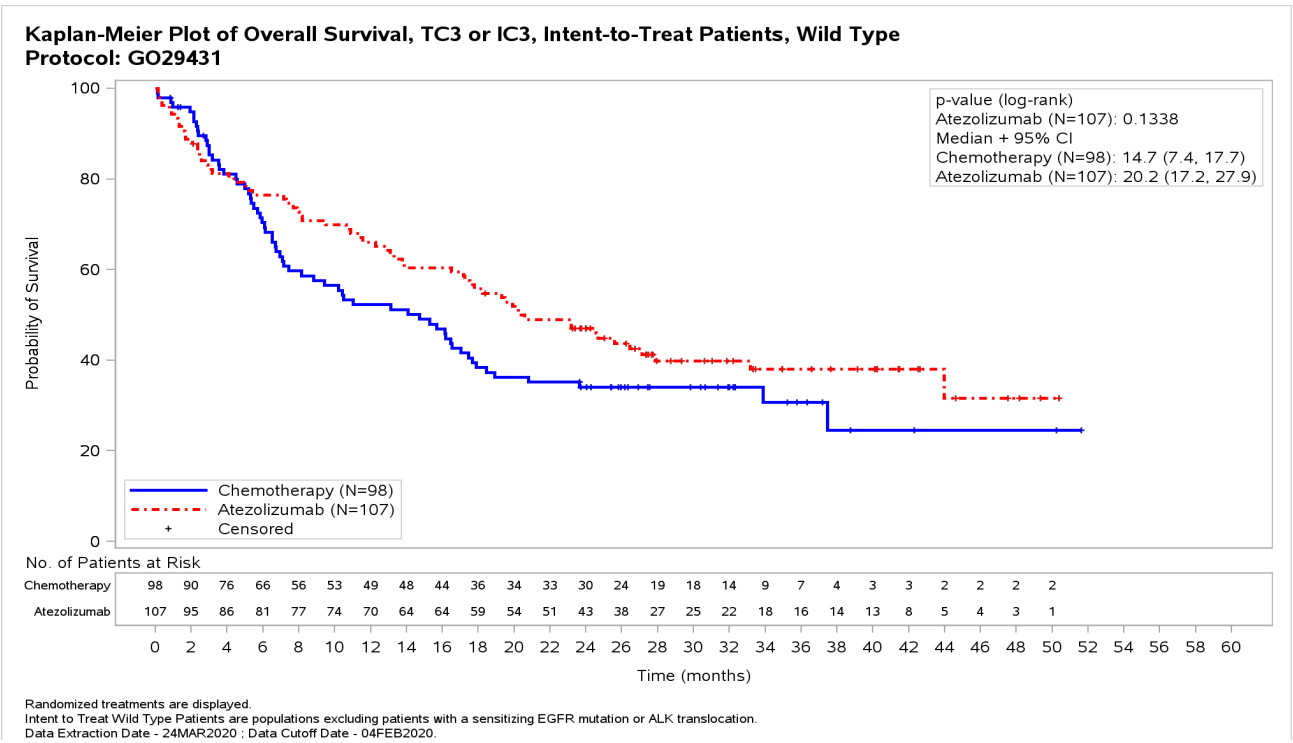


Figure 3: KM Plot of OS with Stratified Analysis (TC3 or IC3-WT Population) CCOD: 4 February 2020

Secondary endpoints

- Progression free survival

Table 10: Progression free survival (TC3 or IC3-WT Population)

Parameter	Interim Analysis (CCOD 10 September 2018)		Updated Analysis* (CCOD 4 February 2020)	
	Chemotherapy	Atezolizumab	Chemotherapy	Atezolizumab
Secondary Endpoints				
Progression-Free Survival				
	n = 98	n = 107	n = 98	n = 107
Patients with event (%)	79 (80.6%)	67 (62.6%)	87 (88.8%)	82 (76.6%)
Median duration of INV-PFS (95% CI) (months)	5.0 (4.2, 5.7)	8.1 (6.8, 11.0)	5.0 (4.2, 5.7)	8.2 (6.8, 11.4)
Stratified Hazard Ratio (95% CI)	0.630 (0.449, 0.884)		0.592 (0.432, 0.812)	
12-month PFS rate	21.6%	36.9%	19.2%	39.2%

CCOD=clinical cutoff date; CI=confidence interval; NE=Not estimable; INV-PFS=investigator assessed-progression free survival; WT=wild-type.
* exploratory analysis for the TC3 or IC3-WT Population at this cut-off date.

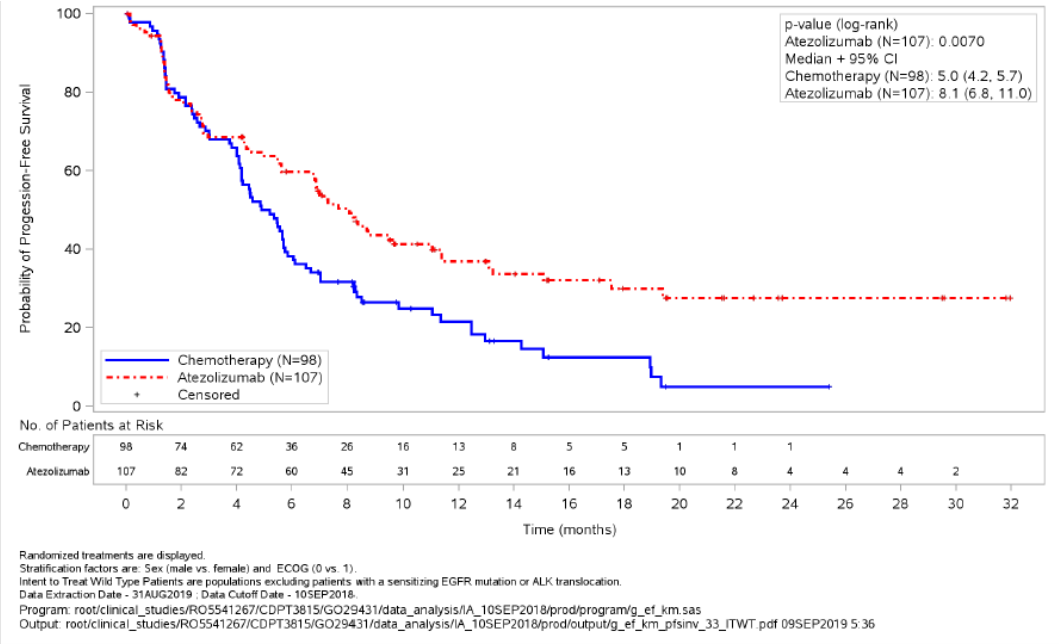


Figure 4: KM Plot for PFS in the TC3 or IC3-WT Population - CCOD: 10 September 2018

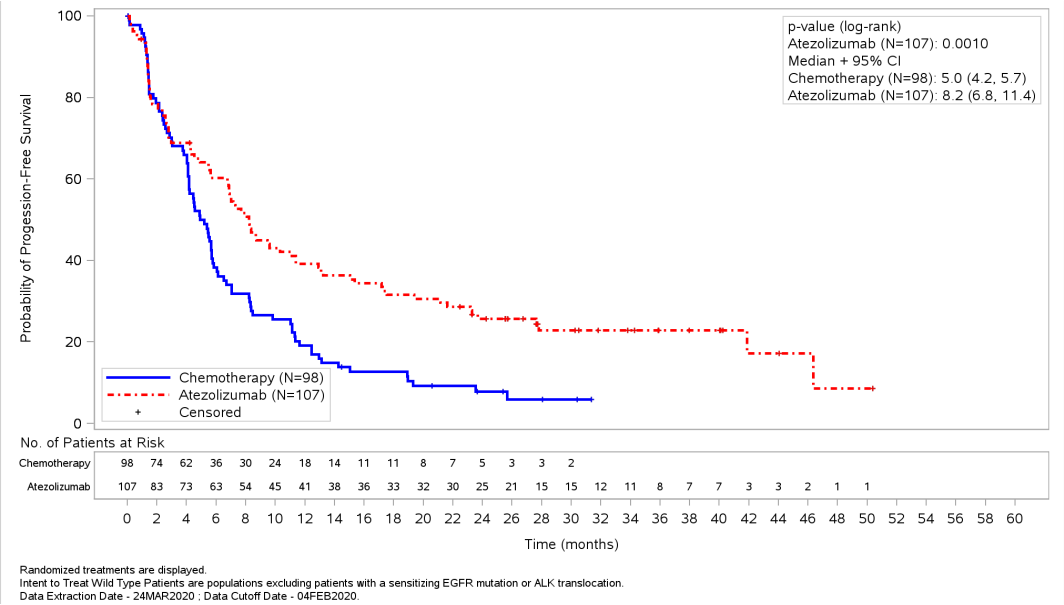


Figure 5: KM Plot of PFS in the TC3 or IC3-WT Population - CCOD: 4 February 2020

Table 11: Landmark PFS-INV analysis at 6 and 12 months (TC3 or IC3-WT population) - CCOD: 10 September 2018

Time to Event Summary for Investigator Assessed PFS, TC3 or IC3, Intent-to-Treat Patients, Wild Type
Protocol: GO29431

Earliest Contributing Event to Investigator Assessed PFS

	Chemotherapy (N=98)		Atezolizumab (N=107)
Time Point Analysis			
6 Months			
Patients remaining at risk	36		60
Event Free Rate (%)	38.30		59.79
95% CI	(28.47, 48.12)		(50.37, 69.21)
Difference in Event Free Rate		21.49	
95% CI		(7.88, 35.10)	
p-value (Z-test)		0.0020	
12 Months			
Patients remaining at risk	13		25
Event Free Rate (%)	21.58		36.92
95% CI	(12.58, 30.58)		(26.98, 46.87)
Difference in Event Free Rate		15.34	
95% CI		(1.93, 28.75)	
p-value (Z-test)		0.0250	

* Censored, ^ Censored and event, NE = Not estimable.
Summaries of Time-to-Event (median, percentiles) were Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.
Wild Type Patients are populations excluding patients with a sensitizing EGFR mutation or ALK translocation.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

- Objective response rate/Duration of response

Table 12: Objective response rate/Duration of response (TC3 or IC3-WT Population)

Parameter	Interim Analysis (CCOD 10 September 2018)		Updated Analysis* (CCOD 4 February 2020)	
	Chemotherapy	Atezolizumab	Chemotherapy	Atezolizumab
Secondary Endpoints				
Objective Response Rate (confirmed)				
	n = 98	n = 107	n = 98	n = 107
ORR (%) (95% CI)	28 (28.6%) (19.90, 38.58)	41 (38.3%) (29.08, 48.22)	28 (28.6%) (19.90, 38.58)	43 (40.2%) (30.82, 50.11)
Duration of Response (confirmed)				
	n = 28	n = 41	n = 28	n = 43
Median DOR (months) (95% CI)	6.7 (5.5, 17.3)	NE (11.8, NE)	8.3 (5.6, 11.0)	38.9 (16.1, NE)

CCOD=clinical cutoff date; CI=confidence interval; DOR=duration of response; NE=Not estimable; OS=overall survival; INV-PFS=investigator assessed-progression free survival; WT=wild-type.
* exploratory analysis for the TC3 or IC3-WT Population at this cut-off date.

Table 13: Best overall confirmed response rate (TC3 or IC3-WT population) - CCOD: 10 September 2018

Confirmed Best Overall Response per RECIST v1.1 - Investigator, TC3 or IC3, Measurable Disease at BL-Investigator, Intent-to-Treat Patients, Wild Type
Protocol: GO29431

	Chemotherapy (N=98)		Atezolizumab (N=107)
Responders	28 (28.6%)		41 (38.3%)
Non-Responders	70 (71.4%)		66 (61.7%)
95% CI for Response Rate (Clopper-Pearson)	(19.90, 38.58)		(29.08, 48.22)
Difference in Response Rates		9.75	
95% CI for Difference in Response Rates (Wald with Continuity Correction)		(-4.07, 23.56)	
p-Value* (Cochran-Mantel-Haenszel)		0.1458	
Odds Ratio*		1.55	
95% CI for Odds Ratio*		(0.86, 2.79)	
Complete Response (CR)	1 (1.0%)		1 (0.9%)
95% CI	(0.03, 5.55)		(0.02, 5.10)
Partial Response (PR)	27 (27.6%)		40 (37.4%)
95% CI	(19.01, 37.50)		(28.22, 47.26)
Stable Disease (SD)	34 (34.7%)		37 (34.6%)
95% CI	(25.36, 44.98)		(25.65, 44.39)
Progressive Disease (PD)	17 (17.3%)		15 (14.0%)
95% CI	(10.44, 26.31)		(8.06, 22.07)
Non-CR / Non-PD	0		0
95% CI	(0.00, 3.69)		(0.00, 3.39)
Missing or unevaluable	19 (19.4%)		14 (13.1%)

BL = Baseline. * Stratified by: Sex (male vs. female) and ECOG (0 vs. 1).
Wald is the normal approximation.
Patients were classified as missing or unevaluable when no post-baseline response assessments were available or all post-baseline response assessments were unevaluable.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Table 14: Summary of DOR (TC3 or IC3-WT patients with a confirmed response per RECIST v1.1) - CCOD: 10 September 2018

Time to Event Summary for Duration of Confirmed Response per RECIST v1.1 - Investigator, TC3 or IC3, Measurable Disease at BL-
Investigator, Intent-to-Treat Patients, Wild Type
Protocol: GO29431

Confirmed Objective Response Duration - Investigator

	Chemotherapy (N=28)	Atezolizumab (N=41)
Patients with event (%)	18 (64.3%)	13 (31.7%)
Earliest contributing event		
Death	0	3
Disease Progression	18	10
Patients without event (%)	10 (35.7%)	28 (68.3%)
Time to Event (Months)		
Median	6.7	NE
95% CI	(5.5, 17.3)	(11.8, NE)
25% and 75%-ile	4.8, 17.3	8.0, NE
Range	2.6 to 23.9*	1.8* to 29.3*
Stratified Analysis		
p-value (log-rank)	0.0096	
Hazard Ratio	0.365	
95% CI	(0.166, 0.800)	
Unstratified Analysis		
p-value (log-rank)	0.0024	
Hazard Ratio	0.342	
95% CI	(0.166, 0.706)	

* Censored, ^ Censored and event, NE = Not estimable.
Summaries of Time-to-Event (median, percentiles) were Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Stratification factors are: Sex (male vs. female) and ECOG (0 vs. 1).
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Patient-Reported Outcomes (PRO)

PRO questionnaire completion rates were high at baseline for the EORTC QLQ-LC13 and QLQ-C30 (>80%), but low for the SILC (50-60%) for both arms.

Table 15: Baseline patient-reported outcome scores for TC3 or IC3-WT population - CCOD: 10 September 2018

	Chemotherapy (N = 98)	Atezolizumab (N = 107)
	Mean scores (SD)	
	n = 52	n = 61
SILC scales		
Cough	1.15 (1.00)	1.44 (1.03)
Dyspnoea	1.12 (1.01)	1.08 (1.00)
Chest Pain	0.78 (1.02)	0.82 (0.93)
Select EORTC QLQ-LC13 scales	**n = 83**	**n = 95**
Coughing	29.32 (25.18)	36.14 (24.63)
Pain in chest	15.26 (25.13)	20.00 (23.52)
Dyspnoea	25.03 (23.46)	23.98 (24.27)
Pain in arm or shoulder	16.87 (29.62)	18.25 (27.40)
Select EORTC QLQ-C30 scales	**n = 84**	**n = 96**
Fatigue	32.67 (23.16)	36.81 (25.30)
Appetite loss	22.62 (29.80)	25.69 (30.77)
Physical functioning	75.08 (19.45)	74.24 (21.88)
Role functioning	70.83 (28.79)	72.05 (29.76)
Social functioning	79.56 (23.62)	76.91 (25.63)
Emotional functioning	77.98 (17.72)	73.52 (24.18)
Cognitive functioning	85.71 (18.32)	86.11 (17.72)
Global health status or HRQoL	59.92 (21.51)	62.76 (20.09)

HRQoL=health-related quality of life; PBO=placebo; PRO=patient-reported outcome; SD=standard deviation.

Note: The score range for each QLQ-LC13 and QLQ-C30 scale is 0 to 100, with higher scores indicating either worse symptoms, better functioning, or better HRQoL. The score range for each SILC symptom score is 0 to 4, with a higher score indicating worsening symptoms.

