EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 July 2019
EMA/CHMP/557475/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tecentriq

International non-proprietary name: atezolizumab

Procedure No. EMEA/H/C/004143/II/0018

Note

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

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Table of contents

List of abbreviations

ADA	anti-drug antibody, also called anti-therapeutic antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
Atezo	Atezolizumab
CCOD	clinical cut-off date
CD47	Cluster of Differentiation 47
CE	Carboplatin + Etoposide
CI	confidence interval
CMC	chemistry, manufacturing, and control
Cmin	minimum serum or plasma concentration
CNS	central nervous system
CR	complete response
CSR	Clinical Study Report
DOR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group Performance status
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-LC13	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module
ES-SCLC	extensive-stage small cell lung cancer
EU	European Union
FNA	fine needle aspiration
HR	hazard ratio
HRQoL	Health-Related Quality of Life
iDMC	Independent Data Monitoring Committee
IgG1	immunoglobulin G1
IHC	immunohistochemistry
IL-10	Interleukin 10
ITT	intent-to-treat
IV	intravenous
IxRS	Interactive Voice/Web Response System
KM	Kaplan-Meier
MAA	Marketing Authorisation Application
mAb	monoclonal antibody
NPT	non-prior anti-cancer therapy
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBO	placebo

PCI	prophylactic cranial irradiation
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	Pharmacokinetic
PopPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcome
q3w	every three weeks
RECIST	Response Evaluation Criteria for Solid Tumors
RMP	Risk Management Plan
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	Summary of Biopharmaceutics
SCE	Summary of Clinical Efficacy
SCLC	small cell lung cancer
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
TGF-β	transforming growth factor beta
Ttd	time to deterioration
UC	urothelial carcinoma
US	United States
VALG	Veterans Administration Lung Study Group

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 11 October 2018 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, in combination with carboplatin and etoposide, first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) for Tecentriq; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. RMP version 8.0 has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0220/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0220/2015 was not yet completed as some measures were deferred.

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 applicant 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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

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

Timetable	Actual dates
Submission date	11 October 2018
Start of procedure:	3 November 2018
CHMP Rapporteur Assessment Report	20 December 2018
CHMP Co-Rapporteur Assessment Report	20 December 2018
PRAC Rapporteur Assessment Report	4 January 2019
PRAC members comments	9 January 2019
Updated PRAC Rapporteur Assessment Report	10 January 2019
PRAC Outcome	17 January 2019
CHMP members comments	21 January 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	24 January 2019
Request for supplementary information (RSI)	31 January 2019
Extension of timetable adopted by the CHMP on:	28 February 2019
CHMP Rapporteur Assessment Report	3 June 2019
CHMP members comments	17 June 2019
Request for supplementary information (RSI)	27 June 2019
CHMP Rapporteur Assessment Report	9 July 2019
CHMP members comments	15 July 2019
Updated CHMP Rapporteur Assessment Report	n/a
The CHMP adopted a report on the novelty of the indication/significant clinical benefit in comparison with existing therapies on date (Appendix 1)	25 July 2019
Opinion	25 July 2019

2. Scientific discussion

2.1. Introduction

2.1.1. Disease or condition

2.1.2. Epidemiology

Lung cancer remains the leading cause of cancer death worldwide. NSCLC is the predominant subtype, accounting for approximately 85% of all cases (Molina et al. 2008; Howlader et al. 2014). Small cell lung cancer accounts for approximately 15% of all cases, and is distinguished from NSCLC by its rapid growth, early development of metastatic disease, and initial responsiveness to platinum-based doublet chemotherapy (Govindan et al. 2006).

2.1.3. Biologic features

SCLC is characterised by uniform round to spindled-shaped small cells, sparse cytoplasm, high mitotic index, necrotic areas (ESMO, 2013).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

SCLC is characterised by a rapid doubling time, high growth fraction, and early development of widespread metastases. The majority of the patients with SCLC present with hematogenous metastases. One third of the patients present with limited disease confined to the chest (NCCN, 2019).

The Veterans Administration Lung Group (VALG) proposed a clinical two-stage system for SCLC that distinguishes limited stage and extensive stage. Limited-stage is defined as being limited to one hemithorax, including mediastinal, contralateral hilar and ipsilateral supraclavicular lymph nodes, whereas extensive-stage represents tumour spread beyond these regions (Zelen 1973). Poor prognostic factors for survival in patients with SCLC include extensive-stage (ES) disease, poor ECOG PS, weight loss, and markers associated with excessive bulk of disease (e.g., elevated lactate dehydrogenase) (Yip et al. 2000; Foster et al. 2009).

2.1.5. Management

Patients with limited-stage SCLC can be treated with chemotherapy and radiation with the potential for long-term survival (Stinchcombe et al. 2010). However, the majority (approximately 70%) of patients with SCLC are diagnosed with ES-SCLC, which has poor survival prospects: the median OS is approximately 10 months with a 1-year OS rate of approximately 40% (Socinski et al. 2009). Chemotherapy alone can palliate symptoms and prolong survival for patients with ES-SCLC; however, long-term survival is rare (Johnson et al. 2004; DeMets et al. 2010).

The current standard first-line treatment for patients with ES-SCLC is platinum-based chemotherapy with etoposide, a topoisomerase II inhibitor (NCCN 2018, Fruh et al. 2013). The combination of cisplatin or carboplatin with etoposide has shown response rates ranging from 60% to 70% in patients with ES-SCLC (Rossi et al. 2012). Several studies using cisplatin or carboplatin with etoposide (at various doses) have shown consistent outcomes, suggesting their efficacy is equivalent in patients with ES-SCLC. A meta-analysis of four randomized studies compared cisplatin-based versus carboplatin based regimens in patients with SCLC (Rossi et al. 2012). Of the 663 patients included in this meta-analysis, 68% had extensive-stage disease. In patients receiving cisplatin- versus carboplatin-containing regimens, there was no significant difference observed in response rate (67% vs. 66%), PFS (median: 5.5 vs. 5.3 months; hazard ratio [HR]: 1.10; 95% confidence interval [CI]: 0.94, 1.29) or OS (median: 9.6 vs. 9.4 months; HR: 1.08; 95% CI: 0.92, 1.27), suggesting equivalent efficacy in patients with ES-SCLC. Carboplatin is frequently substituted for cisplatin in clinical practice as it reduces the risk of emesis, neuropathy, nephropathy and fluid overload from cisplatin intravenous (IV) hydration protocols that patients may not tolerate. Etoposide in combination with cisplatin or carboplatin is nationally authorised for the treatment of SCLC

Despite the impressive response rates observed with first-line chemotherapy regimens, most patients with ES SCLC develop chemotherapy resistant disease and their prognosis is poor. Therefore, there is need for improved treatment options for patients with ES-SCLC (Chute et al 1999).

About the product

Atezolizumab is an Fc-engineered humanized immunoglobulin (IgG1) monoclonal antibody (MAb) targeting the programmed death-ligand 1 (PD-L1). Binding of atezolizumab to PD-L1 inhibits the interaction of the PD-1 and B7.1 receptors. Both of these interactions are reported to provide inhibitory signals to T cells.

Tecentriq is currently authorised as 840 mg concentrate for solution for infusion (positive opinion adopted by CHMP but pending EC decision at the time of adoption of this procedure) and 1,200 mg concentrate for solution for infusion.

Tecentriq is currently authorised in the following indications:

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

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

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

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

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

The current application is submitted to extend the authorised indication to the use of atezolizumab in combination with carboplatin and etoposide for the treatment of ES-SCLC in patients who have not received previous systemic therapy. The evidence comes from pivotal study IMpower133, a phase III, multicentre, randomised, double-blind, placebo-controlled study.

The following new indication is recommended by the CHMP:

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

During the induction phase, the recommended dose of Tecentriq is 1,200 mg administered by intravenous infusion followed by carboplatin, and then etoposide administered by intravenous infusion on day 1. Etoposide is also administered by intravenous infusion on days 2 and 3. This regimen is administered every three weeks for four cycles.

The induction phase is followed by a maintenance phase without chemotherapy in which 1,200 mg Tecentriq is administered by intravenous infusion every three weeks.

It is recommended that patients are treated with Tecentriq until disease progression or unmanageable toxicity. Treatment beyond disease progression may be considered at the discretion of the physician (see section 4.2 of the SmPC).

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

No new nonclinical data has been provided to support this application. 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 applicant.

The applicant 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

Study	Design	Patient Population	Number of Patients Enrolled	Treatment	Primary Efficacy Endpoint	Timing of Primary Analysis (Clinical Cutoff Date)
Pivotal Study						
GO30081 (IMpower133)	Phase I/III, global, randomized, double-blind, placebo-controlled study	Patients ≥18 years with histologically or cytologically confirmed ES-SCLC (per the VALG staging system), ECOG PS 0 or 1 and no prior systemic therapy.	Total: n = 403 n = 201 Atezo + CE n = 202 PBO + CE	Atezolizumab fixed dose of 1200 mg IV q3w Carboplatin AUC of 5 mg/mL/min IV q3w and Etoposide 100 mg/m² IV q3w	Investigator-assessed PFS per RECIST v1.1 and OS	The OS interim analysis was performed when approximately 240 OS events in the ITT population were observed. The pre-specified primary analysis of PFS was planned to be conducted at the time of the OS interim analysis. (24 April 2018)

ECOG PS = Eastern Cooperative Oncology Group Performance Status; ES-SCLC = extensive-stage small cell lung cancer; IV = intravenous; q3w = every 3 weeks; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria for Solid Tumors; VALG = Veterans Administration Lung Study Group.

2.3.2. Pharmacokinetics

The PK of atezolizumab in ES-SCLC was characterized based on data from the Phase I/III study, IMpower133.

Pharmacokinetics in target population

The descriptive statistics of the available Cmax (30 minutes following the end of the atezolizumab infusion) and Cmin (pre-dose) serum concentrations of atezolizumab for the Atezo + CE arm following 1200 mg q3w IV administration are summarized in the table below. A total of 195 patients had evaluable atezolizumab PK. Mean serum atezolizumab concentrations over time are shown in Figure 1. Steady-state was reached by approximately Cycle 3 based on evaluation of trough concentration (C_{min}).

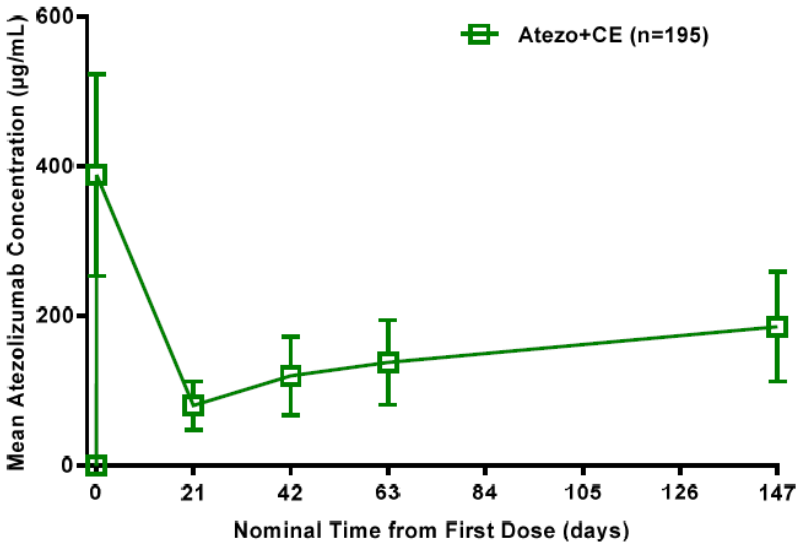
Table 1: Summary Statistics for Atezolizumab Cmax and Cmin Following Multiple IV Doses of Atezolizumab1200 mg, Administered Every 3 Weeks in Combination with Carboplatin and Etoposide

Treatment	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)
Atezo + CE	C1D1	0	194	NR	NR	NE	NR	NR	0	0
	C1D1	0.0625	185	389	135	258	669	0.03	395	779
	C1D21	21	174	80.6	32.1	71.6	84.5	0.03	79.1	275
	C2D21	42	166	120	52.3	112	39.7	33	114	528
	C3D21	63	156	138	56.4	119	102	0.03	130	333
	C7D21	147	88	186	73.5	171	44.5	49.1	177	364

AM = Arithmetic Mean; Atezo + CE = atezolizumab in combination with carboplatin and etoposide; C_{max} = maximum serum concentration; C_{min} = trough or 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. Predose Cycle 1 is C1D1, 0 days. C_{max} is C1D1 30 minutes post end of infusion. Predose Cycle 2 is C1D21, predose Cycle 3 is C2D21, C_{max} is C3D1 30 minutes post end of infusion etc.

Data source: IMpower133 CSR, Table 31



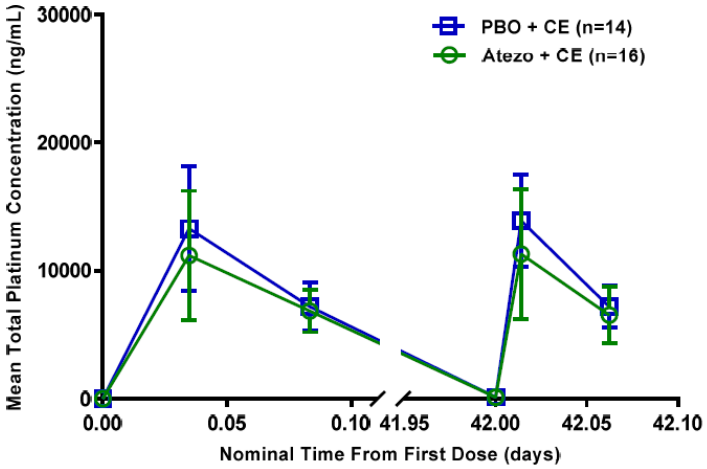
Atezo + CE = atezolizumab in combination with carboplatin and etoposide; SD = standard deviation

Data source: IMpower133 CSR, Figure 11

Figure 1: Mean (±SD) Plot of Atezolizumab Serum Concentrations versus Time Following Multiple IV Doses of Atezolizumab 1200 mg, Administered Every 3 Weeks in Combination with Carboplatin and Etoposide

Carboplatin Pharmacokinetics

A total of 30 patients had evaluable carboplatin PK (16 patients from the Atezo + CE arm and 14 patients from the PBO + CE arm). The mean plasma carboplatin concentrations over time are presented in Figure 2, and show that the concentration-time profiles of carboplatin are similar between treatment arms.