Ancillary analyses

Sensitivity analyses for OS

Table 16: Analysis of OS discounting for NPT with 10, 20, or 30% benefit reduction (TC3 or IC3-WT population) - CCOD: 10 September 2018

	Chemotherapy (n=98)	Atezolizumab (n=107)
10% Benefit Reduction		
Median OS (months) (95%CI)	12.6 (7.3, 15.7)	20.2 (16.1, NE)
Stratified Analysis		
p-value (log-rank)	0.0097[a]	
HR (95% CI)	0.59 (0.40, 0.88)	
20% Benefit Reduction		
Median OS (months) (95%CI)	12.1 (7.1, 14.9)	20.9 (15.0, NE)
Stratified Analysis		
p-value (log-rank)	0.0068[a]	
HR (95% CI)	0.58 (0.39, 0.86)	
30% Benefit Reduction		
Median OS (months) (95%CI)	11.6 (6.9, 14.1)	20.2 (13.5, NE)
Stratified Analysis		
p-value (log-rank)	0.0065[a]	
HR (95% CI)	0.58 (0.39, 0.86)	

CI=confidence interval; HR=hazard ratio; NE=not estimable; OS=overall survival; WT=wild-type

[a] p-value is descriptive only

Table 17: Sensitivity Analyses for Overall Survival Based on "Replacement Approach" to Define PD-L1 Status - CCOD: 10 September 2018

Key Analysis Population Stratified HR (95%CI) p-value	Primary Analysis for OS	Sensitivity Analysis based on "Replacement Approach"
N TC3 or IC3-WT IA boundary**: α=0.0413	n=205 0.595 (0.398, 0.890) p-value=0.0106	n=206 0.606 (0.407, 0.902) p-value=0.0128*
N TC2/3 or IC2/3-WT IA boundary**: α=0.0400	n=328 0.717 (0.520, 0.989) p-value=0.0416	n=329 0.714 (0.517, 0.986) p-value=0.0400*
N TC1/2/3 or IC1/2/3-WT IA boundary**: α=0.0374	n=554 0.832 (0.649, 1.067) p-value=0.1481*	n=540 0.836 (0.650, 1.074) p-value=0.1605*

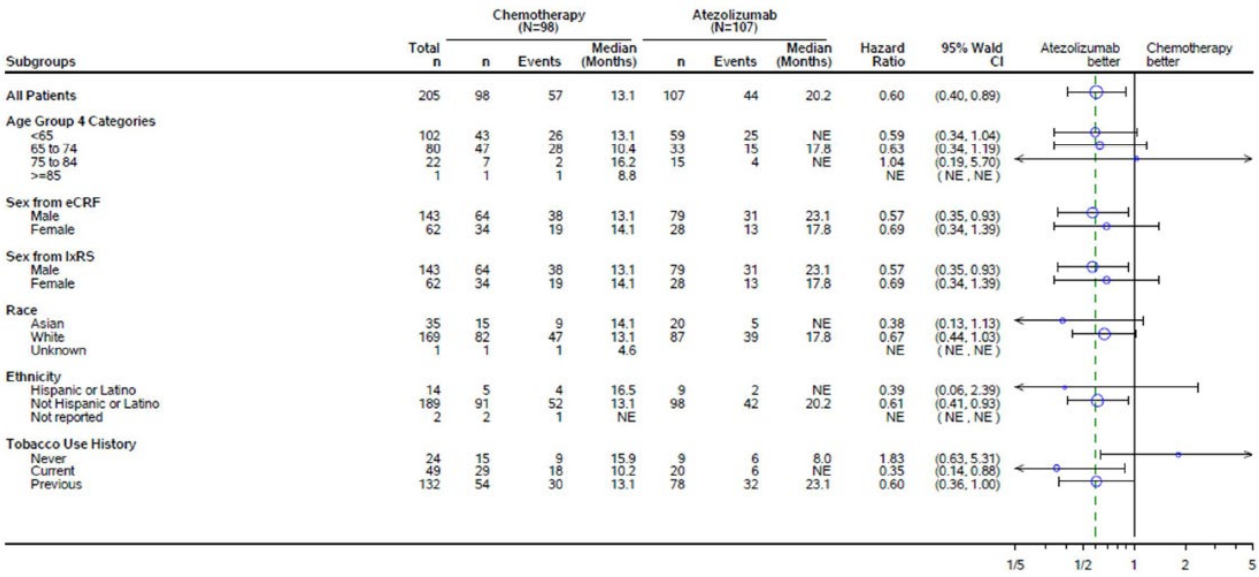
*only for descriptive purpose
**adjusted for the observed number of events for the primary analysis in each patient population at the interim analysis

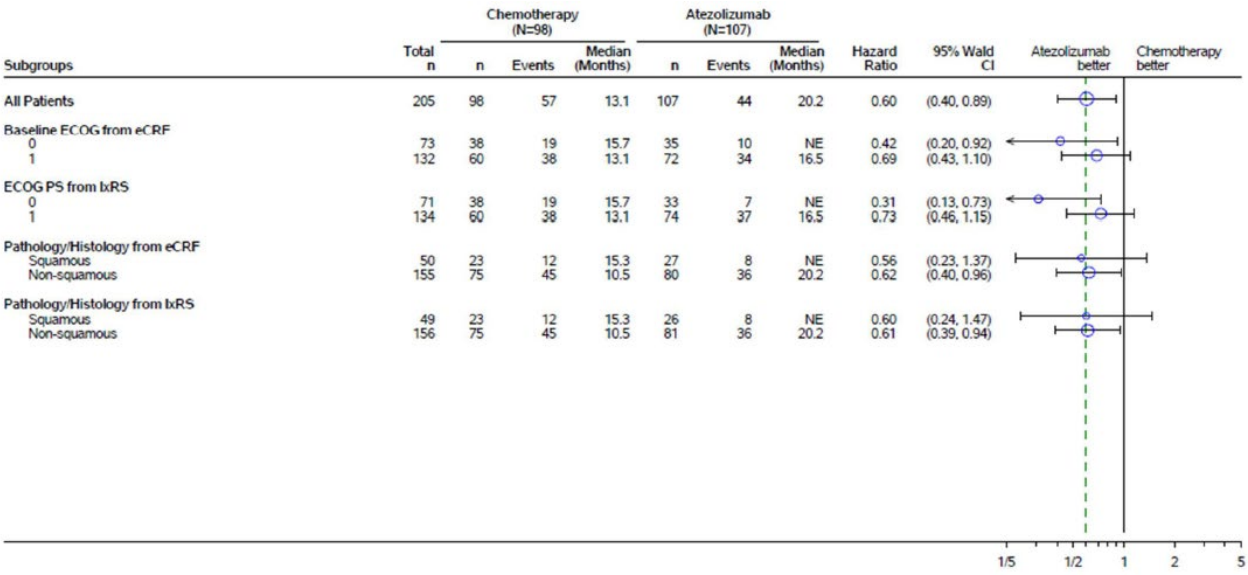
Table 18: Sensitivity Analyses for Overall Survival Based on "Exclusion Approach" to Define PD-L1 Status - CCOD: 10 September 2018

Key Analysis Population Stratified HR (95%CI) p-value	Primary Analysis for OS	Sensitivity Analysis Based on "Exclusion Approach"
N TC3 or IC3-WT IA boundary**: α=0.0413	n=205 0.595 (0.398, 0.890) p-value=0.0106	n=183 0.596 (0.391, 0.908) p-value=0.0149*
N TC2/3 or IC2/3-WT IA boundary**: α=0.0400	n=328 0.717 (0.520, 0.989) p-value=0.0416	n=289 0.736 (0.524, 1.035) p-value=0.0773*
N TC1/2/3 or IC1/2/3-WT IA boundary**: α=0.0374	n=554 0.832 (0.649, 1.067) p-value=0.1481*	n=452 0.824 (0.628, 1.081) p-value=0.1623*

*only for descriptive purpose
**adjusted for the observed number of events for the primary analysis in each patient population at the interim analysis

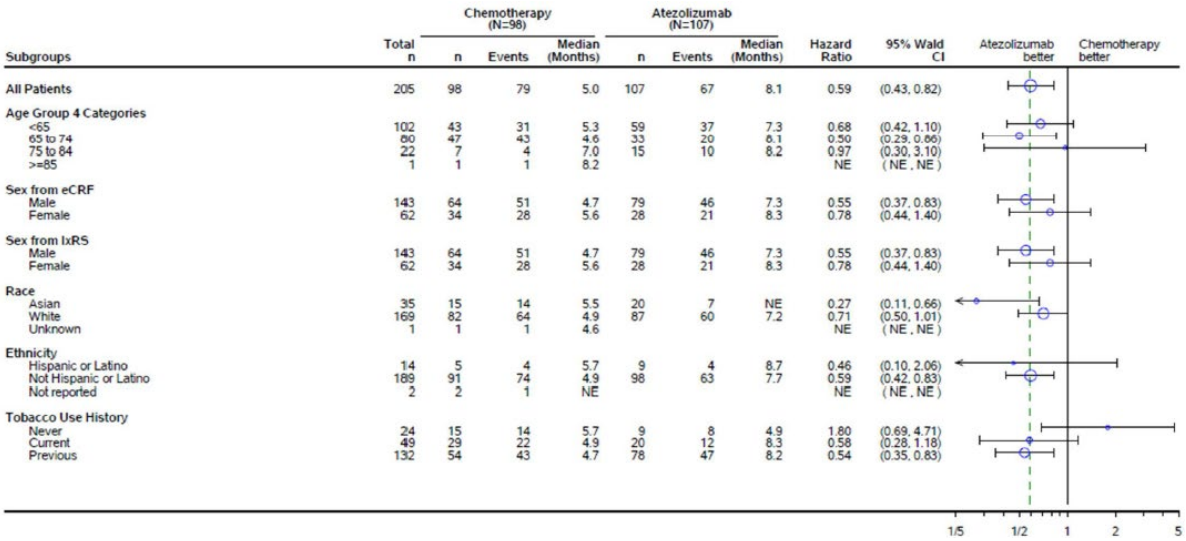
Subgroup analyses of OS and PFS

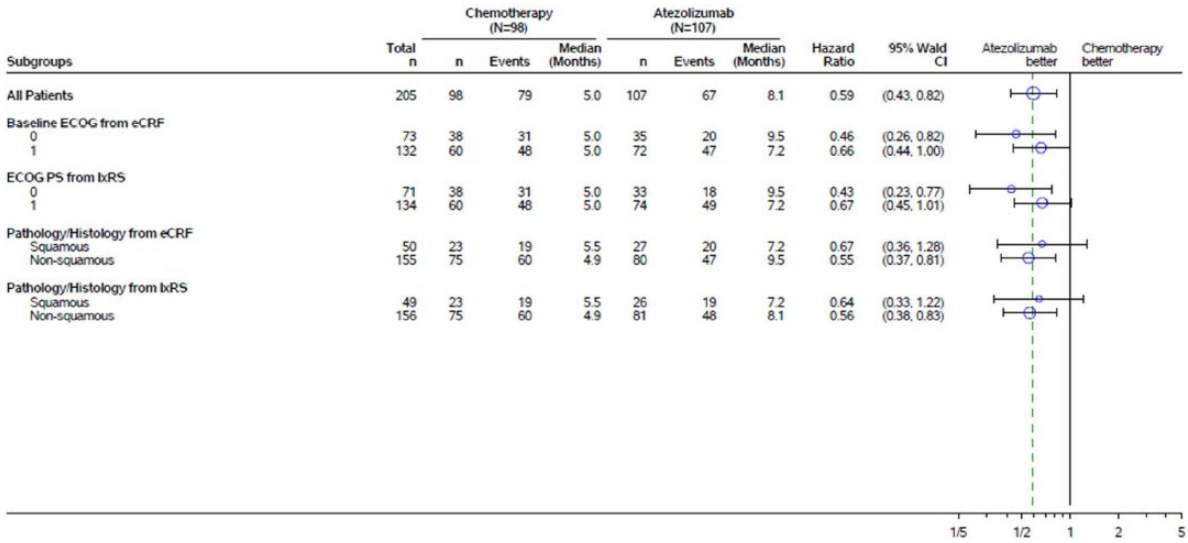


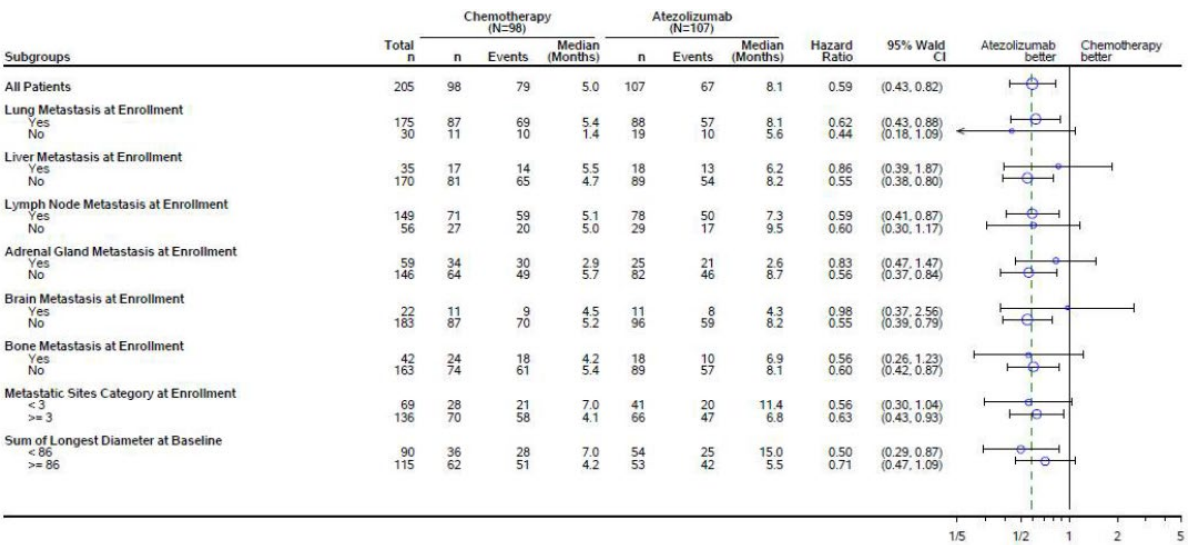


NE = Not estimable; Median Survival was estimated from Kaplan-Meier method. Unstratified hazard ratio relative to Chemotherapy and 95% CI for the hazard ratio were estimated using Cox regression. The vertical dashed line indicates the hazard ratio for all patients. The diameter of the circle is proportional to the square root of the total number of events. Randomized treatments are displayed.
Intent to Treat Wild Type Patients are populations excluding patients with a sensitizing EGFR mutation or ALK translocation.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Figure 6: Subgroup analysis of OS by selected demographics and baseline disease characteristics (TC3 or IC3-WT population) - CCOD: 10 September 2018







NE = Not estimable; Median Progression-Free Survival was estimated from Kaplan-Meier method. Unstratified hazard ratio relative to Chemotherapy and 95% CI for the hazard ratio were estimated using Cox regression. The vertical dashed line indicates the hazard ratio for all patients. The diameter of the circle is proportional to the square root of the total number of events.
Randomized treatments are displayed.
Intent to Treat Wild Type Patients are populations excluding patients with a sensitizing EGFR mutation or ALK translocation.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Figure 7: Subgroup analysis of PFS by selected demographics and baseline disease characteristics (TC3 or IC3-WT population) - CCOD: 10 September 2018

Efficacy by PD-L1 Status (SP263 and 22c3 Assays) and bTMB Status

Pre-specified OS and PFS-INV subgroup analyses using the SP263 and 22C3 assays as well as bTMB were conducted within the enrolled SP142-selected TC1/2/3 or IC1/2/3-WT patients. OS and PFS improvement with atezolizumab treatment was observed in PD-L1-high patients (TC ≥50% for SP263 and TPS ≥50% for 22C3; Table 5.4.13) using both SP263 and 22c3 assays. Likewise, an improvement in OS and PFS was observed in high bTMB (≥16) patients treated with atezolizumab compared with chemotherapy**.**

Alternative, validated PD-L1 IHC assays (SP263 and 22C3) were used to define PD-L1 subgroups based on PD-L1 expression specifically on TCs.

Within the IMpower110 enrolled WT population (TC1/2/3 or IC1/2/3-WT; N=554), 54% of patients had tumors with SP263 ≥50% TC expression and 49% of patients had tumors with 22C3 ≥50% TPS compared to 39% as selected with SP142-assay. In these two PD-L1 high subgroups, improvements in OS and PFS were observed in the atezolizumab arm compared with the chemotherapy arm (Table 31). Both TC specific PD-L1 IHC assays identify a broader patient population compared to SP142 TC3 or IC3.

Table 19: OS and PFS by High PD-L1 Expression Subgroups (Defined by the SP263 and 22C3 Assays) and bTMB Subgroup (TC1/2/3 or IC1/2/3 WT Population)

Subgroup	OS					PFS				
	Atezolizumab		Chemotherapy		HR[c] 95% CI	Atezolizumab		Chemotherapy		HR[c] 95% CI
	n	Median (Months)	n	Median (Months)		N	Median (Months)	n	Median (Months)	
PD-L1 Subgroups Defined by the VENTANA SP142 Assay (BEP, n = 554)										
ITT (TC1/2/3 or IC1/2/3) WT[a]	277	17.5	277	14.1	0.83 (0.65, 1.07)	277	5.7	277	5.5	0.77 (0.63, 0.94)
TC3 or IC3 WT[b]	107	20.2	98	13.1	0.59 (0.40, 0.89)	107	8.1	98	5.0	0.63 (0.45, 0.88)
PD-L1 Subgroups Defined by the Dako 22C3 Assay (BEP, n = 534[d])										
22C3 BEP	268	17.5	266	14.1	0.82 (0.64, 1.06)	268	5.8	266	5.6	0.76 (0.62, 0.93)
TPS ≥ 50%	134	20.2	126	11.0	0.60 (0.42, 0.86)	134	7.3	126	5.4	0.61 (0.46, 0.82)
PD-L1 Subgroups Defined by the VENTANA SP263 Assay (BEP, n = 546[d])										
SP263 BEP	271	17.2	275	14.9	0.85 (0.66, 1.09)	271	5.7	275	5.5	0.77 (0.63, 0.94)
TC ≥ 50%	150	19.5	143	16.1	0.71 (0.50, 1.00)	150	7.0	143	4.9	0.67 (0.51, 0.89)
bTMB Subgroups Defined by the Foundation Medicine Assay (BEP, n = 389[d])										
bTMB BEP	196	13.3	193	15.3	0.98 (0.74, 1.30)	196	5.5	193	5.4	0.88 (0.70, 1.11)
≥ 16	42	13.9	45	8.5	0.75 (0.41, 1.35)	42	6.8	45	4.4	0.55 (0.33, 0.92)

BEP=biomarker-evaluable population; bTMB=blood tumor mutation burden; IC=tumor-infiltrating immune cells; PD-L1=programmed death-ligand 1; TC=tumor cells.

[a] TC1/2/3 or IC1/2/3-WT population represents the SP142-enrolled IMpower110 population without *EGFR* or *ALK* genetic alterations.

[b] TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1.

[c] Stratified HRs for SP142 and unstratified HRs for 22C3, SP263 and bTMB.

[d] BEP is calculated within the WT population.