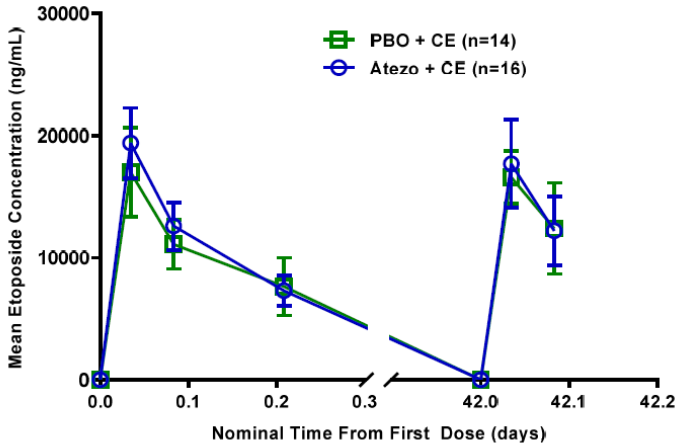


Atezo + CE = atezolizumab in combination with carboplatin and etoposide; AUC = area under the concentration–time curve; PBO + CE = placebo in combination with carboplatin and etoposide; SD = standard deviation
Data source: IMpower133 CSR, Figure 12

Figure 2: Mean (±SD) Plot of Carboplatin Plasma Concentrations versus Time Following Multiple IV Doses of Carboplatin AUC 5 mg/mL*min, Administered Every 3 Weeks in Combination with Etoposide, with or without Atezolizumab

Etoposide Pharmacokinetics

A total of 30 patients had evaluable etoposide PK (16 patients from the Atezo + CE arm and 14 patients from the PBO + CE arm). The mean plasma etoposide concentrations over time are presented in Figure 3, and show that the concentration-time profiles of etoposide are similar between treatment arms. The data suggest administration of carboplatin and atezolizumab in combination with etoposide do not impact the PK of etoposide.



Atezo + CE = atezolizumab in combination with carboplatin and etoposide; IV = intravenous; PBO + CE = placebo in combination with carboplatin and etoposide; SD = standard deviation
Data source: IMpower133 CSR, Figure 13

Figure 3: Mean (±SD) Plot of Etoposide Plasma Concentrations versus Time Following Multiple IV Doses of Etoposide 100 mg/m2, Administered on Days 1, 2, and 3 of Every 3 Week Cycle in Combination with Carboplatin, with or without Atezolizumab

Pharmacokinetics by Treatment-Emergent ADA Status

Atezolizumab concentrations up to Cycle 7 Day 21 (or pre-dose Cycle 8) by treatment-emergent ADA status are summarized in Table 2 for all atezolizumab patients who were both PK and ADA-evaluable. The

geometric mean Cmin estimates for Cycle 7 Day 21 (or pre-dose Cycle 8) in the Atezo + CE arm were 135 µg/mL and 179 µg/mL for ADA-positive and ADA-negative patients, respectively.

Mean serum atezolizumab concentrations over time by ADA status are shown in Table 2. Average atezolizumab Cmin for both ADA-positive and ADA-negative patients approached a plateau (or steady-state) between 4–8 cycles of dosing.

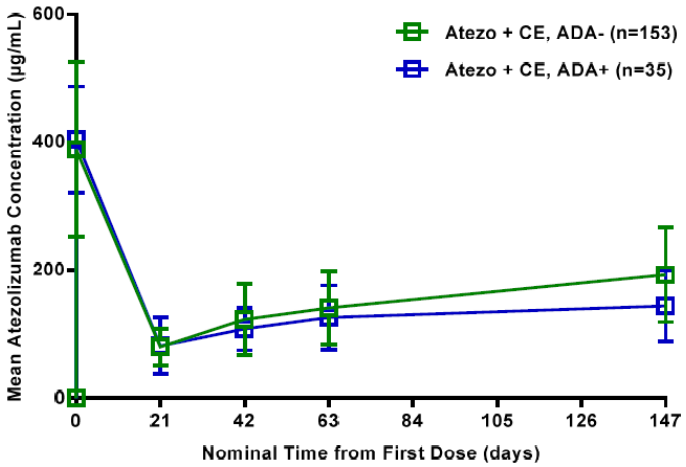
Table 2: Summary Statistics for Atezolizumab Cmax and Cmin Following Multiple IV Doses of Atezolizumab 1200 mg Given Every 3 Weeks in Combination with Carboplatin and Etoposide by Treatment-Emergent ADA status

ADA Status	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)
Negative	C1D1	0	152	NR	NR	NE	NR	NR	0	0
	C1D1	0.0625	144	389	136	262	628	0.03	393	779
	C1D21	21	141	80.3	28.7	71.1	92.8	0.03	79.5	156
	C2D21	42	136	123	55.3	114	40.9	33	115	528
	C3D21	63	128	141	57.4	122	107	0.03	130	333
	C7D21	147	74	193	74.2	179	43.9	49.1	186	364
Positive	C1D1	0	35	NR	NR	NE	NR	NR	0	0
	C1D1	0.0625	34	404	83.4	395	21.7	237	396	577
	C1D21	21	33	81.8	44.1	73.8	46.2	34.7	73.2	275
	C2D21	42	30	108	33.5	103	33	56	110	173
	C3D21	63	28	126	50.4	108	79.3	6.88	130	212
	C7D21	147	14	144	55.4	135	40	65.9	137	261

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

[1] Visit is denoted by Cycle abbreviated by "C" and Day abbreviated by "D". For example, C1D1 corresponds to Cycle 1, Day 1, etc. Predose Cycle 1 is C1D1 0 days. C_{max} is C1D1 5-10 minutes prior to end of infusion, Predose Cycle 3 is C2D21, C_{max} is C3D1 5-10 minutes prior to end of infusion etc.