Table 20: PFS-INV by PD-L1 status (SP263 and 22C3 Assays) and bTMB status (TC1/2/3 or IC1/2/3 WT Population)

Key Biomarker Subgroups	Chemotherapy	Atezolizumab
SP263 Biomarker Evaluable	N=275	N=271
TC≥50%	n=143	n=150
Median PFS-INV (95% CI)	4.9 (4.0, 5.6)	7.0 (5.6, 8.7)
HR (95% CI) *	0.674 (0.511, 0.890)	
TC≥25%	n=168	n=168
Median PFS-INV (95% CI)	4.9 (4.2, 5.6)	6.9 (5.6, 8.4)
HR (95% CI) *	0.698 (0.539, 0.904)	
TC≥1%	n=210	n=212
Median PFS-INV (95% CI)	5.4 (4.4, 5.7)	6.8 (5.5, 8.0)
HR (95% CI) *	0.725 (0.577, 0.910)	
TC<1%	n=65	n=59
Median PFS-INV (95% CI)	5.6 (4.4, 7.4)	4.6 (1.9, 6.6)
HR (95% CI) *	0.944 (0.628, 1.420)	
22C3 Biomarker Evaluable	N=266	N=268
TPS≥50%	n=126	n=134
Median PFS-INV (95% CI)	5.4 (4.3, 5.7)	7.3 (5.9, 11.4)
HR (95% CI) *	0.613 (0.456, 0.824)	
TPS≥1%	n=201	n=213
Median PFS-INV (95% CI)	5.5 (4.5, 5.7)	6.9 (5.6, 8.1)
HR (95% CI) *	0.741 (0.589, 0.934)	
TPS<1%	n=65	n=55
Median PFS-INV (95% CI)	5.6 (4.4, 6.5)	4.3 (1.9, 6.6)
HR (95% CI) *	0.866 (0.568, 1.319)	
bTMB Biomarker Evaluable	N=193	N=196
≥20	n=29	n=27
Median PFS-INV (95% CI)	5.2 (3.2, 6.4)	6.8 (4.3, 17.2)
HR (95% CI) *	0.560 (0.295, 1.062)	
≥16	n=45	n=42
Median PFS-INV (95% CI)	4.4 (2.8, 5.7)	6.8, (4.3, 11.6)
HR (95% CI) *	0.553 (0.331, 0.924)	
≥10	n=83	n=92
Median PFS-INV (95% CI)	4.3 (3.1, 5.4)	5.5 (2.8, 6.8)
HR (95% CI) *	0.743 (0.525, 1.052)	
<10	n=110	n=104
Median PFS-INV (95% CI)	5.7 (4.9, 6.9)	5.5 (2.8, 6.9)
HR (95% CI) *	1.026 (0.758, 1.388)	

bTMB=blood tumor mutation burden, CI=confidence interval, NE=not estimable, PFS-INV=investigator-assessed progression-free survival, TPS=tumor proportion score, WT=wild type

Summaries of Time-to-Event (median, percentiles) were Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.

WT patients are populations excluding patients with a sensitizing EGFR mutation or ALK translocation.

* Unstratified analysis

Early deaths

A higher proportion of patients experienced death within the first 2.5 months in the atezolizumab arm (16/107, 15.0%) as compared to the chemotherapy arm (10/98, 10.2%).

Subgroup Analyses of Efficacy Endpoints by Treatment-Emergent ADA Status

In unadjusted exploratory analyses, which did not take into account the imbalances in baseline characteristics between ADA subgroups, for both PFS and OS, the percentage of patients with events was numerically higher for ADA-positive patients, and the median time to event was shorter (Table 33). The proportion of responders was numerically lower in the ADA-positive subgroup compared with ADA-negative.

Table 21: OS, PFS, and ORR by Atezolizumab ADA Status, Atezolizumab ADA-Evaluable Patients in the TC3 or IC3-WT Population

	Atezolizumab Arm	
Efficacy Endpoint	**ADA– (N=75)**	**ADA+ (N=23)**
OS		
Patients with event (%)	39 (52.0%)	17 (73.9%)
Median time to event – months (95% CI)	27.1 (20.2, NE)	13.8 (4.9, 23.1)
PFS: INV-assessed		
Patients with event (%)	42 (56.0%)	18 (78.3%)
Median time to event – months (95% CI)	9.6 (7.7, 17.5)	4.5 (2.3, 8.2)
Confirmed ORR		
Responders (%)	34 (45.3%)	7 (30.4%)
95% CI for response rates	(33.79, 57.25)	(13.21, 52.92)

ADA=anti-drug antibody; CI=confidence interval; INV-PFS=investigator-assessed progression-free survival; NE=not estimable; OS=overall survival.

OS data is per CCOD of 4FEB2020 and ADA status is per CCOD of 10SEP2018.

Early deaths by ADA status

The MAH submitted a listing of early deaths according to ADA status (data not shown). Overall, there were 44 deaths within the first 5 months after randomization; 21 in the chemotherapy arm vs. 23 in the atezolizumab arm. Of the 23 early deaths in the atezolizumab arm, the ADA status was as follows: 8 ADA-positive (including 4 patients who subsequently tested ADA-negative at later timepoints), 9 ADA-negative, and 6 patients with missing postbaseline ADA results.

Summary of main study– IMpower110

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

Table 22: Summary of Efficacy for IMpower110

Title: IMpower110:		
Study identifier	GO29431	
Design	Phase III, open-label, randomised study of atezolizumab compared with a platinum agent in combination with either pemetrexed or gemcitabine for PD-L1-selected chemotherapy-naïve patients with stage IV non-squamous or squamous NSCLC	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	31 months not applicable not applicable

Hypothesis	Superiority			
Treatments groups	Atezolizumab monotherapy		Atezolizumab 1200 mg Q3W until PD or loss of clinical benefit, number randomized: 107	
	Chemotherapy		A platinum agent (cisplatin or carboplatin) in combination with either pemetrexed or gemcitabine treatment for 4-6 cycles, number randomized: 98	
Endpoints and definitions	Primary endpoint	OS	Overall survival in the TC3 or IC3-WT population	
	Secondary endpoint	PFS-INV	PFS by investigator in the TC3 or IC3-WT population	
	Secondary other:	ORR, DOR	Overall response rate, Duration of response	
Database lock	10 September 2018			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	The TC3 or IC3-WT population			
Effect estimate per comparison and estimate variability	Treatment group	Atezolizumab	Chemotherapy	Hazard ratio
	Number of subjects	N=107	N=98	
	OS (months)	20.2	13.1	0.59*
	95% CI	16.5; NE	7.4; 16.5	0.40; 0.89
	PFS (months)	8.1	5.0	0.63
	95% CI	6.8; 11.0	4.2; 5.7	0.45; 0.88
	ORR confirmed (%) 95% CI	38.3 29.08; 48.22	28.6 19.90; 38.58	NA
	DOR (months 95% CI	NE 11.8; NE	6.7 5.5; 17.3	NA
Notes	*The OS KM curves crossed, so the proportional hazard assumption for calculating HR was not met.			
Analysis description	**Secondary analysis:**			
Analysis population and time point description	The TC3 or IC3-WT population, updated DCO 4 Feb 2020			
Effect estimate per comparison and estimate variability	Treatment group	Atezolizumab	Chemotherapy	Hazard ratio
	Number of subjects	N=107	N=98	
	OS (months)	20.2	14.7	0.764
	95% CI	16.5; NE	7.4; 17.7	0.536; 1.087
	PFS (months)	8.2	5.0	0.592
	95% CI	6.8; 11.4	4.2; 5.7	0.432; 0.812
	ORR confirmed (%) 95% CI	40.2 30.82; 50.11	28.6 19.90; 38.58	NA
	DOR (months 95% CI	38.9 16.1; NE	8.3 5.6; 11.0	NA

Clinical studies in special populations

The consistency of OS, PFS-INV, and ORR results was investigated by estimating the treatment effect in pre-defined subgroups based on key demographics (age, sex, race/ethnicity) and baseline prognostic characteristics (e.g., histology, ECOG performance status, smoking history, number of metastatic sites, location of metastases, size of primary tumor, etc.). Randomization was not stratified by all those pre-defined subgroups and some groups included small sample size. The MAH did not provide data in the paediatric population.

Separate efficacy data in elderly patients have not been provided. However, subgroup analyses in subjects ≤65 and 65-74 years indicate a similar efficacy for both age groups regarding OS and lower HR values for the higher age group (for PFS). Limited data are available for ≥75 years (Figure 17 and Figure 18).

2.4.3. Discussion on clinical efficacy

The MAH applied for the first-line treatment with atezolizumab monotherapy of a PD-L1 selected patient population with metastatic NSCLC based on the multicenter, randomised, phase 3 IMpower110 trial, which is comparing atezolizumab monotherapy with platinum-based chemotherapy in chemotherapy-naïve patients. In total, 572 patients in the pivotal trial were recruited from 144 centres across 19 countries, which is acceptable as a relevant number of patients were from regions comparable to the EU. The study was fully recruited by 31 months and updated efficacy data are presented with a median follow-up time for survival was ~31 months and used the data cut-off 04 February 2020.

Design and conduct of clinical studies

The design of the pivotal study is in principle acceptable; however, it is noted that the design and the protocol were changed multiple times during the study in particular after the data cut-off date. The SAP was also amended to incorporate the changes made in the protocol. The initial data cut-off date was 10 September 2018, and the SAP was updated on the 2 April 2019. The primary endpoint was changed three times; from PFS only to PFS and OS as co-primary endpoints and lastly to OS only.

Enrolment was restricted to subjects with PD-L1 positive tumours (Tumour PD-L1 expression (TC1/2/3 or IC1/2/3; corresponding to ≥1% PD L1 expressing TCs and ≥1% of tumour area occupied by PD-L1 expressing ICs). Only patients in good performance status (ECOG performance status of 0 or 1) with only mild renal or hepatic insufficiency were included (GFR ≥60 mL/min; AST/ALT ≤1.5XULN, ALP ≤2.5XULN).

The patient population was expanded to include patients with squamous NSCLC, and this subgroup ended up comprising 24% of the targeted study population. Patients with CNS metastases were eligible provided that certain criteria were met, and this is endorsed. The key exclusion criteria are also endorsed.

The primary endpoint was to be tested in three different populations. To keep the type I error control at 5%, the Applicant defined a hierarchical testing. The strategy chosen to control for multiple endpoints is agreed. The Applicant planned for an interim analysis of OS. To correct for multiple looks, the Lan-DeMets approximation to the Pocock boundary was implemented. The Applicant added the TC3 or IC3 population as the first testing hierarchy in Protocol Version 9 (finalized on 14 March 2019). Before this, the TC2/3 or IC2/3 population had been defined as the primary analysis population.

The very late time point of this update in the open-label study and the inadvertent data access by statisticians in December 2018 raised concerns that these changes could have been driven by knowledge

of the pivotal IMpower110 study results and thus, a GCP inspection was triggered by the CHMP. The GCP inspection team was not able to exclude that protocol amendment V9 was not influenced by knowledge based on internal study data and the decision-making process was not documented adequately. Because the "Biostats team working on this study had – by error – access to RAVE data, including the actual exposure/treatment", the GCP inspectors considered it possible that "population-level efficacy analyses by actual treatment were performed prior to the database lock and Treatment Assignment Information (TAI) release". The MAH has argued that the "extracted RAVE data did not contain any Treatment Assignment Information, i.e. no IxRS randomization code, nor did it contain PD-L1 status linked to an actual patient ID. The biostatistics team could therefore not have performed any analyses in the TC2/3 or IC2/3-wild type (WT) population or the TC3 or IC3-WT population." The MAH claimed that the key changes implemented in protocol version 9, including incorporation of TC3 or IC3-WT population into the testing hierarchy, were driven by data external to Study IMpower110, mainly from three anti-PD-1/PD-L1 monotherapy 1L NSCLC studies (Checkmate-026, KEYNOTE-042 and MYSTIC), indicating that OS benefit was greatest in patients that express higher levels of PD-L1. Moreover, a detailed biomarker review of IMpower150 study and biomarker status in the external studies suggested that TC3/IC3 population had the highest probability of response. Relevant for these analyses are the MYSTIC study results by PD-L1 expression subgroups (Rizvie et al 2018) and a presentation at the European Society for Medical Oncology Immuno-Oncology (ESMO-IO) Congress on 13 December 2018 including additional analyses by PD-L1 status in the TC≥50%, TC≥1% and TC <1% for subgroups treated with durvalumab versus chemotherapy. Hence, it was agreed that these external data could have led to the changes made by the Applicant later on. Since the Applicant has provided an explanation and clarification for the chain of events that led to the changes of the testing hierarchy of the results of Impower110, the CHMP concluded that it seems scientifically based that external data did lead to the decision to introduce the changes to the protocol, etc. However, the practice of changing the primary endpoint and hierarchical testing in an ongoing open-label study is still criticized and the Applicant should refrain from this approach in future open-label clinical studies. GCP issues should also be addressed as recommended in the GCP inspection report and the Applicant can expect that in future applications, there will be continued focus on GCP compliance.

The sample size calculations presented in the latest version of the protocol seem adequate. The stratification factors were sex, ECOG performance status, histology and PD-L1 tumour expression status, and they are all considered relevant from a clinical point of view. However, when considering the limited sample size of the relevant PD-L1 selected target population i.e. 205 patients randomised, the number of stratification factors should have been more limited.

The comparator of platinum-based chemotherapy is no longer standard of care for the targeted PD-L1 selected patient population; and at the time of study design, promising efficacy results were already emerging with immunotherapy. For a while now, the SOC for the targeted PD-L1 selected patient population has included immunotherapy either as monotherapy or in combination with chemotherapy, but this change in SOC was not obvious at the time of study initiation in 2015, so the choice of comparator is acceptable.

The objective of the pivotal trial is OS as primary endpoint and key secondary endpoints were INV-PFS, INV-ORR, DOR by RECIST 1.1, and efficacy according to PD-L1 expression. It is acceptable to use investigator-assessed objectives as secondary objectives, if the primary objective is measured by a hard endpoint such as OS. However, the robustness of the PFS result in this open-label study allowing treatment with atezolizumab beyond progression could have been greatly improved by the use of an independent review of the scan results, which was not done. The secondary endpoints were not controlled for multiplicity and therefore the p-values are considered descriptive.

Exclusion of patients with ALK-positive or EGFR mutated tumours are endorsed, as several studies have not established efficacy of atezolizumab in these sub-populations. Prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease were allowed, as long as the treatment-free interval was of at least 6 months from randomization. This led to the inclusion of patients, who might not benefit from re-introduction of platinum-based chemotherapy.

Efficacy data and additional analyses

The primary endpoint of **OS** benefit in the PD-L1 selected population was met. However, the KM OS curves cross after approximately 4 months of therapy, so initially, treatment with chemotherapy is superior to atezolizumab monotherapy and the shape of the curve indicate early deaths with atezolizumab. This is concerning and the higher number of deaths within 2.5 months after randomisation observed with atezolizumab compared with chemotherapy (potentially due a delayed onset of atezolizumab effect) is reflected in section 4.4 of the SmPC for the prescribers to consider, although no risk factors could be identified.

The updated KM OS curves begin to separate approximately 5 months after treatment initiation and from then on, atezolizumab monotherapy is superior to chemotherapy. At the IA of IMpower110 (CCOD 10 September 2018), a statistically significant and clinically meaningful OS benefit was demonstrated with first-line (1L) atezolizumab monotherapy compared to platinum-based chemotherapy in the TC3 or IC3-WT population (median OS: 20.2 vs. 13.1 months, HR 0.595 [95%CI: 0.398, 0.890]; p-value=0.0106). Because the OS data were not fully mature at this analysis time point (around 50% event rates), the Applicant presented an OS update after an additional 17 months of follow-up (CCOD: 4 February 2020).

Updated efficacy data in the TC3 or IC3-WT population showed an OS **HR** of **0.764** [95%CI, 0.563, **1.087**] with a median OS of 20.2 vs. 14.7 months, respectively. Thus, the point estimate of the OS HR increased and OS analysis was not nominal significant with longer follow-up. Considering the shapes of the KM curves and the median OS, it appears that this change was mainly driven by the performance of the comparator arm. The median OS became longer only in the chemotherapy arm (13.1 months at IA and 14.7 months at the updated analysis). The Applicant argued that this may be due to the use of subsequent immunotherapy (34.7% in the chemotherapy arm), which was substantiated by additional analysis via discount method and RPSFT method and can be followed in general. Considering that only one third of the patients received immunotherapy post-progression, this might not be sufficient to fully explain the catching up of the chemotherapy control arm. However, this does not impact the benefit in OS shown for atezolizumab monotherapy.

The key secondary endpoint **PFS-INV** was reached in both treatment arms; however, the difference could not be formally tested, since the pre-specified IA alpha boundary was not crossed for the TC2/3 or IC2/3-WT population. The initially observed INV-PFS benefit (HR 0.63) was confirmed with the updated data and showed a difference of 3.2 months (HR 0.59 [95%CI: 0.43, 0.81]. Updated confirmed **ORR** was also increased from 28.6% with chemotherapy to 40.2% with atezolizumab and it is noted, that the increase was due to more patients achieving a PR with atezolizumab. The updated median **DOR** was statistically significantly increased from 8.3 months (95%CI: 5.6; 11.0) to 38.9 months (95%CI: 16.1; NE) with atezolizumab. Taking into account that the sample sizes are small i.e. 43 responders on atezolizumab, the induced responses were durable and DOR were clinically meaningfully prolonged with atezolizumab monotherapy. In addition, it has to be acknowledged that the efficacy results of atezolizumab monotherapy appear consistent with published external data from other PD1/PDL1-inhibitors in similar treatment settings, despite the limitations of cross-trial comparisons.

Additional pre-specified analyses were conducted to evaluate efficacy by PD-L1 status assessed by the VENTANA PD-L1 (SP263) Assay and by the PD-L1 IHC 22C3 pharmDxTM Kit in all randomised patients (n=554), but the assay data is considered exploratory and is therefore not presented in the SmPC.