Data source: IMpower133 CSR, Table 67



ADA = anti-drug antibodies; Atezo + CE = atezolizumab in combination with carboplatin and etoposide; SD = standard deviation

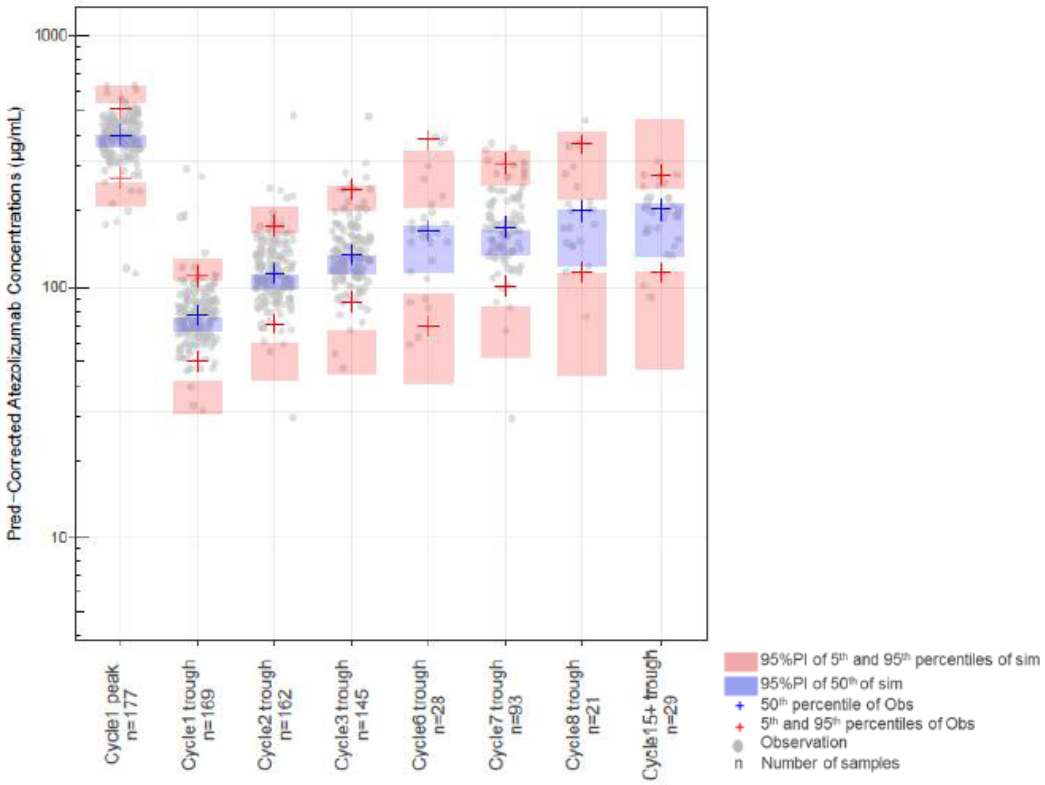
Data source: IMpower133 CSR, Figure 16

Figure 4: Mean (±SD) Plot of Atezolizumab Concentrations versus Time Following Multiple IV Doses of Atezolizumab 1200 mg Given Every 3 Weeks in Combination with Carboplatin and Etoposide by Treatment-Emergent ADA Status

Population PK analysis

The Phase I popPK Model was subjected to an external validation for mUC, NSCLC, and ES-SCLC separately, using PK data collected in IMvigor210 and IMvigor211 for mUC, data collected in BIRCH, POPLAR, FIR, OAK and IMpower150 for NSCLC and data collected in IMpower133 for ES-SCLC.

The prediction-corrected visual predictive check suggested that the median, 95th, and 5th percentiles of observed Cmax and Cmin were generally within the prediction intervals of the Phase I popPK Model (Figure 5). Covariate effects (i.e., BWT, gender, ADA status, albumin levels and tumor burden) in the IMpower133 data were generally consistent with those identified in the popPK Model. Both Cycle 1 and steady-state exposure metrics were similar to those estimated in other atezolizumab monotherapy studies.



popPK = population pharmacokinetics; VPC = visual predictive check.

Source: IMpower133 external-validation popPK Report 1090018, Figure 2

Figure 5: Predicted-Corrected Visual Predictive Check Atezolizumab Concentration in IMpower133 Using the Phase I PopPK Model

2.3.3. Discussion on clinical pharmacology

The recommended dose of atezolizumab is 1200 mg administered as an IV infusion q3w. Study IMpower130 evaluated atezolizumab at this dose level and schedule in chemotherapy-naïve patients with NSCLC, in combination with carboplatin and nab- paclitaxel. The rationale for the recommended dose was based on data from nonclinical studies and available clinical data from Study PCD4989g (see European Public Assessment Report for the initial marketing authorisation). In addition, results from the studies OAK, BIRCH and POPLAR support the selection of the 1200 mg q3w dose level in patients with locally advanced or metastatic NSCLC.

The starting point for the population PK analysis submitted in the current variation application was the previous population PK analysis based on dataset including subjects from phase I clinical studies

PCD4989g and JO28944). This "Phase I popPK Model" was subsequently subjected to an external evaluation with the use of atezolizumab PK data collected in Study IMpower133.

The goodness-of-fit plots for population and individual predictions appeared adequate. The Phase 1 popPK Model is suitable to describe the individual PK data from the IMpower130 Study and seems suitable for determination of atezolizumab exposure metrics. The co-administration of chemotherapy (carboplatin + etoposide) did not seem to influence atezolizumab PK. The data submitted also suggest that administration of etoposide and atezolizumab in combination with carboplatin do not impact the PK of carboplatin.

In general, the observed concentrations in this setting fall within the range of predicted concentrations, at least during the first cycle, indicating that the definitive population PK model developed on monotherapy data provides an adequate description of the pharmacokinetics of atezolizumab in combination with carboplatin and etoposide. The data available support the use of the same dose of 1200 mg q3w for atezolizumab.

Since atezolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected. Based on PK data from IMpower133, there is no evidence of a PK drug-drug interaction with the co-administration of atezolizumab with carboplatin and etoposide.

While PK and ADA samples had to be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for atezolizumab in these patients were generally not needed for the safe conduct or proper interpretation of this study. Sponsor personnel responsible for performing PK and ADA assays were unblinded to patients' treatment assignment to identify appropriate samples to be analyzed. Samples from patients assigned to the comparator arm were not analyzed for atezolizumab concentration except by request (e.g., to evaluate a possible error in dosing). Atezolizumab ADA samples collected on Day 1 of Cycle 1 could be analysed for all patients, while subsequent samples from patients assigned to the comparator arm were not to be analyzed for ADA unless requested.

The baseline prevalence of atezolizumab ADAs was 2.0% in the atezolizumab - CE arm for atezolizumab-treated patients with a baseline ADA sample. The post-baseline treatment-emergent ADA incidence was 18.6%. The rates of treatment emerged ADA are considered to be high. Treatment emergent ADAs did not appear to have a clinically meaningful impact, the number of ADA positive subjects is too small (n=35) to draw firm conclusions. There was a trend for slightly lower exposure in ADA-positive patients; however the C_{min} in all ADA-positive patients was in excess of the target serum concentration of 6 µg/mL. The MAH is recommended to further investigate the effect of neutralizing antibodies on atezolizumab pharmacokinetics and efficacy of atezolizumab (see also clinical efficacy).