The incidence of treatment-emergent ADA in the population of IMpower110 was 24.3% (23.5% in the TC3 or IC3-WT population). These high rates of treatment-emergent ADA in patients treated with atezolizumab remains somewhat worrisome; nevertheless, the OS and ORR results for the targeted population could be regarded as comparable to those of the SOC platinum-based chemotherapy. Therefore, in 1L NSCLC the incidence of ADA+ and the reduced efficacy in ADA positive patients is not an objection for the currently applied patient population. The small numbers and missing values make this analysis difficult to interpret, but ADA status does not seem to have a major impact on early mortality. However, this does not preclude a detrimental effect on longer-term efficacy and as ADA often takes time to develop. This was reflected in section 4.8 of the SmPC.

PRO data have also been presented and results indicate no detrimental effects of either of the study treatments. However, these data should be interpreted with caution and are therefore not presented in the SmPC.

2.4.4. Conclusions on the clinical efficacy

The efficacy results from the pivotal IMpower110 study shows superior efficacy in terms of OS of atezolizumab monotherapy compared to platinum-based chemotherapy for the first-line treatment of PD-L1 selected patients with metastatic NSCLC.

2.5. Clinical safety

Introduction

Safety data for the use of atezolizumab in patients with chemotherapy-naive squamous or non-squamous metastatic NSCLC in the IMpower110 are presented versus the chemotherapy arm; hence, Atezolizumab versus Cisplatin/Carboplatin + Pemetrexed/Gemcitabine.

The safety database includes data from 549 patients, who received any amount of study treatment in the IMpower110 study (286 patients treated with atezolizumab and 263 patients treated with chemotherapy). The Atezo Mono Pooled population (n=3854) includes the data from the 286 patients treated in the atezolizumab arm of IMpower110 and the 3568 patient-pooled monotherapy population as currently presented in the approved Tecentriq SmPC.

Patient exposure

Table 23: Exposure to study treatment (safety-evaluable population) – CCOD: 10 September 2018

	Chemotherapy n=263				Atezolizumab n=286
	Cisplatin n=90	Carboplatin n=177	Gemcitabine n=75	Pemetrexed n=191	
Treatment duration (M)					
Median	2.1	2.3	2.6	3.5	5.3
Min – Max	0 - 5	0 - 5	0 - 5	0 - 20	0 - 33
Treatment duration (M)					
0 to ≤2 months	29 (32.2%)	55 (31.1%)	23 (30.7%)		
>2 to ≤4 months	59 (65.6%)	113 (63.8%)	42 (56.0%)		
>4 to ≤6 months	2 (2.2%)	9 (5.1%)	10 (13.3%)		
Treatment duration (M)					
0 to ≤3 months				84 (44.0%)	97 (33.9%)
>3 to ≤6 months				50 (26.2%)	52 (18.2%)
>6 to ≤12 months				42 (22.0%)	81 (28.3%)
>12 months				15 (7.9%)	56 (19.6%)
Dose intensity (%)					
Median	98.8	97.7	92.1	97.7	99.4
Min – Max	71 - 102	67 - 102	64 - 101	67 - 102	55 - 108
Number of doses received					
Median	4.0	4.0	8.0	6.0	8.0
Min – Max	1 - 6	1 - 6	1 - 12	1 - 28	1 - 49

Source: t_ex_atz_SE_10Sep2018_29431, t_ex_car_SE_10Sep2018_29431, t_ex_cis_SE_10Sep2018_29431, t_ex_gem_SE_10Sep2018_29431, t_ex_pem_SE_10Sep2018_29431

Table 24: Exposure to study treatment (safety-evaluable population)

	Interim Analysis (CCOD: 10 September 2018)					Updated Analysis (CCOD: 4 February 2020)				
	Chemotherapy n = 263				Atezolizumab n = 286	Chemotherapy n = 263				Atezolizumab * n = 286
	Cisplatin n = 90	Carboplatin n = 177	Gemcitabine n = 75	Pemetrexed n = 191		Cisplatin n = 90	Carboplatin n = 177	Gemcitabine n = 75	Pemetrexed n = 191	
Median Treatment duration (Month)	2.1	2.3	2.6	3.5	5.3	2.1	2.3	2.6	3.5	5.3
Min – Max	0 - 5	0 - 5	0 - 5	0 - 20	0 - 33	0 - 5	0 - 5	0 - 5	0 - 30	0 - 50
Median Dose intensity (%)	98.8	97.7	92.1	97.7	99.4	98.8	97.7	92.1	97.7	98.8
Min – Max	71 - 102	67 - 102	64 - 101	67 - 102	55 - 108	71 - 102	67 - 102	64 - 101	67 - 102	55 - 108
Number of doses (Median)	4	4	8	6	8	4	4	8	6	8
Min – Max	1 - 6	1 - 6	1 - 12	1 - 28	1 - 49	1 - 6	1 - 6	1 - 12	1 - 44	1 - 73

CCOD=clinical cut-off date; Min=minimum; Max=maximum.

* Two patients in the atezolizumab arm also received gemcitabine and carboplatin treatment.

Source: CSR Table 39 and Appendix 4, Appendix 5, Appendix 6, Appendix 7, Appendix 8.

Adverse events

Table 25: Overall summary of adverse events (safety-evaluable population)

	Overall (N=549)	
	Chemotherapy (N=263)	Atezolizumab (N=286)
Total number of patients with at least one adverse event	250 (95.1%)	263 (92.0%)
Total number of events	2092	2237
Total number of patients with at least one		
Treatment-related AE	224 (85.2%)	180 (62.9%)
Grade 3-4 AE	140 (53.2%)	97 (33.9%)
Treatment-related Grade 3-4 AE	118 (44.9%)	41 (14.3%)
Grade 5 AE	11 (4.2%)	12 (4.2%)
Treatment-related Grade 5 AE	1 (0.4%)	0
Serious Adverse Event	77 (29.3%)	91 (31.8%)
Treatment-Related Serious Adverse Event	41 (15.6%)	27 (9.4%)
AE leading to any treatment withdrawal	45 (17.1%)	21 (7.3%)
- Atezolizumab	0	21 (7.3%)
- Cisplatin	10 (3.8%)	0
- Carboplatin	16 (6.1%)	0
- Pemetrexed	30 (11.4%)	0
- Gemcitabine	13 (4.9%)	0
AE leading to dose modification/interruption	117 (44.5%)	90 (31.5%)
- Atezolizumab	0	89 (31.1%)
- Cisplatin	27 (10.3%)	0
- Carboplatin	64 (24.3%)	1 (0.3%)
- Pemetrexed	78 (29.7%)	0
- Gemcitabine	37 (14.1%)	1 (0.3%)

Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v22.1. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.
Counts in "Grade 3-4 AE" are number of patients whose highest grades of AE are 3 or 4.
Data Extraction Date - 24MAR2020 ; Data Cutoff Date - 04FEB2020.

Table 26: Adverse events with an incidence rate of at least 10% in any treatment arm by system organ class and preferred term (safety-evaluable population)

Adverse Events with an Incidence Rate of at Least 10% in Any Treatment Arm by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: GO29431

	Overall (N=549)	
MedDRA System Organ Class MedDRA Preferred Term	Chemotherapy (N=263)	Atezolizumab (N=286)
Total number of patients with at least one adverse event	219 (83.3%)	194 (67.8%)
Gastrointestinal disorders		
Total number of patients with at least one adverse event	134 (51.0%)	91 (31.8%)
Nausea	89 (33.8%)	39 (13.6%)
Constipation	57 (21.7%)	35 (12.2%)
Diarrhoea	31 (11.8%)	32 (11.2%)
Vomiting	34 (12.9%)	18 (6.3%)
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event	161 (61.2%)	50 (17.5%)
Anaemia	125 (47.5%)	44 (15.4%)
Neutropenia	74 (28.1%)	4 (1.4%)
Thrombocytopenia	44 (16.7%)	7 (2.4%)
General disorders and administration site conditions		
Total number of patients with at least one adverse event	102 (38.8%)	98 (34.3%)
Asthenia	46 (17.5%)	37 (12.9%)
Fatigue	46 (17.5%)	37 (12.9%)
Pyrexia	23 (8.7%)	39 (13.6%)
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	42 (16.0%)	59 (20.6%)
Dyspnoea	26 (9.9%)	40 (14.0%)
Cough	25 (9.5%)	34 (11.9%)
Metabolism and nutrition disorders		
Total number of patients with at least one adverse event	50 (19.0%)	44 (15.4%)
Decreased appetite	50 (19.0%)	44 (15.4%)
Investigations		
Total number of patients with at least one adverse event	15 (5.7%)	30 (10.5%)
Alanine aminotransferase increased	15 (5.7%)	30 (10.5%)

Investigator text for AEs encoded using MedDRA v22.0. All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient. To the SOC (System Organ Class) Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC. Percentages are based on N in the column headings. AEs collected after first treatment dose are included.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Table 27: Adverse events with at least 5% difference between treatment arms by system organ class and preferred term (safety-evaluable population)

Adverse Events with a Difference of at Least 5% between Treatment Arms by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: GO29431

	Overall (N=549)	
MedDRA System Organ Class MedDRA Preferred Term	Chemotherapy (N=263)	Atezolizumab (N=286)
Total number of patients with at least one adverse event	249 (94.7%)	258 (90.2%)
Overall total number of events	1994	1839
Gastrointestinal disorders		
Total number of patients with at least one adverse event	143 (54.4%)	124 (43.4%)
Total number of events	369	230
Nausea	89 (33.8%)	39 (13.6%)
Constipation	57 (21.7%)	35 (12.2%)
Vomiting	34 (12.9%)	18 (6.3%)
Investigations		
Total number of patients with at least one adverse event	97 (36.9%)	79 (27.6%)
Total number of events	199	204
Aspartate aminotransferase increased	9 (3.4%)	28 (9.8%)
Blood creatinine increased	23 (8.7%)	8 (2.8%)
Platelet count decreased	22 (8.4%)	1 (0.3%)
Neutrophil count decreased	19 (7.2%)	0
Skin and subcutaneous tissue disorders		
Total number of patients with at least one adverse event	46 (17.5%)	76 (26.6%)
Total number of events	59	112
Pruritus	4 (1.5%)	19 (6.6%)
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event	168 (63.9%)	55 (19.2%)
Total number of events	416	99
Anaemia	125 (47.5%)	44 (15.4%)
Thrombocytopenia	44 (16.7%)	7 (2.4%)
Neutropenia	74 (28.1%)	4 (1.4%)
Leukopenia	21 (8.0%)	3 (1.0%)
Endocrine disorders		
Total number of patients with at least one adverse event	4 (1.5%)	35 (12.2%)
Total number of events	4	40
Hypothyroidism	2 (0.8%)	22 (7.7%)

Investigator text for AEs encoded using MedDRA v22.0. All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient. To the SOC (System Organ Class) Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC. Percentages are based on N in the column headings. AEs collected after first treatment dose are included.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Table 28: Adverse events related to any study treatment with an incidence rate of at least 10% by system organ class and preferred term (safety-evaluable population)

Adverse Events Related to Any Study Treatment with an Incidence Rate of at Least 10% by System Organ Class and Preferred Term, Safety-
Evaluable Patients
Protocol: GO29431

	Overall (N=549)	
MedDRA System Organ Class MedDRA Preferred Term	Chemotherapy (N=263)	Atezolizumab (N=286)
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event	155 (58.9%)	16 (5.6%)
Anaemia	119 (45.2%)	10 (3.5%)
Neutropenia	72 (27.4%)	3 (1.0%)
Thrombocytopenia	44 (16.7%)	5 (1.7%)
Gastrointestinal disorders		
Total number of patients with at least one adverse event	103 (39.2%)	29 (10.1%)
Nausea	83 (31.6%)	20 (7.0%)
Constipation	35 (13.3%)	10 (3.5%)
Vomiting	32 (12.2%)	4 (1.4%)
General disorders and administration site conditions		
Total number of patients with at least one adverse event	65 (24.7%)	42 (14.7%)
Asthenia	35 (13.3%)	21 (7.3%)
Fatigue	32 (12.2%)	22 (7.7%)
Metabolism and nutrition disorders		
Total number of patients with at least one adverse event	42 (16.0%)	20 (7.0%)
Decreased appetite	42 (16.0%)	20 (7.0%)

Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. For frequency counts
by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of
"Total number of events" rows, the multiple occurrences of the same AE in an individual are counted separately.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Table 29: Grade 3-4 adverse events with an incidence of at least 5% in any treatment arm (safety-evaluable population)

Grade 3 or 4 Adverse Events, Incidence of at Least 5% in Any Treatment Arm by System Organ Class and Preferred Term, Safety-Evaluable
Patients
Protocol: GO29431

	Overall (N=549)	
MedDRA System Organ Class MedDRA Preferred Term	Chemotherapy (N=263)	Atezolizumab (N=286)
Total number of patients with at least one adverse event	87 (33.1%)	7 (2.4%)
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event	87 (33.1%)	7 (2.4%)
Anaemia	48 (18.3%)	5 (1.7%)
Neutropenia	46 (17.5%)	2 (0.7%)
Thrombocytopenia	19 (7.2%)	1 (0.3%)

Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. For frequency counts
by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of
"Total number of events" rows, the multiple occurrences of the same AE in an individual are counted separately.
Total Number of Patients and Total Number of Events summary rows include patients who have a maximum grade of 3 or 4 in any one
Preferred Term.
For accurate totals for only maximum grades 3 and 4 Patients please refer to the t_ae_ctc_3catv_SE table.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Table 30: Grade 3-4 adverse events with a difference of at least 2% between treatment arms (safety-evaluable population)

Grade 3 or 4 Adverse Events with a Difference of at Least 2% between Treatment Arms by Preferred Term, Safety-Evaluable Patients
Protocol: GO29431

MedDRA Preferred Term	Overall (N=549) Chemotherapy (N=263)	Overall (N=549) Atezolizumab (N=286)
Total number of patients with at least one adverse event	141 (53.6%)	91 (31.8%)
Total number of events	285	145
Anaemia	48 (18.3%)	5 (1.7%)
Neutropenia	46 (17.5%)	2 (0.7%)
Thrombocytopenia	19 (7.2%)	1 (0.3%)
Platelet count decreased	11 (4.2%)	0
Neutrophil count decreased	10 (3.8%)	0
Febrile neutropenia	9 (3.4%)	0

Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, the multiple occurrences of the same AE in an individual are counted only once. AEs collected after first treatment dose are included.
Total Number of Patients and Total Number of Events summary rows include patients who have a maximum grade of 3 or 4 in any one Preferred Term.
For accurate totals for only maximum grades 3 and 4 Patients please refer to the t_ae_ctc_3catv_SE table.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Table 31: Overview of safety profile (Safety-evaluable population)

Parameter	Interim Analysis (CCOD: 10 September 2018) Chemotherapy (n=263)	Interim Analysis (CCOD: 10 September 2018) Atezolizumab (n=286)	Updated Analysis (CCOD: 4 February 2020) Chemotherapy (n=263)	Updated Analysis (CCOD: 4 February 2020) Atezolizumab (n=286)
Total number of patients with at least one AE	249 (94.7%)	258 (90.2%)	250 (95.1%)	263 (92.0%)
Treatment-related AE	224 (85.2%)	173 (60.5%)	224 (85.2%)	180 (62.9%)
Grade 3-4 AE	138 (52.5%)	86 (30.1%)	140 (53.2%)	97 (33.9%)
Treatment-related Grade 3-4 AE	116 (44.1%)	37 (12.9%)	118 (44.9%)	41 (14.3%)
Grade 5 AE	11 (4.2%)	11 (3.8%)	11 (4.2%)	12 (4.2%)
Treatment-related Grade 5 AE	1 (0.4%)	0	1 (0.4%)	0
Serious AE	75 (28.5%)	81 (28.3%)	77 (29.3%)	91 (31.8%)
Treatment-related serious AE	41 (15.6%)	24 (8.4%)	41 (15.6%)	27 (9.4%)
AE leading to any treatment withdrawal	43 (16.3%)	18 (6.3%)	45 (17.1%)	21 (7.3%)
AE leading to any dose modification/interruption	116*(44.1%)	74 (25.9%)	117 (44.5%)	90 (31.5%)
AESI	44 (16.7%)	115 (40.2%)	48 (18.3%)	132 (46.2%)
Grade 3-4 AESI	4 (1.5%)	19 (6.6%)	4 (1.5%)	25 (8.7%)
Serious AESI	3 (1.1%)	15 (5.2%)	3 (1.1%)	19 (6.6%)
AESIs leading to any study drug withdrawal	3 (1.1%)	7 (2.4%)	3 (1.1%)	8 (2.8%)
All Grade Atezo AESI requiring use of corticosteroids	3 (1.1%)	30 (10.5%)	4 (1.5%)	38 (13.3%)

AE=adverse event; AESI=adverse event of special interest; CCOD=clinical cut-off date.
* Due to a data entry issue, this number also includes one patient that did not have a dose modification/interruption.
Source: CSR Table 38 and 50, Appendix 1, Appendix 2, Appendix 3.