2.3.4. Conclusions on clinical pharmacology

The clinical pharmacology of atezolizumab has previously been characterized and the PK investigations in IMPower133 overall confirm previous findings. The PK of atezolizumab is similar when administered in combination with carboplatin and etoposide without evidence of drug-drug interactions, no unexpected interactions with covariates have been identified and the proposed dose of 1200 mg q3w seems to be appropriate and is endorsed.

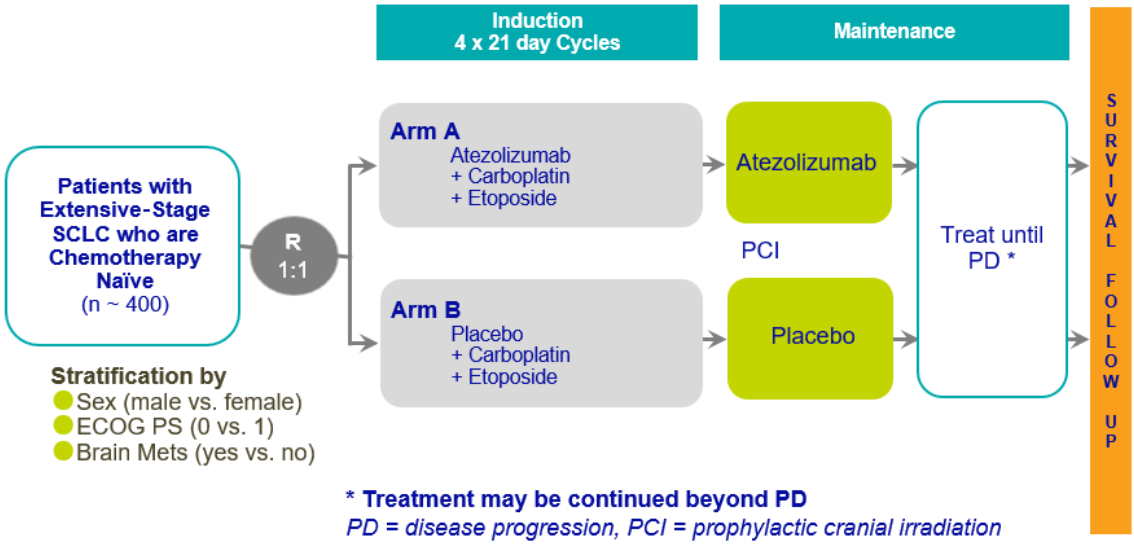
2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No additional dose-response study was performed.

2.4.2. Main study

IMpower133 (study GO30081): A Phase I/III, randomized, double-blind, placebo-controlled study of carboplatin plus etoposide with or without atezolizumab (anti-PD-L1 antibody) in patients with untreated extensive-stage small cell lung cancer



* including worsening of laboratory values [e.g., new or worsening hypercalcemia])

ECOG PS = Eastern Cooperative Oncology Group performance status; PCI = prophylactic cranial irradiation; PD = progressive disease; SCLC = small cell lung cancer

Figure 6: Overview of Study Design for IMpower133

The study included a Phase I safety run-in period in order to establish tolerability of the study treatment. After a minimum of 12 patients were enrolled in each treatment arm and received at least two cycles of study treatment, unblinded safety data were reviewed by an independent data monitoring committee (iDMC). Subsequently, the iDMC reviewed safety data approximately every 6 months during the study.

Methods

Study participants

Patients enrolled into this study were unselected for PD-L1 expression. A baseline tissue sample was required to be submitted during the study; however, PD-L1 testing was not required during screening.

Inclusion criteria:

- Signed Informed Consent Form.
- Male or female, 18 years of age or older.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Histologically or cytologically confirmed ES-SCLC per the Veterans Administration Lung Study Group (VALG) staging system.
- No prior systemic treatment for ES-SCLC.

- Patients who received prior chemoradiotherapy for limited-stage SCLC must have been treated with curative intent and experienced a treatment-free interval of at least 6 months since last chemotherapy, radiotherapy, or chemoradiotherapy cycle from diagnosis of extensive-stage SCLC.
- 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 evidence of interim progression between the completion of CNS-directed therapy and randomization
    - Patients with new asymptomatic CNS metastases detected at the screening scan had to receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients could be eligible without the need for an additional brain scan prior to randomization, if all other criteria were met.
- Measurable disease, as defined by RECIST v1.1. Previously irradiated lesions could only be considered as measurable disease if disease progression had been unequivocally documented at that site since radiation and the previously irradiated lesion was not the only site of disease.
- Adequate hematologic and end organ function.
- Patients had to submit a pre-treatment tumor tissue sample. Any available tumor tissue sample could be submitted. The tissue sample should have been submitted before or within 4 weeks after randomization; however, patients could be enrolled into the study before the pre-treatment tumor tissue sample was submitted.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 5 months after the last dose of study treatment.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures.

<u>Exclusion criteria:</u>

- 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 had been clinically stable for ≥ 1 week prior to randomization.
- Leptomeningeal disease.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently). Patients with indwelling catheters (e.g., PleurX®) were allowed regardless of drainage frequency.
- Uncontrolled or symptomatic hypercalcemia. Patients who were receiving denosumab prior to randomization had to be willing and eligible to discontinue its use and replace it with a bisphosphonate while in the study.

- Malignancies other than SCLC 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).
- Women who were pregnant, lactating, or intending to become pregnant during the study.
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.
    - Patients with a history of autoimmune-related hypothyroidism on thyroid replacement hormone therapy were eligible.
    - Patients with controlled Type I diabetes mellitus on an insulin regimen were eligible.
    - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis were excluded).
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) was permitted.
- Positive test result for human immunodeficiency virus (HIV). All patients were tested for HIV; patients who tested positive for HIV were excluded.
- Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test result at screening) or hepatitis C virus (HCV).
- Active tuberculosis.
- Severe infections at the time of randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to randomization, unstable arrhythmias, or unstable angina. Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction < 50% must have been on a stable medical regimen that was optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.
- Major surgical procedure other than for diagnosis within 28 days prior to randomization or anticipation of need for a major surgical procedure during the course of the study.
- Prior allogeneic bone marrow transplantation or solid organ transplant.
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicated the use of an investigational drug or that could affect the interpretation of the results or render the patient at high risk for treatment complications.
- Patients with illnesses or conditions that interfered with their capacity to understand, follow, and/or comply with study procedures.

- Treatment with any other investigational agent with therapeutic intent within 28 days prior to randomization.
- Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation that such a live attenuated vaccine would be required during the study Patients could not receive live, attenuated influenza vaccines within 4 weeks prior to randomization, during treatment, and for 5 months following the last dose of atezolizumab/placebo.
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti-PD-1, and anti-PD-L1 therapeutic antibodies.
- Treatment with systemic immunosuppressive medications (including, but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 1 week prior to randomization.
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
- Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation.
- History of allergic reactions to carboplatin or etoposide.

Treatments

The induction phase of the study consisted of four cycles of atezolizumab/placebo plus chemotherapy, with each cycle being 21 days in duration. On Day 1 of each cycle, study drug infusions were administered in the following order:

Arm A: atezolizumab → carboplatin → etoposide (ATZ + CE)

Arm B: placebo → carboplatin → etoposide (PBO + CE)

During the induction phase, study treatment was administered in the following manner:

- Day 1: Atezolizumab 1200 mg or placebo administered intravenously over 60 minutes
- Day 1: Carboplatin to reach AUC 5 mg/mL/min administered intravenously over 30-60 minutes
- Day 1-3: Etoposide 100 mg/m^2 administered intravenously over 60 minutes.

If one component of study treatment was discontinued permanently because of tolerability concerns, the patient was allowed to continue with other components of study treatment until disease progression if agreed upon by the investigator and patient.

Following the induction phase, patients continued maintenance therapy with either atezolizumab or placebo (21 day-cycles). During the maintenance phase, prophylactic cranial irradiation was permitted per local standard-of-care. Thoracic radiation with curative intent or the intent to eliminate residual disease was not permitted. Palliative thoracic radiation was allowed. Treatment had to be discontinued in all patients (in both treatment arms) who exhibited evidence of disease progression per RECIST v1.1.

Table 3: Intravenous Treatment Regimen (IMpower133)

Treatment regimen	Induction (Four 21-Day Cycles)	Maintenance (21-Day Cycles)
A	atezolizumab (1,200 mg)[a] + carboplatin (AUC 5)[b] + etoposide (100 mg/m^2)[b,c]	atezolizumab (1,200 mg) [a]
B	placebo + carboplatin (AUC 5)[b] + etoposide (100 mg/m^2)[b,c]	placebo

[a]Atezolizumab was administered until loss of clinical benefit as assessed by investigator
[b]Carboplatin and etoposide were administered until completion of 4 cycles, or progressive disease or unacceptable toxicity, whichever occurs first
[c]Etoposide was administered on day 1, 2 and 3 of each cycle

Treatment beyond progression:

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents since progressive disease (PD) by initial radiographic evaluation may not necessarily reflect therapeutic failure. In order to better accommodate standard clinical practice which is guided by the fact that patients with ES-SCLC whose disease progresses after first-line treatment have limited treatment options and such options have limited efficacy and significant toxicity, patients could be considered for treatment beyond radiographic disease progression per RECIST v1.1, at the discretion of the investigator and after appropriate discussion with the patient and obtaining informed consent, only if all of the following criteria were met:

- Evidence of clinical benefit as assessed by the investigator
- No decline in ECOG PS that could be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that could not be managed by protocol-allowed medical interventions
- Patients must provide written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial progression

Patients were fully informed of the risk of continuing study treatment in spite of apparent radiographic progression, and consent was documented appropriately before study treatment could continue. Investigators made a careful assessment of the potential benefit of continuing study treatment beyond radiographic disease progression, considering radiographic data and the clinical status of the patient.

Patients who continued treatment beyond radiographic disease progression per RECIST v1.1 were closely monitored clinically and with a follow-up scan in 6 weeks or sooner if symptomatic deterioration occurred. Treatment had to be discontinued if clinical deterioration due to disease progression occurred at any time, or if persistent disease growth was confirmed in a follow-up scan. In addition, patients had to be discontinued for unacceptable toxicity or for any other signs or symptoms of deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status.

<u>Dose modification:</u>

No dose reductions for atezolizumab/placebo were permitted. Patients could temporarily suspend treatment with atezolizumab/placebo for up to 105 days beyond the last dose if they experienced an AE that required a dose to be withheld. If atezolizumab/placebo was withheld because of AEs for more than 105 days beyond the last dose, then the patient was discontinued from atezolizumab/placebo treatment. Exceptions required Medical Monitor approval. If a patient had to be tapered off steroids used to treat AEs, atezolizumab could be withheld for additional time beyond 105 days from the last dose until steroids were discontinued or reduced to prednisone dose (or dose equivalent) ≤ 10 mg/day. The acceptable length of interruption depended on agreement between the investigator and the Medical Monitor.

Dose modifications for carboplatin and etoposide were permitted for toxicity according to the prescribing information and local standard-of-care. Once reduced, the dose could not be increased back to 100%. Treatment with carboplatin or etoposide was recommended to be discontinued if a patient experienced any hematologic or non-hematologic Grade 3 or Grade 4 toxicity after two dose reductions or treatment was delayed for more than 63 days due to toxicities.

Tumour assessments:

Tumour assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Patients who met established criteria and who agreed to be treated beyond disease progression had tumour assessments conducted every 6 weeks until treatment discontinuation.

Objectives

Co-primary efficacy objectives:

- To evaluate the efficacy of Atezo + CE compared with PBO + CE in the intent-to-treat (ITT) patient population as measured by investigator-assessed PFS according to RECIST v1.1
- To evaluate the efficacy of Atezo + CE compared with PBO + CE in the ITT patient population as measured by OS

Secondary efficacy objectives:

- To evaluate the efficacy of Atezo + CE compared with PBO + CE in the ITT population as measured by investigator-assessed objective response rate (ORR) according to RECIST v1.1
- To evaluate the efficacy of Atezo + CE compared with PBO + CE in the ITT population as measured by investigator-assessed duration of response (DOR) according to RECIST v1.1
- To evaluate the PFS rate at 6 months and at 1 year in each treatment arm for the ITT population
- To evaluate the OS rate at 1 and 2 years in each treatment arm for the ITT population
- To determine the impact of atezolizumab as measured by time to deterioration (TTD) in patient-reported lung cancer symptoms of cough, dyspnea (single-item and multi-item subscales), chest pain, arm/shoulder pain, or fatigue using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13) in patients treated with Atezo + CE compared with PBO + CE in the ITT population

Safety objectives:

- To evaluate the safety and tolerability of Atezo + CE compared with PBO + CE
- To evaluate the incidence and titers of anti-therapeutic antibodies (anti-drug antibodies; ADA) against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics (PK), safety, and efficacy

Pharmacokinetic objective:

- To characterize the pharmacokinetics of atezolizumab, carboplatin, and etoposide in patients with chemotherapy-naive ES-SCLC.