Adverse events of special interest

Table 32: Summary of adverse events of special interest (safety-evaluable population)

	Overall (N=549)	
	Chemotherapy (N=263)	Atezolizumab (N=286)
Total number of patients with at least one AESI	48 (18.3%)	132 (46.2%)
Total number of AESI events	74	254
Total number of patients with at least one		
Treatment-related AESI	28 (10.6%)	101 (35.3%)
Grade 3-4 AESI	4 (1.5%)	25 (8.7%)
Treatment-related Grade 3-4 AESI	3 (1.1%)	19 (6.6%)
Serious AESI	3 (1.1%)	19 (6.6%)
Treatment-Related Serious AESI	2 (0.8%)	17 (5.9%)
AESI leading to any treatment withdrawal/dose modification/dose interruption	5 (1.9%)	39 (13.6%)
AESI leading to any withdrawal from treatment	3 (1.1%)	8 (2.8%)
- Atezolizumab	0	8 (2.8%)
- Carboplatin	2 (0.8%)	0
- Pemetrexed	1 (0.4%)	0
- Gemcitabine	2 (0.8%)	0
AESI leading to any dose modification/interruption	2 (0.8%)	35 (12.2%)
- Atezolizumab	0	35 (12.2%)
- Cisplatin	1 (0.4%)	0
- Gemcitabine	2 (0.8%)	0
AE of Special Interest Medical Concepts: patients with at least one		
Immune-Mediated Hep. (Diag & Lab Ab)	25 (9.5%)	47 (16.4%)
Immune-Mediated Rash	20 (7.6%)	53 (18.5%)
Immune-Mediated Hepatitis (Lab Abnormal)	25 (9.5%)	46 (16.1%)
Immune-Mediated Hypothyroidism	5 (1.9%)	30 (10.5%)
Immune-Mediated Hyperthyroidism	2 (0.8%)	14 (4.9%)
Immune-Mediated Pneumonitis	1 (0.4%)	12 (4.2%)
Immune-Mediated Diabetes Mellitus	1 (0.4%)	5 (1.7%)
Infusion-Related Reactions	0	4 (1.4%)
Immune-Mediated Hepatitis (Diagnosis)	2 (0.8%)	2 (0.7%)
Immune-Mediated Adrenal Insufficiency	0	3 (1.0%)
Immune-Mediated Colitis	0	3 (1.0%)
Immune-Mediated Pancreatitis	0	3 (1.0%)
Immune-Mediated Myositis	1 (0.4%)	1 (0.3%)
Immune-Mediated Nephritis	1 (0.4%)	1 (0.3%)
Immune-Mediated Ocular Inflam. Toxic	0	2 (0.7%)
Immune-Mediated Severe Cutaneous React.	0	2 (0.7%)
Immune-Mediated Myositis+Rhabdomyolysis	1 (0.4%)	1 (0.3%)
Immune-Mediated Vasculitis	0	1 (0.3%)
Immune-Mediated Myocarditis	0	1 (0.3%)
Haemophagocytic Lymphohistiocytosis	0	1 (0.3%)

AESI = Adverse Event of Special Interest. Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v22.1. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. AEs collected after first treatment dose are included.
Data Extraction Date - 24MAR2020 ; Data Cutoff Date - 04FEB2020.

Adverse drug reactions

The table below reflects the adverse drug reactions related to Tecentriq as identified in the pooled safety dataset for atezolizumab monotherapy (n=3854).

Table 33: Adverse drug reactions for atezolizumab monotherapy (n= 3854)

Atezolizumab monotherapy (n=3,854)		**System Organ Class ADR**
Frequency (All Grades)	Incidence % (All Grades)	
Infections and infestations		
Very common	478 (12.4%)	urinary tract infection[a]
Blood and lymphatic system disorders		
Common	140 (3.6%)	thrombocytopenia[b]
Immune system disorders		
Common	63 (1.6%)	infusion-related reaction[c]
Endocrine disorders		
Common	244 (6.3%)	hypothyroidism[d]
Common	61 (1.6%)	hyperthyroidism[e]
Uncommon	16 (0.4%)	diabetes mellitus[f]
Uncommon	15 (0.4%)	adrenal insufficiency[g]
Rare	3 (<0.1%)	hypophysitis[h]

Metabolism and nutrition disorders		
Very common	904 (23.5%)	decreased appetite
Common	159 (4.1%)	hypokalemia[i]
Common	193 (5.0%)	hyponatremia[j]
Common	134 (3.5%)	hyperglycaemia
Nervous system disorders		
Very common	419 (10.9%)	headache
Uncommon	5 (0.1%)	Guillain-Barré syndrome[k]
Uncommon	14 (0.4%)	meningoencephalitis[l]
Rare	1 (<0.1%)	myasthenic syndrome[m]
Eye disorders		
Rare	3 (<0.1%)	uveitis
Cardiac disorders		
Rare	1 (<0.1%)	myocarditis[n]
Vascular disorders		
Common	109 (2.8%)	hypotension
Respiratory, thoracic, and mediastinal disorders		
Very common	742 (19.3%)	cough
Very common	719 (18.7%)	dyspnoea
Common	111 (2.9%)	pneumonitis[o]
Common	75 (1.9%)	hypoxia[p]
Common	113 (2.9%)	nasal congestion
Common	182 (4.7%)	nasopharyngitis
Gastrointestinal disorders		
Very common	841 (21.8%)	nausea
Very common	525 (13.6%)	vomiting
Very common	745 (19.3%)	diarrhoea[q]
Common	306 (7.9%)	abdominal pain
Common	46 (1.2%)	colitis[r]
Common	92 (2.4%)	dysphagia
Common	153 (4.0%)	oropharyngeal pain[s]
Uncommon	30 (0.8%)	pancreatitis[t]
Hepatobiliary disorders		
Common	229 (5.9%)	AST increased
Common	222 (5.8%)	ALT increased
Common	68 (1.8%)	hepatitis[u]
Skin and subcutaneous tissue disorders		
Very common	758 (19.7%)	rash[v]
Very common	522 (13.5%)	pruritus
Common	225 (5.8%)	dry skin
Uncommon	20 (0.5%)	psoriasis
Uncommon	26 (0.7%)	severe cutaneous adverse reactions[w]
Rare	1 (<0.1%)	pemphigoid
Musculoskeletal and connective tissue disorders		
Very common	506 (13.1%)	arthralgia
Very common	539 (14.0%)	back pain
Very common	551 (14.3%)	musculoskeletal pain[x]
uncommon	16 (0.4%)	myositis[y]
Renal and urinary disorders		
Common	220 (5.7%)	blood creatinine increased[z]
Uncommon	9 (0.2%)	nephritis[aa]
General disorders and administration site conditions		
Very common	760 (19.7%)	pyrexia
Very common	1275 (33.1%)	fatigue
Very common	537 (13.9%)	asthenia
Common	212 (5.5%)	influenza like illness
Common	236 (6.1%)	chills

a. Includes reports of urinary tract infection, cystitis, pyelonephritis, escherichia urinary tract infection, urinary tract infection bacterial, kidney infection, pyelonephritis acute, pyelonephritis chronic, pyelitis, renal abscess, streptococcal urinary tract infection, urethritis, urinary tract infection fungal, urinary tract infection pseudomonal.

b. Includes reports of thrombocytopenia, platelet count decreased.

c. Includes reports of infusion related reaction, cytokine release syndrome, hypersensitivity, anaphylaxis.

d. Includes reports of autoimmune hypothyroidism, autoimmune thyroiditis, blood thyroid stimulating hormone abnormal, blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, euthyroid sick syndrome, goitre,

hypothyroidism, immune-related hypothyroidism, myxedema, myxoedema coma, thyroid disorder, thyroid function test abnormal, thyroiditis, thyroiditis acute, thyroxine decreased, thyroxine free decreased, thyroxine free increased, thyroxine increased, tri-iodothyronine decreased, tri-iodothyronine free abnormal, tri-iodothyronine free decreased, tri-iodothyronine free increased, silent thyroiditis, thyroiditis chronic.

e. Includes reports of hyperthyroidism, Basedow's disease, endocrine ophthalmopathy, exophthalmos.
f. Includes reports of diabetes mellitus, type 1 diabetes mellitus, diabetic ketoacidosis, ketoacidosis.
g. Includes reports of adrenal insufficiency, glucocorticoid deficiency, primary adrenal insufficiency.
h. Includes reports of hypophysitis, temperature regulation disorder.
i. Includes reports of hypokalaemia, blood potassium decreased.
j. Includes reports of hyponatraemia, blood sodium decreased.
k. Includes reports of Guillain Barré syndrome, demyelinating polyneuropathy.
l. Includes reports of encephalitis, meningitis, photophobia.
m. Includes reports of myasthenia gravis.
n. Includes reports of autoimmune myocarditis.
o. Includes reports of pneumonitis, lung infiltration, bronchiolitis, immune-related pneumonitis, interstitial lung disease, lung opacity, pulmonary toxicity, radiation pneumonitis.
p. Includes reports of hypoxia, oxygen saturation decreased, pO2 decreased.
q. Includes reports of diarrhoea, defaecation urgency, frequent bowel movements, diarrhoea haemorrhagic, gastrointestinal hypermotility.
r. Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic, colitis ulcerative, immune-related enterocolitis.
s. Includes reports of oropharyngeal pain, oropharyngeal discomfort, throat irritation.
t. Includes reports of autoimmune pancreatitis, pancreatitis, pancreatitis acute, lipase increased, amylase increased.
u. Includes reports of ascites, autoimmune hepatitis, hepatocellular injury, hepatitis, hepatitis acute, hepatotoxicity, liver disorder, drug-induced liver injury, hepatic failure, hepatic steatosis, hepatic lesion, oesophageal varices haemorrhage, varices oesophageal.
v. Includes reports of acne, acne pustular, blister, blood blister, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis exfoliative, drug eruption, eczema, eczema infected, erythema, erythema of eyelid, eyelid rash, fixed eruption, folliculitis, furuncle, hand dermatitis, lip blister, oral blood blister, palmar-plantar erythrodysaesthesia syndrome, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash papulosquamous, rash pruritic, rash pustular, rash vesicular, scrotal dermatitis, seborrhoeic dermatitis, skin exfoliation, skin toxicity, skin ulcer.
w. Includes reports of dermatitis bullous, exfoliative rash, erythema multiforme, dermatitis exfoliative generalised, toxic skin eruption, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis, cutaneous vasculitis.
x. Includes reports of musculoskeletal pain, myalgia, bone pain.
y. Includes reports of myositis, rhabdomyolysis, polymyalgia rheumatica, dermatomyositis, muscle abscess, myoglobin urine present.
z. Includes reports of blood creatinine increased, hypercreatininaemia.
aa. Includes reports of autoimmune nephritis, nephritis, Henoch-Schonlein Purpura nephritis, paraneoplastic glomerulonephritis, tubulointerstitial nephritis.

Serious adverse event/deaths/other significant events

Table 34: Serious adverse events reported in ≥ 2% of patients in either treatment arms (safety-evaluable population)

Serious Adverse Events, Incidence of at Least 2% in Any Treatment Arm by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: GO29431

	Overall (N=549)	
MedDRA System Organ Class MedDRA Preferred Term	Chemotherapy (N=263)	Atezolizumab (N=286)
Total number of patients with at least one adverse event	28 (10.6%)	19 (6.6%)
Infections and infestations		
Total number of patients with at least one adverse event	11 (4.2%)	8 (2.8%)
Pneumonia	11 (4.2%)	8 (2.8%)
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event	16 (6.1%)	2 (0.7%)
Anaemia	9 (3.4%)	1 (0.3%)
Thrombocytopenia	9 (3.4%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	1 (0.4%)	11 (3.8%)
Pneumonitis	1 (0.4%)	6 (2.1%)
Chronic obstructive pulmonary disease	0	6 (2.1%)

Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, the multiple occurrences of the same AE in an individual are counted separately.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Table 35: Death and the cause of death (safety-evaluable population)

	Chemotherapy (N=263)	Atezolizumab (N=286)	All Patients (N=549)
All Deaths	126 (47.9%)	125 (43.7%)	251 (45.7%)
Adverse Event	11 (4.2%)	11 (3.8%)	22 (4.0%)
Progressive Disease	107 (40.7%)	103 (36.0%)	210 (38.3%)
Other	8 (3.0%)	11 (3.8%)	19 (3.5%)

Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Table 36: Adverse events leading to death (safety-evaluable population)

	Overall (N=549)	
MedDRA System Organ Class MedDRA Preferred Term	Chemotherapy (N=263)	Atezolizumab (N=286)
Total number of patients with at least one adverse event	11 (4.2%)	11 (3.8%)
Overall total number of events	11	11
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	1 (0.4%)	3 (1.0%)
Total number of events	1	3
Aspiration	0	1 (0.3%)
Chronic obstructive pulmonary disease	0	1 (0.3%)
Pulmonary embolism	0	1 (0.3%)
Acute pulmonary oedema	1 (0.4%)	0
Cardiac disorders		
Total number of patients with at least one adverse event	3 (1.1%)	2 (0.7%)
Total number of events	3	2
Acute myocardial infarction	0	1 (0.3%)
Cardiac arrest	2 (0.8%)	1 (0.3%)
Cardiac failure	1 (0.4%)	0
General disorders and administration site conditions		
Total number of patients with at least one adverse event	3 (1.1%)	2 (0.7%)
Total number of events	3	2
Death	3 (1.1%)	2 (0.7%)
Gastrointestinal disorders		
Total number of patients with at least one adverse event	0	1 (0.3%)
Total number of events	0	1
Mechanical ileus	0	1 (0.3%)
Infections and infestations		
Total number of patients with at least one adverse event	3 (1.1%)	1 (0.3%)
Total number of events	3	1
Sepsis	0	1 (0.3%)
Pneumonia	1 (0.4%)	0
Respiratory tract infection	1 (0.4%)	0
Tuberculosis	1 (0.4%)	0
Nervous system disorders		
Total number of patients with at least one adverse event	0	1 (0.3%)
Total number of events	0	1
Cerebral infarction	0	1 (0.3%)
Product issues		
Total number of patients with at least one adverse event	0	1 (0.3%)
Total number of events	0	1
Device occlusion	0	1 (0.3%)
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event	1 (0.4%)	0
Total number of events	1	0
Pancytopenia	1 (0.4%)	0

Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, the multiple occurrences of the same AE in an individual are counted separately.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Laboratory findings

Table 37: Summary of clinically relevant laboratory shifts from baseline

Summary of Laboratory Grade Shifts from NCI-CTCAE Grade missing, 0-2 at Baseline to Grade 3-4 Post-Baseline, Safety-Evaluable Patients

Laboratory Test Category Laboratory Test	Grade Direction	Chemotherapy (N=263)	Atezolizumab (N=286)
Chemistry			
Albumin (g/L)	Low	3/255 (1.2%)	1/281 (0.4%)
Alkaline Phosphatase (U/L)	High	1/255 (0.4%)	7/281 (2.5%)
Bilirubin (umol/L)	High	1/259 (0.4%)	9/280 (3.2%)
Calcium (mmol/L)	High	1/258 (0.4%)	10/279 (3.6%)
	Low	6/257 (2.3%)	3/279 (1.1%)
Creatinine (umol/L)	High	5/259 (1.9%)	2/281 (0.7%)
Glucose (mmol/L)	Low	1/257 (0.4%)	1/280 (0.4%)
Magnesium (mmol/L)	High	5/255 (2.0%)	12/277 (4.3%)
	Low	4/257 (1.6%)	1/280 (0.4%)
Phosphorus (mmol/L)	Low	4/254 (1.6%)	10/279 (3.6%)
Potassium (mmol/L)	High	7/256 (2.7%)	11/281 (3.9%)
	Low	6/257 (2.3%)	3/281 (1.1%)
SGOT/AST (U/L)	High	2/259 (0.8%)	9/281 (3.2%)
SGPT/ALT (U/L)	High	2/259 (0.8%)	9/281 (3.2%)
Sodium (mmol/L)	High	0/259	0/281
	Low	12/252 (4.8%)	24/277 (8.7%)
Coagulation			
Activated Partial Thromboplastin Time (sec)	High	1/141 (0.7%)	0/107
International Normalized Ratio (FRACTION)	High	2/151 (1.3%)	2/114 (1.8%)
Hematology			
Hemoglobin (g/L)	High	1/260 (0.4%)	1/281 (0.4%)
	Low	53/260 (20.4%)	5/281 (1.8%)
Lymphocytes Abs (10^9/L)	High	0/259	0/278
	Low	44/259 (17.0%)	25/277 (9.0%)
Neutrophils, Total, Abs (10^9/L)	Low	69/260 (26.5%)	2/281 (0.7%)
Platelet (10^9/L)	Low	34/260 (13.1%)	2/281 (0.7%)
White Blood Cell Count (10^9/L)	High	1/257 (0.4%)	0/281
	Low	40/260 (15.4%)	1/281 (0.4%)

NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events. Extended NCI-CTCAEv4 was used. For each laboratory test, patients with at least one post-baseline assessment were included in the analysis. For each cell, the denominator is the number of patients with baseline values of NCI-CTCAE Grade 0-2 in the specified direction of abnormality or with missing baseline values. Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Two patients in the atezolizumab arm had laboratory abnormalities suggestive of Hy's law, however none of these cases qualified as true Hy's law as the liver function abnormalities could be attributed to alternate etiologies. One patient developed elevated liver function tests after 1 cycle of atezolizumab on study Day 16, which was confounded by his liver metastasis at enrollment and the development of new liver lesion revealed by tumor assessment on study Day 19. Atezolizumab was permanently discontinued. The patient received treatment with systemic corticosteroids, after which his ALT and AST followed a downward trend though bilirubin remained at a high level on study Day 21.

Another patient developed elevated liver function tests after 1 cycle of atezolizumab on study Day 23, which was confounded by his liver metastasis at enrollment and a concurrently developed cholangitis associated with the self-administered herbal treatment after study treatment initiation. The patient

continued receiving Cycle 2 treatment on Study Day 23. His cholangitis and transaminitis were managed with percutaneous transhepatic biliary drainage without systemic corticosteroid treatment.

Shifts in Thyroid Stimulating Hormone

The majority of patients with normal thyroid stimulating hormone (TSH) at baseline maintained normal TSH post-baseline. A higher proportion of patients in the atezolizumab arm had treatment-emergent TSH abnormalities (defined as normal at baseline and abnormal at post-baseline) compared to the chemotherapy arm (TSH high: 5% chemotherapy vs. 13% atezolizumab; TSH low: 9% vs. 11%).

ECG/Vital signs

The overall incidence of clinically-significant ECG abnormalities post-baseline was low and was balanced between the two treatment arms. Four patients in the chemotherapy arm and 1 patient in the atezolizumab arm had a clinically significant ECG abnormality at baseline. No post-baseline clinically significant ECG abnormalities were reported among these patients.