Exploratory objectives:

- To evaluate investigator-assessed PFS, ORR, and DOR according to immune-modified RECIST for the atezolizumab-containing treatment arm in the ITT population
- To evaluate the relationship between tumor biomarkers (including but not limited to PD-L1, PD-1, somatic mutations, blood tumour mutation burden [bTMB], and others), as defined by immunohistochemistry (IHC) or quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR), next generation sequencing (NGS), and/or other methods and measures of efficacy
- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue, blood, plasma and serum and their association with disease status, mechanisms of resistance, and/or response to study treatment
- To evaluate and compare patient's health status as assessed by the EuroQoL 5 Dimensions 5-Level (EQ-5D-5L) questionnaire to generate utility scores for use in economic models for reimbursement
- To determine the impact of Atezo + CE compared with PBO + CE as measured by change from baseline in patient-reported outcomes (PRO) of health-related quality of life (HRQoL), lung cancer-related symptoms, physical functioning, and health status as assessed by the EORTC QLQ-C30 and LC13
- To evaluate the impact of chemotherapy (both carboplatin and etoposide) on peripheral and tumor-specific T-cell populations during and after induction therapy and its relationship to efficacy and safety outcomes

Outcomes/endpoints

Endpoint / SAP Section	Definition	Censoring	Methodology
Co-Primary Endpoints			
PFS per RECIST v1.1 by investigator Section 4.4.1.1	Time from randomization to first documented PD or death from any cause, whichever occurred first	• Patients who were alive and who did not experience PD at time of analysis were censored at date of the last tumor assessment. • Patients with no post-baseline tumor assessment were censored at date of randomization plus 1 day.	• Kaplan-Meier methodology, stratified log-rank test and stratified Cox regression model. • Stratification factors should be the same as for randomization including: sex [male vs. female], ECOG performance status [0 vs. 1], and brain metastasis [Yes vs. No], as recorded in the IxRS, unless at least one stratum had less than 10 events. If that happened, the stratification factor which contained the level with the smallest number of patients was removed from the stratified analyses until there was no stratum with less than 10 events.
OS Section 4.4.1.2	Time from randomization to death from any cause	• Patients who were not reported as having died at time of analysis were censored at the date last known to be alive. • Patients who did not have post-baseline information were censored at the date of randomization plus 1 day.	Same methods as for PFS co-primary endpoint

ORR (confirmation not required) per RECIST v1.1 by investigator Section 4.4.2.1	Proportion of patients with an objective response, either CR or PR	N/A	• Clopper-Pearson method for 95% CI of response rates • 95% CI for the difference in ORRs between the two treatment arms was estimated using the normal approximation to the binomial distribution method
DOR (confirmation not required) per RECIST v1.1 by investigator Section 4.4.2.2	Time from the first documented objective response to documented PD or death from any cause, whichever occurred first	• Patients who were alive and who did not experience PD at time of analysis were censored at the date of the last tumor assessment. • If no tumor assessments were performed after the date of the first occurrence of the objective response (CR or PR), DOR was censored at the date of the first occurrence of the objective response plus 1 day.	Same methods as for PFS co-primary endpoint
OS at 1– and 2–year landmark timepoints Section 4.4.2.3	Same as above	Same as above	• Kaplan-Meier methodology with 95% CI calculated with the standard error derived from the Greenwood formula • 95% CI for the difference in OS rates between the two treatment arms was estimated using the normal approximation method
PFS at 6 month and 1 year landmark timepoints Section 4.4.2.3	Same as above	Same as above	• Same as above

CI = confidence interval; CR = complete response; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; IRF = independent review facility; ITT = intent-to-treat; IxRS = interactive voice/Web response system; N/A = not applicable; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAP = statistical analysis plan.

Sample size

Approximately 400 patients were to be randomized into the global enrollment phase of this study to the ATZ+CE arm and the PBO+CE arm in a 1:1 ratio.

There are two co-primary efficacy endpoints: PFS and OS. To control the overall two-sided Type I error rate at 0.05, the two-sided significance levels of 0.005 and 0.045 were allocated to the primary comparisons for PFS and OS, respectively.

The following sample size calculation applies to the global enrollment phase, excluding the China extension cohort, unless otherwise noted.

The sample size of the study is determined by the analysis of OS. To detect an improvement of HR = 0.68 in OS using a log-rank test, approximately 306 deaths in the ITT population will be required to achieve 91% power at a two-sided significance level of 0.045. One OS interim analysis will be performed when approximately 240 OS events in the ITT population are observed, which by estimation will occur at approximately 25 months after the first patient is randomized. The final analysis of OS will be performed when approximately 306 OS events in the ITT population have been observed, which is expected at approximately 36 months after the first patient is randomized.

The primary analysis of PFS is planned to be conducted at the time of the OS interim analysis, and is estimated to be when approximately 295 PFS events in the ITT population have occurred, which is expected at approximately 25 months after the first patient is randomized. This provides 99% power to detect an improvement of HR = 0.55 in PFS at a two-sided significance level of 0.005. There will be no interim analysis for PFS.

The calculation of sample size and estimates of the analysis timelines are based on the following assumptions:

- PFS and OS are exponentially distributed.
- The median duration of PFS in the control arm is 6 months.
- The median duration of OS in the control arm is 10 months.
- The interim and final analyses of OS use the Lan-DeMets alpha spending function to approximate the O'Brien-Fleming boundary.
- The dropout rate is 5% over 12 months for PFS and OS.

Table 4: Power and minimum detectable difference for the proposed design of each primary endpoint

Primary Endpoint	Expected No. of Events	Target HR	Two-Sided Type I Error	Power	MDD HR
PFS	295	0.55	0.005	99%	0.721
PFS	295	0.55	0.05	99.9%	0.796
OS	306	0.68	0.045	91%	0.790 [a]
OS	306	0.68	0.05	92%	0.794 [a]

HR = hazard ratio; MDD = minimum detectable difference; PFS = progression-free survival; OS = overall survival.

[a] At final analysis conditional on interim analysis with 78% information fraction.

Randomisation

Eligible patients were stratified by sex (male vs. female), ECOG PS (0 vs. 1), and presence of brain metastases (yes vs. no) and randomized 1:1 to receive either ATZ+CE or PBO+CE. Randomization occurred in a 1:1 ratio using a permuted-block randomization method.

Blinding (masking)

This was a double-blind study. The Sponsor and its agents (with the exception of the IxRS service provider [the external independent statistical coordinating center responsible for verifying patient randomization and study treatment kit assignments], PK/pharmacodynamic laboratory personnel, and the iDMC members); the study site personnel, including the investigator; and the patient were blinded to treatment assignment.

Statistical methods

Analysis populations:

- ITT population: Defined as all randomized patients, regardless of whether the patient received the assigned treatment. ITT patients were analyzed according to the treatment assigned at randomization by the IxRS.
- Pharmacokinetic-Evaluable Population: PK analyses were based on PK observations from all patients who had received atezolizumab, carboplatin, or etoposide treatment and who provided at least one evaluable atezolizumab PK sample.
- Safety Population: Included all treated patients, defined as patients who received any amount of any component of study treatment. For the safety analyses, patients who received any amount of atezolizumab were analyzed as part of the Atezo + CE arm, even if atezolizumab was given in error.