Post baseline, clinically significant ECG abnormalities were reported in 2 patients in the chemotherapy arm and 3 patients in the atezolizumab arm, although the baseline ECG results of these patients were either normal or abnormal but not clinically significant. In the chemotherapy arm, one patient developed a Grade 2 myocardial ischaemia and a Grade 1 atrioventricular block on Study Days 64 and 85, respectively, with clinically significant ECG abnormalities reported on the same day. The other patient developed a Grade 1 ejection fraction decreased on Study Day 27 and clinically significant ECG abnormality was reported on Study Day 127. In the atezolizumab arm, one patient developed a Grade 1 atrial fibrillation on Study Day 621, with clinically significant ECG abnormalities reported on Study Days 631 and 673. The other patient developed a Grade 2 atrial fibrillation on Study Day 363, with clinically significant ECG abnormalities reported 1 day later. The third patient did not have reported AEs under the Cardiac Disorders SOC.

No clinically relevant difference in vital signs was observed between the two treatment arms.

Anti-Drug Antibodies

Subgroup Analyses of Safety by Treatment-Emergent ADA Status

In the ADA evaluable population, the atezolizumab ADA incidence rate was 24.3% post-baseline. The post-baseline ADA incidence rate in the TC3 or IC3 WT population was 23.5%. Among ADA-evaluable patients in the safety evaluable population, ADA-negative and ADA-positive patients received atezolizumab for a median duration of 6.8 and 4.9 months (median of 10 and 8 cycles), respectively. An overview of safety by ADA status is shown in Table 50.

Table 38: Safety Summary Profile by Atezolizumab ADA Status (ADA-Evaluable Atezolizumab Patients in Safety Evaluable Population)

	ADA- (N=202)	ADA+ (N=65)
Total number of patients with at least one adverse event	182 (90.1%)	64 (98.5%)
Total number of events	1332	473
Total number of patients with at least one		
Treatment-related AE	128 (63.4%)	41 (63.1%)
Grade 3-4 AE	58 (28.7%)	26 (40.0%)
Treatment-related Grade 3-4 AE	23 (11.4%)	11 (16.9%)
Grade 5 AE	3 (1.5%)	2 (3.1%)
Serious Adverse Event	45 (22.3%)	25 (38.5%)
Treatment-Related Serious Adverse Event	15 (7.4%)	6 (9.2%)
AE leading to atezolizumab treatment withdrawal	10 (5.0%)	5 (7.7%)
AE leading to dose modification/interruption	51 (25.2%)	20 (30.8%)

Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.
Counts in "Grade 3-4 AE" are number of patients whose highest grades of AE are 3 or 4.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

No preferred terms with a ≥5% higher incidence of Grade 3 or grade 4 AEs were seen between ADA-positive and ADA-negative patients.

SAEs were observed at a higher frequency in ADA-positive compared with ADA-negative patients. These SAEs were observed in few patients and were not driven by any specific PT. The most frequent (> 1 patient) SAEs reported in ADA-positive patients were pneumonia (5 [3%] ADA-negative vs 3 [5%] ADA-positive patients), and respiratory tract infection (0 vs 3 patients [5%], respectively). All other SAEs reported in the ADA-positive patients were single occurrences and distributed across multiple SOCs.

Infusion related reactions were infrequent and observed in both ADA- and ADA+ patients; all cases were of grade 1 or 2 intensity (Table 51) and none of the patient withdrew atezolizumab due to an infusion related reaction.

A grade 4 anaphylactic reaction was reported in the ADA-positive subgroup; the event occurred on Day 22 (ADAs were detected in this patient on Day 21). The event was considered by the investigator as related to atezolizumab treatment and atezolizumab was discontinued. The event resolved within 1 day.

A grade 4 haemophagocytic lymphohistiocytosis event was reported in the ADA-positive subgroup; the event occurred on Day 115 (ADAs were detected in this patient on Days 21 and 63). The event was considered by the investigator as related to atezolizumab treatment. The event resolved after 27 days.

Table 39: Selected Adverse Events by Highest NCI CTCAE Grade by ADA Status (ADA Evaluable Atezolizumab Patients in Safety Evaluable Population)

		ADA- (N=202)	ADA+ (N=65)
MedDRA preferred term	Grade		
Infusion related reaction	1	0	1 (1.5%)
	2	1 (0.5%)	2 (3.1%)
Hypersensitivity	2	0	1 (1.5%)
	3	1 (0.5%)	0
Anaphylactic reaction	4	0	1 (1.5%)
Haemophagocytic lymphohistiocytosis	4	0	1 (1.5%)

Two grade 5 events were seen in ADA-positive patients. These patients both had early ADA-positive samples but had subsequent ADA-negative sample results which were taken prior to the grade 5 AE.

The incidence of **AESIs** was lower in ADA-positive (36.9%) compared with ADA-negative patients (44.6%), as were the incidence of treatment-related AESIs (26.2% vs. 35.1%). Nonetheless, the incidence of grade 3-4 AESIs (6.4% ADA- vs. 7.7% ADA+), serious AESIs (5.4% vs. 4.6%), and AESIs leading to treatment discontinuation (2.5% vs. 1.5%) was overall balanced between the ADA- and ADA+ patients. There were no AESI medical concepts with ≥5% difference in incidence between patients with different ADA status.

AESI PTs with incidence ≥2% higher in the ADA+ patients included ALT increased (10.4% vs. 13.8%), AST increased (9.4% vs. 13.8%), erythema (1.0 vs. 3.1%), and infusion related reaction (0.5% vs. 4.6%); with incidence ≥2% higher in the ADA- patients included GGT increased (2.5% vs. 0), hyperthyroidism (5.4% vs. 1.5%), of which events of grade 3-4 severity were overall balanced.

Table 40: Overview of AESI, ADA Evaluable Atezolizumab Treated Patients

	ADA- (N=202)	ADA+ (N=65)
Total number of patients with at least one AESI	90 (44.6%)	24 (36.9%)
Total number of AESI events	161	52
Total number of patients with at least one		
Treatment-related AESI	71 (35.1%)	17 (26.2%)
Grade 3-4 AESI	13 (6.4%)	5 (7.7%)
Treatment-related Grade 3-4 AESI	9 (4.5%)	5 (7.7%)
Serious AESI	11 (5.4%)	3 (4.6%)
Treatment-Related Serious AESI	9 (4.5%)	3 (4.6%)
AESI leading to any treatment withdrawal/dose modification/dose interruption	22 (10.9%)	9 (13.8%)
AESI leading to any withdrawal from treatment	5 (2.5%)	1 (1.5%)
- Atezolizumab	5 (2.5%)	1 (1.5%)
AESI leading to any dose modification/interruption	19 (9.4%)	8 (12.3%)
- Atezolizumab	19 (9.4%)	8 (12.3%)
AE of Special Interest Medical Concepts: patients with at least one		
Immune-Mediated Hep. (Diag & Lab Ab)	32 (15.8%)	13 (20.0%)
Immune-Mediated Hepatitis (Lab Abnormal)	31 (15.3%)	13 (20.0%)
Immune-Mediated Rash	35 (17.3%)	9 (13.8%)
Immune-Mediated Hypothyroidism	21 (10.4%)	6 (9.2%)
Immune-Mediated Hyperthyroidism	11 (5.4%)	2 (3.1%)
Immune-Mediated Pneumonitis	8 (4.0%)	2 (3.1%)
Infusion-Related Reactions	1 (0.5%)	3 (4.6%)
Immune-Mediated Colitis	3 (1.5%)	0
Immune-Mediated Diabetes Mellitus	0	2 (3.1%)
Immune-Mediated Adrenal Insufficiency	2 (1.0%)	0
Immune-Mediated Myositis	1 (0.5%)	0
Immune-Mediated Severe Cutaneous React.	1 (0.5%)	1 (1.5%)
Immune-Mediated Hepatitis (Diagnosis)	1 (0.5%)	0
Immune-Mediated Myositis+Rhabdomyolysis	1 (0.5%)	0
Immune-Mediated Nephritis	1 (0.5%)	0
Immune-Mediated Vasculitis	1 (0.5%)	0
Immune-Mediated Myocarditis	1 (0.5%)	0

AESI = Adverse Event of Special Interest. Only events reported in the Adverse Events Form are included.

Safety in special populations

Intrinsic factors

Table 41: Overview of safety by age (safety-evaluable population)

	Overall (N=549)								
	Chemotherapy (N=263)					Atezolizumab (N=286)			
	< 65 (N=127)	>= 65 (N=136)	65 to 74 (N=114)	75 to 84 (N=21)	>= 85 (N=1)	< 65 (N=149)	>= 65 (N=137)	65 to 74 (N=109)	75 to 84 (N=28)
Total number of patients with at least one adverse event	121 (95.3%)	128 (94.1%)	106 (93.0%)	21 (100.0%)	1 (100.0%)	134 (89.9%)	124 (90.5%)	101 (92.7%)	23 (82.1%)
Total number of events	942	1052	861	187	4	977	862	688	174
Total number of patients with at least one									
Treatment-related AE	111 (87.4%)	113 (83.1%)	92 (80.7%)	20 (95.2%)	1 (100.0%)	85 (57.0%)	88 (64.2%)	70 (64.2%)	18 (64.3%)
Grade 3-4 AE	70 (55.1%)	68 (50.0%)	53 (46.5%)	14 (66.7%)	1 (100.0%)	44 (29.5%)	42 (30.7%)	36 (33.0%)	6 (21.4%)
Treatment-related Grade 3-4 AE	57 (44.9%)	59 (43.4%)	44 (38.6%)	14 (66.7%)	1 (100.0%)	14 (9.4%)	23 (16.8%)	19 (17.4%)	4 (14.3%)
Grade 5 AE	5 (3.9%)	6 (4.4%)	5 (4.4%)	1 (4.8%)	0	6 (4.0%)	5 (3.6%)	4 (3.7%)	1 (3.6%)
Treatment-related Grade 5 AE	1 (0.8%)	0	0	0	0	0	0	0	0
Serious Adverse Event	34 (26.8%)	41 (30.1%)	32 (28.1%)	9 (42.9%)	0	44 (29.5%)	37 (27.0%)	31 (28.4%)	6 (21.4%)
Treatment-Related Serious Adverse Event	18 (14.2%)	23 (16.9%)	15 (13.2%)	8 (38.1%)	0	12 (8.1%)	12 (8.8%)	10 (9.2%)	2 (7.1%)
AE leading to any treatment withdrawal	13 (10.2%)	30 (22.1%)	25 (21.9%)	4 (19.0%)	1 (100.0%)	5 (3.4%)	13 (9.5%)	11 (10.1%)	2 (7.1%)
- Atezolizumab	0	0	0	0	0	5 (3.4%)	13 (9.5%)	11 (10.1%)	2 (7.1%)
- Cisplatin	5 (3.9%)	5 (3.7%)	5 (4.4%)	0	0	0	0	0	0
- Carboplatin	2 (1.6%)	13 (9.6%)	11 (9.6%)	2 (9.5%)	0	0	0	0	0
- Pemetrexed	9 (7.1%)	19 (14.0%)	16 (14.0%)	2 (9.5%)	1 (100.0%)	0	0	0	0
- Gemcitabine	4 (3.1%)	9 (6.6%)	7 (6.1%)	2 (9.5%)	0	0	0	0	0
AE leading to dose modification/ interruption	50 (39.4%)	66 (48.5%)	53 (46.5%)	13 (61.9%)	0	32 (21.5%)	42 (30.7%)	33 (30.3%)	9 (32.1%)
- Atezolizumab	0	0	0	0	0	32 (21.5%)	41 (29.9%)	32 (29.4%)	9 (32.1%)
- Cisplatin	17 (13.4%)	10 (7.4%)	9 (7.9%)	1 (4.8%)	0	0	0	0	0
- Carboplatin	22 (17.3%)	42 (30.9%)	32 (28.1%)	10 (47.6%)	0	0	1 (0.7%)	1 (0.9%)	0
- Pemetrexed	34 (26.8%)	43 (31.6%)	33 (28.9%)	10 (47.6%)	0	0	0	0	0
- Gemcitabine	15 (11.8%)	22 (16.2%)	19 (16.7%)	3 (14.3%)	0	0	1 (0.7%)	1 (0.9%)	0

Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.
Counts in "Grade 3-4 AE" are number of patients whose highest grades of AE are 3 or 4.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Table 42: Overview of safety by gender (safety-evaluable population)

	Overall (N=549)			
	Chemotherapy (N=263)		Atezolizumab (N=286)	
	Female (N=81)	Male (N=182)	Female (N=87)	Male (N=199)
Total number of patients with at least one adverse event	76 (93.8%)	173 (95.1%)	82 (94.3%)	176 (88.4%)
Total number of events	678	1316	661	1178
Total number of patients with at least one				
Treatment-related AE	72 (88.9%)	152 (83.5%)	54 (62.1%)	119 (59.8%)
Grade 3-4 AE	44 (54.3%)	94 (51.6%)	26 (29.9%)	60 (30.2%)
Treatment-related Grade 3-4 AE	36 (44.4%)	80 (44.0%)	16 (18.4%)	21 (10.6%)
Grade 5 AE	3 (3.7%)	8 (4.4%)	3 (3.4%)	8 (4.0%)
Treatment-related Grade 5 AE	0	1 (0.5%)	0	0
Serious Adverse Event	23 (28.4%)	52 (28.6%)	27 (31.0%)	54 (27.1%)
Treatment-Related Serious Adverse Event	14 (17.3%)	27 (14.8%)	11 (12.6%)	13 (6.5%)
AE leading to any treatment withdrawal	14 (17.3%)	29 (15.9%)	10 (11.5%)	8 (4.0%)
- Atezolizumab	0	0	10 (11.5%)	8 (4.0%)
- Cisplatin	5 (6.2%)	5 (2.7%)	0	0
- Carboplatin	3 (3.7%)	12 (6.6%)	0	0
- Pemetrexed	9 (11.1%)	19 (10.4%)	0	0
- Gemcitabine	3 (3.7%)	10 (5.5%)	0	0
AE leading to dose modification/interruption	40 (49.4%)	76 (41.8%)	15 (17.2%)	59 (29.6%)
- Atezolizumab	0	0	15 (17.2%)	58 (29.1%)
- Cisplatin	12 (14.8%)	15 (8.2%)	0	0
- Carboplatin	19 (23.5%)	45 (24.7%)	0	1 (0.5%)
- Pemetrexed	30 (37.0%)	47 (25.8%)	0	0
- Gemcitabine	10 (12.3%)	27 (14.8%)	0	1 (0.5%)

Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.
Counts in "Grade 3-4 AE" are number of patients whose highest grades of AE are 3 or 4.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Table 43: Overview of safety by race (safety-evaluable population)

	Overall (N=549)							
	Chemotherapy (N=263)				Atezolizumab (N=286)			
	White (N=224)	Black (N=2)	Asian (N=32)	Other (N=5)	White (N=233)	Black (N=2)	Asian (N=48)	Other (N=3)
Total number of patients with at least one adverse event	210 (93.8%)	2 (100.0%)	32 (100.0%)	5 (100.0%)	206 (88.4%)	2 (100.0%)	47 (97.9%)	3 (100.0%)
Total number of events	1618	18	327	31	1444	20	360	15
Total number of patients with at least one								
Treatment-related AE	186 (83.0%)	2 (100.0%)	32 (100.0%)	4 (80.0%)	132 (56.7%)	1 (50.0%)	38 (79.2%)	2 (66.7%)
Grade 3-4 AE	111 (49.6%)	2 (100.0%)	22 (68.8%)	3 (60.0%)	68 (29.2%)	0	17 (35.4%)	1 (33.3%)
Treatment-related Grade 3-4 AE	91 (40.6%)	2 (100.0%)	20 (62.5%)	3 (60.0%)	29 (12.4%)	0	8 (16.7%)	0
Grade 5 AE	10 (4.5%)	0	1 (3.1%)	0	11 (4.7%)	0	0	0
Treatment-related Grade 5 AE	1 (0.4%)	0	0	0	0	0	0	0
Serious Adverse Event	65 (29.0%)	0	8 (25.0%)	2 (40.0%)	61 (26.2%)	0	20 (41.7%)	0
Treatment-Related Serious Adverse Event	33 (14.7%)	0	7 (21.9%)	1 (20.0%)	15 (6.4%)	0	9 (18.8%)	0
AE leading to any treatment withdrawal	33 (14.7%)	0	7 (21.9%)	3 (60.0%)	12 (5.2%)	0	6 (12.5%)	0
- Atezolizumab	0	0	0	0	12 (5.2%)	0	6 (12.5%)	0
- Cisplatin	7 (3.1%)	0	1 (3.1%)	2 (40.0%)	0	0	0	0
- Carboplatin	10 (4.5%)	0	4 (12.5%)	1 (20.0%)	0	0	0	0
- Pemetrexed	21 (9.4%)	0	6 (18.8%)	1 (20.0%)	0	0	0	0
- Gemcitabine	11 (4.9%)	0	1 (3.1%)	1 (20.0%)	0	0	0	0
AE leading to dose modification/interruption	93 (41.5%)	0	20 (62.5%)	3 (60.0%)	53 (22.7%)	0	21 (43.8%)	0
- Atezolizumab	0	0	0	0	52 (22.3%)	0	21 (43.8%)	0
- Cisplatin	17 (7.6%)	0	8 (25.0%)	2 (40.0%)	0	0	0	0
- Carboplatin	52 (23.2%)	0	11 (34.4%)	1 (20.0%)	1 (0.4%)	0	0	0
- Pemetrexed	61 (27.2%)	0	15 (46.9%)	1 (20.0%)	0	0	0	0
- Gemcitabine	30 (13.4%)	0	5 (15.6%)	2 (40.0%)	1 (0.4%)	0	0	0

Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.
Counts in "Grade 3-4 AE" are number of patients whose highest grades of AE are 3 or 4.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Extrinsic factors

Table 44: Overview of safety by region (safety-evaluable population)

	Overall (N=549)							
	Chemotherapy (N=263)				Atezolizumab (N=286)			
	Asia-Pacific (N=31)	Central and South America (N=14)	Europe and Middle East (N=213)	North America (N=5)	Asia-Pacific (N=47)	Central and South America (N=15)	Europe and Middle East (N=215)	North America (N=9)
Total number of patients with at least one adverse event	31 (100.0%)	14 (100.0%)	199 (93.4%)	5 (100.0%)	46 (97.9%)	15 (100.0%)	188 (87.4%)	9 (100.0%)
Total number of events	313	151	1480	50	347	119	1200	173
Total number of patients with at least one								
Treatment-related AE	31 (100.0%)	13 (92.9%)	175 (82.2%)	5 (100.0%)	38 (80.9%)	9 (60.0%)	118 (54.9%)	8 (88.9%)
Grade 3-4 AE	22 (71.0%)	9 (64.3%)	105 (49.3%)	2 (40.0%)	17 (36.2%)	4 (26.7%)	61 (28.4%)	4 (44.4%)
Treatment-related Grade 3-4 AE	20 (64.5%)	8 (57.1%)	86 (40.4%)	2 (40.0%)	8 (17.0%)	1 (6.7%)	25 (11.6%)	3 (33.3%)
Grade 5 AE	1 (3.2%)	1 (7.1%)	9 (4.2%)	0	0	0	10 (4.7%)	1 (11.1%)
Treatment-related Grade 5 AE	0	0	1 (0.5%)	0	0	0	0	0
Serious Adverse Event	8 (25.8%)	5 (35.7%)	61 (28.6%)	1 (20.0%)	19 (40.4%)	1 (6.7%)	57 (26.5%)	4 (44.4%)
Treatment-Related Serious Adverse Event	7 (22.6%)	2 (14.3%)	31 (14.6%)	1 (20.0%)	9 (19.1%)	0	14 (6.5%)	1 (11.1%)
AE leading to any treatment withdrawal	7 (22.6%)	2 (14.3%)	34 (16.0%)	0	6 (12.8%)	0	12 (5.6%)	0
- Atezolizumab	0	0	0	0	6 (12.8%)	0	12 (5.6%)	0
- Cisplatin	1 (3.2%)	0	9 (4.2%)	0	0	0	0	0
- Carboplatin	4 (12.9%)	1 (7.1%)	10 (4.7%)	0	0	0	0	0
- Pemetrexed	6 (19.4%)	2 (14.3%)	20 (9.4%)	0	0	0	0	0
- Gemcitabine	1 (3.2%)	0	12 (5.6%)	0	0	0	0	0
AE leading to dose modification/interruption	19 (61.3%)	5 (35.7%)	90 (42.3%)	2 (40.0%)	21 (44.7%)	4 (26.7%)	48 (22.3%)	1 (11.1%)
- Atezolizumab	0	0	0	0	21 (44.7%)	4 (26.7%)	47 (21.9%)	1 (11.1%)
- Cisplatin	8 (25.8%)	0	19 (8.9%)	0	0	0	0	0
- Carboplatin	10 (32.3%)	3 (21.4%)	49 (23.0%)	2 (40.0%)	0	0	1 (0.5%)	0
- Pemetrexed	14 (45.2%)	3 (21.4%)	58 (27.2%)	2 (40.0%)	0	0	0	0
- Gemcitabine	5 (16.1%)	2 (14.3%)	30 (14.1%)	0	0	0	1 (0.5%)	0

Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Table 45: Overview of safety by tobacco use history (safety-evaluable population)

	Overall (N=549)					
	Chemotherapy (N=263)			Atezolizumab (N=286)		
	Never (N=40)	Current (N=73)	Previous (N=150)	Never (N=44)	Current (N=75)	Previous (N=167)
Total number of patients with at least one adverse event	35 (87.5%)	68 (93.2%)	146 (97.3%)	41 (93.2%)	63 (84.0%)	154 (92.2%)
Total number of events	326	499	1169	266	463	1110
Total number of patients with at least one						
Treatment-related AE	33 (82.5%)	62 (84.9%)	129 (86.0%)	26 (59.1%)	42 (56.0%)	105 (62.9%)
Grade 3-4 AE	21 (52.5%)	37 (50.7%)	80 (53.3%)	11 (25.0%)	25 (33.3%)	50 (29.9%)
Treatment-related Grade 3-4 AE	18 (45.0%)	29 (39.7%)	69 (46.0%)	5 (11.4%)	10 (13.3%)	22 (13.2%)
Grade 5 AE	1 (2.5%)	4 (5.5%)	6 (4.0%)	1 (2.3%)	3 (4.0%)	7 (4.2%)
Treatment-related Grade 5 AE	1 (2.5%)	0	0	0	0	0
Serious Adverse Event	11 (27.5%)	25 (34.2%)	39 (26.0%)	12 (27.3%)	20 (26.7%)	49 (29.3%)
Treatment-Related Serious Adverse Event	9 (22.5%)	11 (15.1%)	21 (14.0%)	6 (13.6%)	4 (5.3%)	14 (8.4%)
AE leading to any treatment withdrawal	6 (15.0%)	14 (19.2%)	23 (15.3%)	3 (6.8%)	1 (1.3%)	14 (8.4%)
- Atezolizumab	0	0	0	3 (6.8%)	1 (1.3%)	14 (8.4%)
- Cisplatin	2 (5.0%)	5 (6.8%)	3 (2.0%)	0	0	0
- Carboplatin	0	5 (6.8%)	10 (6.7%)	0	0	0
- Pemetrexed	4 (10.0%)	10 (13.7%)	14 (9.3%)	0	0	0
- Gemcitabine	1 (2.5%)	4 (5.5%)	8 (5.3%)	0	0	0
AE leading to dose modification/interruption	18 (45.0%)	36 (49.3%)	62 (41.3%)	7 (15.9%)	16 (21.3%)	51 (30.5%)
- Atezolizumab	0	0	0	7 (15.9%)	15 (20.0%)	51 (30.5%)
- Cisplatin	7 (17.5%)	7 (9.6%)	13 (8.7%)	0	0	0
- Carboplatin	7 (17.5%)	19 (26.0%)	38 (25.3%)	0	1 (1.3%)	0
- Pemetrexed	13 (32.5%)	24 (32.9%)	40 (26.7%)	0	0	0
- Gemcitabine	5 (12.5%)	11 (15.1%)	21 (14.0%)	0	1 (1.3%)	0

Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.
Counts in "Grade 3-4 AE" are number of patients whose highest grades of AE are 3 or 4.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Table 46: Overview of safety by ECOG (safety-evaluable population)

	Overall (N=549)			
	Chemotherapy (N=263)		Atezolizumab (N=286)	
	0 (N=98)	1 (N=165)	0 (N=102)	1 (N=184)
Total number of patients with at least one adverse event	94 (95.9%)	155 (93.9%)	93 (91.2%)	165 (89.7%)
Total number of events	829	1165	714	1125
Total number of patients with at least one				
Treatment-related AE	80 (81.6%)	144 (87.3%)	70 (68.6%)	103 (56.0%)
Grade 3-4 AE	50 (51.0%)	88 (53.3%)	35 (34.3%)	51 (27.7%)
Treatment-related Grade 3-4 AE	40 (40.8%)	76 (46.1%)	15 (14.7%)	22 (12.0%)
Grade 5 AE	2 (2.0%)	9 (5.5%)	0	11 (6.0%)
Treatment-related Grade 5 AE	0	1 (0.6%)	0	0
Serious Adverse Event	19 (19.4%)	56 (33.9%)	27 (26.5%)	54 (29.3%)
Treatment-Related Serious Adverse Event	9 (9.2%)	32 (19.4%)	11 (10.8%)	13 (7.1%)
AE leading to any treatment withdrawal	17 (17.3%)	26 (15.8%)	6 (5.9%)	12 (6.5%)
- Atezolizumab	0	0	6 (5.9%)	12 (6.5%)
- Cisplatin	6 (6.1%)	4 (2.4%)	0	0
- Carboplatin	4 (4.1%)	11 (6.7%)	0	0
- Pemetrexed	10 (10.2%)	18 (10.9%)	0	0
- Gemcitabine	6 (6.1%)	7 (4.2%)	0	0
AE leading to dose modification/interruption	43 (43.9%)	73 (44.2%)	29 (28.4%)	45 (24.5%)
- Atezolizumab	0	0	28 (27.5%)	45 (24.5%)
- Cisplatin	11 (11.2%)	16 (9.7%)	0	0
- Carboplatin	22 (22.4%)	42 (25.5%)	1 (1.0%)	0
- Pemetrexed	30 (30.6%)	47 (28.5%)	0	0
- Gemcitabine	13 (13.3%)	24 (14.5%)	1 (1.0%)	0

Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.
Counts in "Grade 3-4 AE" are number of patients whose highest grades of AE are 3 or 4.
Data Extraction Date - 31AUG2019 ; Data Cutoff Date - 10SEP2018.

Safety related to drug-drug interactions and other interactions

No pharmacokinetic drug-drug interaction studies have been submitted with this application.

Discontinuation due to adverse events

Table 47: Adverse events leading to dose modification/interruption reported in ≥ 2% of patients in either treatment arm (safety-evaluable population)

MedDRA System Organ Class MedDRA Preferred Term	Chemotherapy n=263	Atezolizumab n=286
Total number of patients with at least one adverse event	115 (43.7%)	74 (25.9%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Neutropenia	37 (14.1%)	2 (0.7%)
Anaemia	21 (8.0%)	3 (1.0%)
Thrombocytopenia	21 (8.0%)	1 (0.3%)
Leukopenia	8 (3.0%)	0
INVESTIGATIONS		
Blood creatinine increased	10 (3.8%)	2 (0.7%)
Platelet count decreased	11 (4.2%)	0
Neutrophil count decreased	10 (3.8%)	0
White blood cell count decreased	8 (3.0%)	1 (0.3%)
Alanine aminotransferase increased	2 (0.8%)	6 (2.1%)
Aspartate aminotransferase increased	2 (0.8%)	6 (2.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Pneumonitis	0	6 (2.1%)

Source: t_ae_dosint_SE_10Sep2018_29431

Table 48: Safety summary (safety evaluable population)

	IMpower110		Pooled Population		
	Chemotherapy (N=263)	Atezolizumab (N=286)	Atezo Mono NSCLC (N=1636)	Atezo Mono[1] (N=2616)	Atezo Mono[2] (N=3178)
Total number of patients with at least one AE	249 (94.7%)	258 (90.2%)	1554 (95.0%)	2510 (95.9%)	3051 (96.0%)
Total number of events	1994	1839	15964	27653	33364
Total number of patients with at least one					
Related AE	224 (85.2%)	173 (60.5%)	1076 (65.8%)	1760 (67.3%)	2168 (68.2%)
Grade 3-4 AE	138 (52.5%)	86 (30.1%)	665 (40.6%)	1200 (45.9%)	1482 (46.6%)
Related Grade 3-4 AE	116 (44.1%)	37 (12.9%)	226 (13.8%)	382 (14.6%)	496 (15.6%)
Grade 5 AE	11 (4.2%)	11 (3.8%)	67 (4.1%)	87 (3.3%)	119 (3.7%)
Related Grade 5 AE	1 (0.4%)	0	3 (0.2%)	7 (0.3%)	11 (0.3%)
Serious AE	75 (28.5%)	81 (28.3%)	627 (38.3%)	1065 (40.7%)	1309 (41.2%)
Related serious AE	41 (15.6%)	24 (8.4%)	166 (10.1%)	266 (10.2%)	353 (11.1%)
AE leading to any Study Treatment withdrawal	43 (16.3%)	18 (6.3%)	129 (7.9%)	182 (7.0%)	226 (7.1%)
AE leading to any Study Treatment modification/interruption	115 (43.7%)	74 (25.9%)	436 (26.7%)	718 (27.4%)	882 (27.8%)

Atezo=Atezolizumab. Pooled Atezo Mono NSCLC: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK); Pooled Atezo Mono[1]: Pooled Atezo Mono NSCLC + GO27831(PCD4989g non-NSCLC Cohort) + GO29293(IMVIGOR210); Pooled Atezo Mono[2]: Pooled Atezo Mono[1] + GO29294(IMVIGOR211) + WO29074(IMMOTION150 Arm B).
Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. All treatment emergent AEs are included.

Clinical cut-off dates: GO29431:10SEP2018, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, WO29074:17OCT2016

Post marketing experience

Atezolizumab has been globally approved for the treatment of a variety of cancers, including NSCLC, UC, and triple-negative breast cancer. The full list of the 93 countries in which atezolizumab is approved can be found in the most recent Periodic Benefit Risk Evaluation Report (PBRER) (PBRER 1094093).

Since the International Birth Date (18 May 2016) through 17 May 2019, an estimated cumulative total of 106,316 patients have received atezolizumab from marketing experience. During the PSUR covering the period 17 May 2019 to 17 May 2020 (EMEA/H/C/PSUSA/00010644/202005), pemphigoid was considered as a new adverse drug reaction.

2.5.1. Discussion on clinical safety

The safety database of patients, who received atezolizumab in the pivotal IMpower110 study, consisted of 286 patients. The updated median exposure of atezolizumab was 5.3 months (range 0-50) and atezolizumab monotherapy was given until progressive disease or loss of clinical benefit. Considering the known safety profile of atezolizumab monotherapy in both the targeted disease as well as other tumour types, this is considered acceptable.

The Applicant has provided updated safety data based on the clinical cut-off date of 4 February 2020. As expected, incidences of AEs increased with the longer follow-up. These increases are more apparent in the atezolizumab arm, likely associated with later onset of some of the immune-related AEs and the longer exposure of atezolizumab compared with chemotherapy agents (only for pemetrexed, that is given as maintenance therapy, the maximum number of doses increased with the updated CCOD).

In the pivotal study IMpower110, nearly all patients had **adverse events** and ~63% of the AEs with atezolizumab were treatment-related vs 85% of the ADRs observed with chemotherapy. Grade 3 AEs were observed in more patients on chemotherapy (53% vs 34%); as well as treatment-related grade 3 events (45% vs 14%). Overall, more discontinuations occurred with chemotherapy too, i.e. 17.1% vs 7.3% of patients. Dose modifications/interruptions were also more frequent with chemotherapy (44.5% vs 31.5%). However, SAEs occurred in a similar incidence in both treatment arms (~29%).

The most common TEAEs by PT (not updated) in both treatment arms (atezo vs chemo) were GI disorders (51.0% vs 31.8%); blood and lymphatic system (61.2% vs 17.5%); and general disorders such as asthenia (17.5% vs 12.9%), fatigue (17.5% vs 12.9%) and pyrexia (8.7% vs 13.6%). Dyspnoea (9.9% vs 14.0%) and cough (9.5% vs 11.9%) were also common events, which is reflective of the patient population and the underlying disease. The clinically meaningful differences observed between the treatment arms were typically chemotherapy-related AEs, such as nausea, vomiting, decreased platelets and neutrophil count versus immunotherapy-related hypothyroidism observed frequently with atezolizumab. Similar **treatment-related AEs** were observed in the two treatment arms, most frequently anaemia (45.2% vs 3.5%), neutropenia (27.4% vs 1.0%), and nausea (31.6% vs 7.0%), but were much more commonly observed with chemotherapy. Grade 3-4 treatment-related adverse events were most commonly haematological toxicity observed in the chemotherapy arm.

Adverse events of special interest (AESIs) were immune-related events, such as hepatitis (lab abnormalities), rash, hypo- or hyperthyroidism, and pneumonitis and were more frequently observed with atezolizumab vs chemotherapy (46.2% vs 18.3%). Grade 3-4 events were observed in 8.7% vs 1.5% of the patients, while serious AESIs were observed in 6.6% vs 1.1% of the patients, respectively. Systemic corticosteroids were required for ~13% of the patients who received atezolizumab. This is in line with the well-known safety profile of atezolizumab monotherapy and the level of immune-related toxicity is considered acceptable.

Serious adverse events were a little more common with chemotherapy (10.6% vs 6.6%) and it is noted that especially pneumonia, anaemia, and thrombocytopenia were frequent events. However, pneumonitis and COPD were more commonly observed with atezolizumab. Overall, the risk of SAEs is acceptable and the nature of the events are well-known with both of the study treatments. A total of 22 patients died from adverse events in the study, but none were treatment-related **deaths**.

A shift to a clinically relevant change in **laboratory findings** with atezolizumab vs chemotherapy was more commonly observed regarding alkaline phosphatase, bilirubin, high calcium, low phosphorus, high AST, and ALT. As expected, increased haematological toxicity was observed with chemotherapy. Although two cases were suggestive of Hy's law, it is agreed that they should be attributed to the underlying cancer disease and not atezolizumab treatment. No new unknown laboratory toxicities were observed with atezolizumab in the pivotal study, and the laboratory findings are acceptable for the patient population in this palliative setting.

Adverse events leading to **discontinuation** of atezolizumab was rare and observed in only 7.3% of the patients in the IMpower110 study, which is also in line with the available monotherapy safety data; hence, monotherapy with atezolizumab is usually a tolerable treatment and the rate of discontinuations are acceptable. AEs leading to dose interruptions with atezolizumab were observed in 31.5% of the patients, and were most commonly due to pneumonitis, increased AST/ALAT or anaemia, which is acceptable and consistent with the events observed in the monotherapy pools presented.

Safety by region, smoking status or EGOC PS status did not show any clinically significantly differences.

In the ADA evaluable population, the atezolizumab ADA incidence rate was 24.3% post-baseline. Higher incidences of grade 3-4 AEs (40% vs 29%), treatment-related grade 3-4 AEs (17% vs. 11%), SAEs (39% vs. 22%), and AE leading to dose modification/interruption (31% vs. 25%) were observed in the ADA-positive patients compared to the ADA-negative patients. This is especially noteworthy in the context of the lower exposure in the ADA-positive patients and the most pronounced difference was observed in the SOC infections and infestations (SAEs 15% vs. 7%; grade 3-4 AEs 11% vs. 6%). The incidence of AESIs was lower in ADA-positive (36.9%) compared with ADA-negative patients (44.6%); but grade 3-4 AESIs, serious AESIs, and AESIs leading to withdrawal were comparable. In conclusion, the safety profile appears to be overall unfavourable in the ADA-positive population compared to the ADA-negative population; however, no firm conclusions can be drawn in view of the overall small sample size of the ADA-positive patients (n=65) and the general distribution across different PTs (reflected in section 4.8 of the SmPC).

2.5.2. Conclusions on clinical safety

Overall, the safety profile of both chemotherapy and atezolizumab are consistent with previous observations and the known safety profiles of the treatments, while no new safety signals were observed. The treatment-emergent and the treatment-related AEs were more commonly observed with chemotherapy as expected; however, a similar incidence of SAEs were observed in both arms. Adverse events of special interest were immune-related events, which were more commonly observed with atezolizumab, but still within an acceptable and expected range. The toxicity profile appeared worse in the ADA-positive compared to the ADA-negative population with the limitations of small patient numbers.

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

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 12.1 is acceptable.

No new safety concerns were identified as part of this extension of indication. Therefore, the list of safety concerns, the pharmacovigilance plan and the risk minimisation measures remain unchanged and sufficient to address and mitigate the risks in all approved indications.

The CHMP endorsed the Risk Management Plan version 12.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Immune-related hepatitis Immune-related pneumonitis Immune-related colitis Immune-related pancreatitis Immune-related endocrinopathies (diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency and hypophysitis) Immune-related neuropathies (Guillain-Barré syndrome, and myasthenic syndrome / myasthenia gravis) Immune-related meningoencephalitis Infusion-related reactions Immune-related myocarditis Immune-related nephritis Immune-related myositis
Important potential risks	Anti-drug antibodies Embryo-fetal toxicity
Missing information	Long term use Concomitant or sequential use of atezolizumab with intra-vesical Bacillus Calmette-Guérin vaccine for the treatment of urothelial carcinoma

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				

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
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				
WO29635: A Phase IB/II, Open-Label Study of the Safety and Pharmacology of Atezolizumab Administered with or without Bacille Calmette-Guérin in Patients with High Risk Non Muscle-Invasive Bladder Cancer Ongoing	To evaluate the safety and tolerability of atezolizumab as a single agent and in combination with BCG. To identify the DLTs and to determine the MTD or tolerability at the MAD of BCG in combination with atezolizumab	Concomitant or sequential use of atezolizumab with intra-vesical BCG vaccine for the treatment of urothelial carcinoma	Final CSR	June 2022
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	May 2022
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

ADAs = anti-drug antibodies; BCG = bacillus Calmette-Guerin; CSR = Clinical Study Report; DLT = dose-limiting toxicity;MAD = maximum administered dose; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; OS = overall survival; RCC = renal cell carcinoma; TBD=to be determined

Risk minimisation measures

Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
Immune-Related Hepatitis	**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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Immune-Related Pneumonitis	**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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Immune-Related Colitis	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	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	None **Additional pharmacovigilance activities:** None
Immune-Related Pancreatitis	**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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Immune-Related Endocrinopathies (Diabetes Mellitus, Hypothyroidism, Hyperthryroidism, Adrenal Insufficiency, and Hypophysitis)	**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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Immune-Related Neuropathies (Guillain-Barre Syndrome and Myasthenia Gravis)	**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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Immune-Related Meningoencephalitis	**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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
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 Section 4.8 Undesirable effects	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: • Patient alert cards	
Immune-Related Myocarditis	**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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Immune-related nephritis	**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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Immune-related myositis	**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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
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:**	**Routine pharmacovigilance**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Proposed text in E.U. SmPC: None **No Additional risk minimization measures**	**activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Studies: • MO29983 • MO39171
Concomitant or sequential use of atezolizumab with intra-vesical Bacillus Calmette-Guérin vaccine for the treatment of urothelial carcinoma.	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.4 Special Warnings and Precautions for Use: Includes language that patients who were administered a live attenuated vaccine with 28 days prior to enrolment were excluded from clinical trials **No Additional risk minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study WO29635

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. Particularly, physicians are warned about the delayed onset of atezolizumab effect as a higher number of deaths within 2.5 months after randomisation was observed with atezolizumab compared with chemotherapy in study IMpower110 although it was followed by a long-term survival benefit. 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 extension. The new additions follow the same structure and use similar descriptions and terminology as used in the approved package leaflet. Also, the target group of users will be similar between the approved NSCLC indications and the applied NSCLC indication, with no significant age difference. Moreover, the posology proposed in this application is the same as for the approved indications for Tecentriq as monotherapy.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have a PD-L1 expression ≥ 50% tumour cells (TC) or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1).

3.1.2. Available therapies and unmet medical need

Other available standard therapies for the first-line treatment of metastatic NSCLC (without EGFR mutations or ALK translocations) are platinum-based combination chemotherapy using cisplatin or carboplatin combined with agents such as taxanes, vinorelbine, gemcitabine, or pemetrexed, with or without bevacizumab. These therapies results in overall response rates of approximately 20% and 1-year survival ranging from 31% to 36% (Schiller et al. 2002).

Moreover, for the targeted PD-L1 selected patient population immune checkpoint inhibitors, as either monotherapy or in combination with platinum-based chemotherapy, have shown improved outcomes in terms of OS and progression-free survival (PFS) (Reck et al. 2016; Gandhi et al. 2018; Socinski et al. 2018; Mok et al. 2019; West et al. 2019). Therefore, immune-therapy containing regimens have become the current standard of care for patients, who have tumors with high expression of PD-L1 and consequently the median OS have greatly improved by this approach, e.g. to 30 months with pembrolizumab monotherapy (Reck et al. 2019).

Hence, the targeted PD-L1 selected patient population have several other first-line treatment options, usually either an immune checkpoint inhibitor given as monotherapy or in combination with different chemotherapies. Additional treatment options are still needed for patients with metastatic NSCLC and especially for the patients, who are considered ineligible for combination therapy, and for them monotherapy with an immune checkpoint inhibitor such as atezolizumab would be a valuable treatment option.

3.1.3. Main clinical studies

The pivotal trial for this application is the randomized, phase III, global, multicenter, open-label IMpower110 study, which is designed to evaluate the efficacy and safety of atezolizumab monotherapy compared with platinum-based chemotherapy in PD-L1-selected, chemotherapy-naïve patients with metastatic NSCLC. In total, 572 patients were randomised 1:1; however, the relevant targeted PD-L1 selected study population for the applied indication covers only 205 patients, of which 107 patients with mixed histology were randomised to atezolizumab.

3.2. Favourable effects

The primary endpoint is OS and key secondary endpoints are INV-PFS, INV-ORR, DOR by RECIST 1.1, and analysis according to PD-L1 expression. The primary endpoint of **OS** was met in the PD-L1 selected patient population (TC3 or IC3-WT) at the time of the primary analysis. The KM OS curves first cross, and then they later begin to separate after approximately 5 months of therapy, and from then on atezolizumab monotherapy is superior to chemotherapy, and updated data shows a numerical difference in median OS of 5.5 months, which is an improvement from 14.7 months to 20.2 months, HR 0.764 (95%CI: 0.536; 1.087).

The secondary endpoint **PFS-INV** was improved 3.2 months i.e. from 5.0 months with chemotherapy to 8.2 months with atezolizumab monotherapy, HR 0.592 (95%CI: 0.432; 0.812).

Confirmed **ORR** was numerically increased from 28.6% with chemotherapy to 40.2% with atezolizumab. More patients achieved a PR with atezolizumab.

The median **DOR** was statistically significantly increased from 8.3 months (95%CI: 5.6; 11.0) to 38.9 (16.1; NE) with atezolizumab.

3.3. Uncertainties and limitations about favourable effects

The sample size of the pivotal study was large (n=572), but the relevant PD-L1 selected study population was smaller and comprised 205 patients, of which 107 patients with mixed histology were randomised to the atezolizumab arm. Hence, the data is limited in the subgroup of interest (TC3 or IC3) due to small patient numbers.

Additionally, the KM OS curves cross after approximately 4 months of therapy, so initially, treatment with chemotherapy seems superior to atezolizumab monotherapy and the shape of the curve indicate early deaths with atezolizumab. This is reflected in the SmPC.

The design of the pivotal study and the protocol were changed multiple times during the study. Concerns were raised that these changes could have been driven by knowledge of the pivotal IMpower110 study results and thus, a GCP inspection was initiated. Although the GCP inspection couldn't exclude that protocol amendment was not influenced by knowledge based on internal study data and the decision-making process was not documented adequately, this change was accepted by the CHMP as being driven by external data, mainly from three anti-PD-1/PD-L1 monotherapy 1L NSCLC studies (Checkmate-026, KEYNOTE-042 and MYSTIC), indicating that OS benefit was greatest in patients that express higher levels of PD-L1. The CHMP considered that external data did lead to the decision to introduce the changes to the protocol.

Treatment until loss of clinical benefit i.e. beyond progression was allowed, so the robustness of the PFS result in this open-label study could have been greatly improved by the use of an independent review of PFS as well, which was not done.

Atezolizumab exposure is lower and the efficacy seems reduced in ADA-positive patients. The incidences of ADAs and the impact of efficacy for the TC3/IC3 population are reflected in the SmPC.

3.4. Unfavourable effects

In the pivotal study IMpower110, nearly all patients had **adverse events** and ~63% of the AEs with atezolizumab were treatment-related. The most common treatment-emergent AEs by PT in both treatment arms (atezo vs chemo) were GI disorders (51.0% vs 31.8%); blood and lymphatic system (61.2% vs 17.5%); and general disorders such as asthenia (17.5% vs 12.9%), fatigue (17.5% vs

12.9%), and pyrexia (8.7% vs 13.6%). Dyspnoea (9.9% vs 14.0%) and cough (9.5% vs 11.9%) were also commonly observed and reflective of the patient population and the underlying disease.

Similar **treatment-related AEs** were observed in the two treatment arms, most frequently anaemia (45.2% vs 3.5%), neutropenia (27.4% vs 1.0%), and nausea (31.6% vs 7.0%), but were much more commonly observed with chemotherapy. Grade 3-4 treatment-related AEs were most commonly haematological toxicity observed in the chemotherapy arm.

Adverse events of special interest (AESIs) include immune-related events, such as hepatitis (lab abnormalities), rash, hypo- or hyperthyroidism, and pneumonitis and were more frequently observed with atezolizumab vs chemotherapy (46% vs 18.3%). Grade 3-4 events were observed in 8.7% vs 1.5% of the patients, while serious AESIs were observed in 6.6% vs 1.1% of the patients, respectively. Systemic corticosteroids were required for ~13% of the patients who received atezolizumab.

Serious adverse events were a little more common with chemotherapy (10.6% vs 6.6%) and especially pneumonia, anaemia, and thrombocytopenia were frequent events. Moreover, pneumonitis and COPD were more commonly observed with atezolizumab. A total of 22 patients died from adverse events in the study, but none were treatment-related **deaths**.

A shift to a clinically relevant change in **laboratory findings** with atezolizumab vs chemotherapy was more commonly observed regarding alkaline phosphatase, bilirubin, high calcium, low phosphorus, high AST and ALT. No new unknown laboratory toxicities were observed with atezolizumab in the pivotal study.

Adverse events leading to **discontinuation** of atezolizumab were observed in 7.3% of the patients in the IMpower110 study. AEs leading to dose interruptions with atezolizumab were observed in 31.5% of the patients, and were most commonly due to pneumonitis, increased AST/ALAT, and anaemia.

3.5. Uncertainties and limitations about unfavourable effects

The toxicity profile of atezolizumab appeared worse in the ADA-positive compared to the ADA-negative population with the limitations of small patient numbers (see section 4.8 of the SmPC).

3.6. Effects Table

Table 49: Effects Table for Tecentriq for first-line treatment of metastatic NSCLC (TC3 or IC3-WT) (IMpower110 data cut-off: 04 February 2020)

Effect	Short description	Unit	Treatment Tecentriq	Control Chemotherapy	Uncertainties / Strength of evidence
Favourable Effects					
Primary endpoint					
OS	Overall survival	Months	20.2	14.7	HR 0.764 (0.536;1.087)
Secondary endpoints					
INV-PFS	Investigator-assessed	Months	8.2	5.0	HR 0.592 (0.432;0.812)
ORR	Confirmed response rate	%	40.2	28.6	NS
DOR	Duration of response	Months	38.9 (16.1; NE)	8.3 (5.6;11.0)	
Unfavourable Effects					
Gr 3/4 AE		%	33.9	53.2	
SAEs		%	31.8	29.3	
AE leading to disc		%	7.3	17.1	
AESI Grade 3/4		%	8.7	1.5	Higher rates of all-grade AESIs compared with chemotherapy; Severe AESIs comparable with

Effect	Short description	Unit	Treatment Tecentriq	Control Chemotherapy	Uncertainties / Strength of evidence
					pooled Atezo Mono data
Safety by ADA-status			ADA-pos. (n=65)	ADA-neg. (n=202)	Safety profile appears unfavourable for ADA-positive compared to ADA-negative population despite lower exposure with limitation of small sample size
All grade AE		%	99	90	
Grade 3/4 AE		%	40	29	
SAEs		%	39	22	

Abbreviations: AE: Adverse event; ADR: treatment-related AE; SAEs: Serious AEs; Gr.: grade; disc: leading to treatment discontinuation.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The target population of PD-L1 selected chemotherapy-naïve patients with metastatic NSCLC have several effective first-line treatment options, which most often consists of an immune checkpoint inhibitor in monotherapy or in combination with chemotherapy. Hence, atezolizumab monotherapy would be another possible option to the existing therapies, especially for patients who are not eligible for combination therapy.

Efficacy of atezolizumab monotherapy was compared to platinum-based chemotherapy in the first-line setting using OS as the primary objective. The design of the pivotal study and the protocol were changed multiple times during the study; e.g. the Applicant added the TC3 or IC3 population as the first testing hierarchy in Protocol Version 9 (finalized on 14 March 2019). Before this, the TC2/3 or IC2/3 population had been defined as the primary analysis population. The very late time point of this update in the open-label study and the inadvertent data access by statisticians in December 2018 raised concerns that these changes could have been driven by knowledge of the pivotal IMpower110 study results and thus, a GCP inspection was initiated. However, this change was accepted by the CHMP as being driven by external data, mainly from three anti-PD-1/PD-L1 monotherapy 1L NSCLC studies (Checkmate-026, KEYNOTE-042 and MYSTIC), indicating that OS benefit was greatest in patients that express higher levels of PD-L1. Moreover, a detailed biomarker review of IMpower150 study and biomarker status in the external studies suggested that TC3/IC3 population had the highest probability of response. Relevant for these analyses are the MYSTIC study results by PD-L1 expression subgroups, and the MAH provided efficacy results from a publication by Rizvie et al 2018 and an oral presentation from ESMO-IO which included additional analyses by PD-L1 status in the TC≥50%, TC≥1% and TC <1% for subgroups treated with durvalumab versus chemotherapy. Hence, the CHMP concluded that it is plausible that these external data could have led to the changes made by the MAH later on. Based on the elements provided by the MAH, the CHMP considered that external data did lead to the decision to introduce the changes to the protocol. However, the practice of changing the primary endpoint and hierarchical testing in an ongoing open-label study is still criticized and the MAH should refrain from this approach in future open-label clinical studies. GCP issues should also be addressed as recommended during the GCP inspection and the MAH can expect that in future applications, there will be continued focus on GCP compliance.

At the primary analysis of the pivotal study IMpower110 (CCOD 10 September 2018), a statistically significant and clinically meaningful OS benefit was demonstrated with first-line (1L) atezolizumab monotherapy compared to platinum-based chemotherapy in the targeted TC3 or IC3-WT population (median OS: 20.2 vs. 13.1 months, HR 0.595 [95%CI: 0.398, 0.890]; p-value=0.0106). Because the OS data were not fully mature at this analysis time point (around 50% event rates), an OS update after an additional 17 months of follow-up (CCOD: 4 February 2020) was submitted.

A numerical and clinically relevant OS benefit of 5.5 months (HR of 0.764 [95%CI, 0.563, 1.087] was observed, although no longer statistically significant. This change was mainly driven by the performance of the comparator arm, which may have been impacted by subsequent therapies (mainly immunotherapy). Moreover, the OS benefit is supported by a clinically relevant improvement of INV-PFS of 3.2 months (HR 0.592) and durable responses (DOR 38.9 months) for patients in the atezolizumab arm.

Considering also the different and overall more tolerable safety profile of atezolizumab monotherapy compared to chemotherapy (lower incidences of treatment discontinuations, dose modifications, Grade 3-4 AEs, and treatment-related SAE), the overall benefit risk is considered favourable.

3.7.2. Balance of benefits and risks

Efficacy data show superior efficacy of atezolizumab monotherapy compared to platinum-based chemotherapy for the first-line treatment of PD-L1 selected patients with metastatic NSCLC.

The safety profile of monotherapy with atezolizumab in the targeted population is well-established from several clinical studies and no new safety concerns were observed in the pivotal study.

Hence, the B/R balance for the applied indication is positive; although the changes made to the single open-label pivotal study while ongoing is criticized and the MAH should refrain from this approach in future clinical studies.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of atezolizumab monotherapy for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have a PD-L1 expression $\geqslant$ 50% tumour cells (TC) or $\geqslant$ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC is positive.

4. Recommendations

Outcome

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

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

Extension of indication to include the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours express PD-L1 for Tecentriq based on the results of the pivotal study

GO29431 (IMpower110), comparing atezolizumab monotherapy to platinum-based chemotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. The RMP version 12.1 has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

the CHMP has recommended the approval of the variation to the terms of the Marketing Authorisation.

Amendments to the marketing authorisation

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

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 'Tecentriq-H-C-4143-II-33'

Attachments

1. SmPC (changes highlighted) as adopted by the CHMP on 25.03.2021.