- ADA-Evaluable Population: ADA analyses were based on ADA observations from patients who had received atezolizumab treatment and were evaluated for immunogenicity.

Efficacy analyses:

The co-primary efficacy outcome measures for this study are:

- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs first

OS, defined as the time from randomization to death from any cause

The null and alternative hypotheses regarding PFS or OS in the ITT population can be phrased in terms of the PFS or OS survival functions SA(t) and SB(t) for Arm A (ATZ+CE) and Arm B (PBO+CE), respectively:

$$H0: SA(t) = SB(t) \text{ versus } H1: SA(t) \neq SB(t)$$

The Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. The Brookmeyer-Crowley methodology (Brookmeyer and Crowley 1982) will be used to construct the 95% CI for the median PFS for each treatment arm. Cox proportional-hazards models, stratified by sex (male vs. female), ECOG performance status (0 vs. 1), and presence of brain metastases (yes vs. no) will be used to estimate the HR and its 95% CI. The unstratified HR will also be presented. Treatment comparisons will be based on the stratified log-rank test.

Use of the stratification factors implemented at randomization in the Cox model for OS and PFS:

The Study GO30081 Statistical Analysis Plan (SAP) Version 2 was amended (27 February 2018)due to the potential risk of over-stratification (Akazawa et al. 1997). If at least one stratum (i.e., a combination of stratification factor levels across sex [male vs female], Eastern Cooperative Oncology Group [ECOG] performance status [0 vs 1], and brain metastasis [Yes vs No] per interactive voice/Web response system [IxRS]) has less than 10 events (progression-free survival [PFS] or overall survival [OS] events), the stratification factor (one of 3 stratification factors: sex, ECOG performance status, and brain metastasis per IxRS) 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 events (PFS or OS events). The final set of stratification factors used in stratified analyses will be applied to all endpoints where stratified analyses are planned.

Censoring rules:

OS: Patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Patients with no post-baseline information will be censored at the date of randomization plus 1 day.

PFS: Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients without a date of disease progression will be analyzed as censored observations on the date of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day.

Sensitivity analyses:

OS:

The impact of non-protocol-specified anti-cancer therapy on OS will be assessed, in which data from patients who receive non-protocol-specified anti-cancer therapy before a PFS event will be censored at the date before receipt of non-protocol-specified anti-cancer therapy.

The impact of loss to follow-up on OS will be assessed depending on the number of patients who are lost to follow-up. If > 5% of patients are lost to follow-up for OS in either treatment arm, a sensitivity analysis will be performed for the comparisons between two treatment arms in which patients who are lost to follow-up will be considered as having died at the last date they were known to be alive.

PFS:

One sensitivity analysis will be performed to evaluate the potential impact of missing scheduled tumor assessments on the primary analysis of PFS, as determined by the investigator using a PFS event imputation rule

1. If a patient misses two or more assessments scheduled immediately prior to the date of the PFS event, the patient will be counted as having progressed on the date of the first of these missing assessments.

2. Patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits.

The imputation rule will be applied to patients in both treatment arms. Statistical methodologies that are analogous to those used in the primary analysis of PFS will be used for this sensitivity analysis.

Analyses were also presented to assess the impact of non-prior anti-cancer therapy (NPT) on PFS for patient who switched to other treatment before a PFS event.

Control of the type 1 error due to two co-primary endpoints:

To adjust for multiplicity due to having two co-primary endpoints, a group sequential Holm's procedure will be implemented: initially the hypothesis test for PFS will be conducted at a two-sided alpha of 0.005 and OS will be tested at a two-sided alpha of 0.045. Once a null hypothesis is rejected, the test mass predefined for that endpoint becomes available and can be recycled to the other unrejected test.

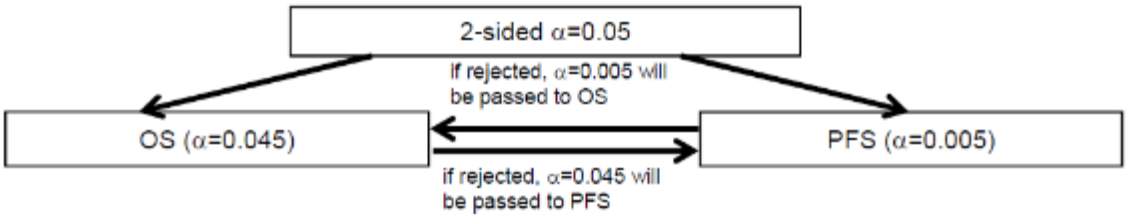


Table 5: Group sequential Holm procedure

Interim analyses:

One interim efficacy analysis of OS is planned for when approximately 240 OS events have been observed. The primary analysis of PFS will be conducted at the same time as the interim OS analysis, and the exact timing of the analysis depends on when 240 OS events in the ITT population have occurred.

The final OS analysis will be conducted when approximately 306 OS events in the ITT population have been observed. This is expected to occur approximately 36 months after the first patient is randomized, but the exact timing of this analysis will depend on the actual number of OS events.

To control the type I error for OS, the stopping boundaries for OS interim and final analyses are to be computed with use of the Lan-DeMets approximation to the O'Brien-Fleming boundary.

An external independent Data Monitoring Committee (iDMC) will be set up to evaluate safety data on an ongoing basis. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an independent Data Coordinating Center. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. Any outcomes of these safety reviews that

affect study conduct will be communicated in a timely manner to the investigators for notification of the institutional review boards/ethics committees. A detailed plan will be included in the iDMC Charter.

Secondary efficacy endpoints

Objective Response Rate (ORR) is defined as the proportion of patients who had an objective response by the investigator using RECIST v1.1. An estimate of ORR and its 95% CI will be calculated with the Clopper Pearson method for each treatment arm. CIs for the difference in ORRs between the two treatment arms will be determined with use of the normal approximation to the binomial distribution. Patients without any post-baseline assessment will be considered non-responders.

Confirmation of response according to RECIST v1.1 was not required, but for the exploratory purposes, ORR with confirmation was to be reported as needed.

Duration or Response (DOR) was to be assessed for patients who had an objective response as determined by the investigator using RECIST v1.1. Patients whose disease has not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DOR will be censored at the date of the first occurrence of a CR or PR plus 1 day. DOR is based on a non-randomized subset of patients (specifically, patients who achieved an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes. The methodologies detailed for the PFS analysis was used for the DOR analysis.

Patient-Reported Outcomes. PROs of HRQoL, lung cancer−related symptoms was measured using EORTC QLQC30 and EORTC QLQ-LC13. The ITT population was used for TTD analyses and to document completion rates. Missing PRO scores were not imputed. Patients whose symptoms have not deteriorated before the last PRO a ssessment is completed were to be censored at the date of the last PRO assessment. Patients with no baseline assessment or post-baseline assessments were to be censored at the date of randomization plus 1 day.

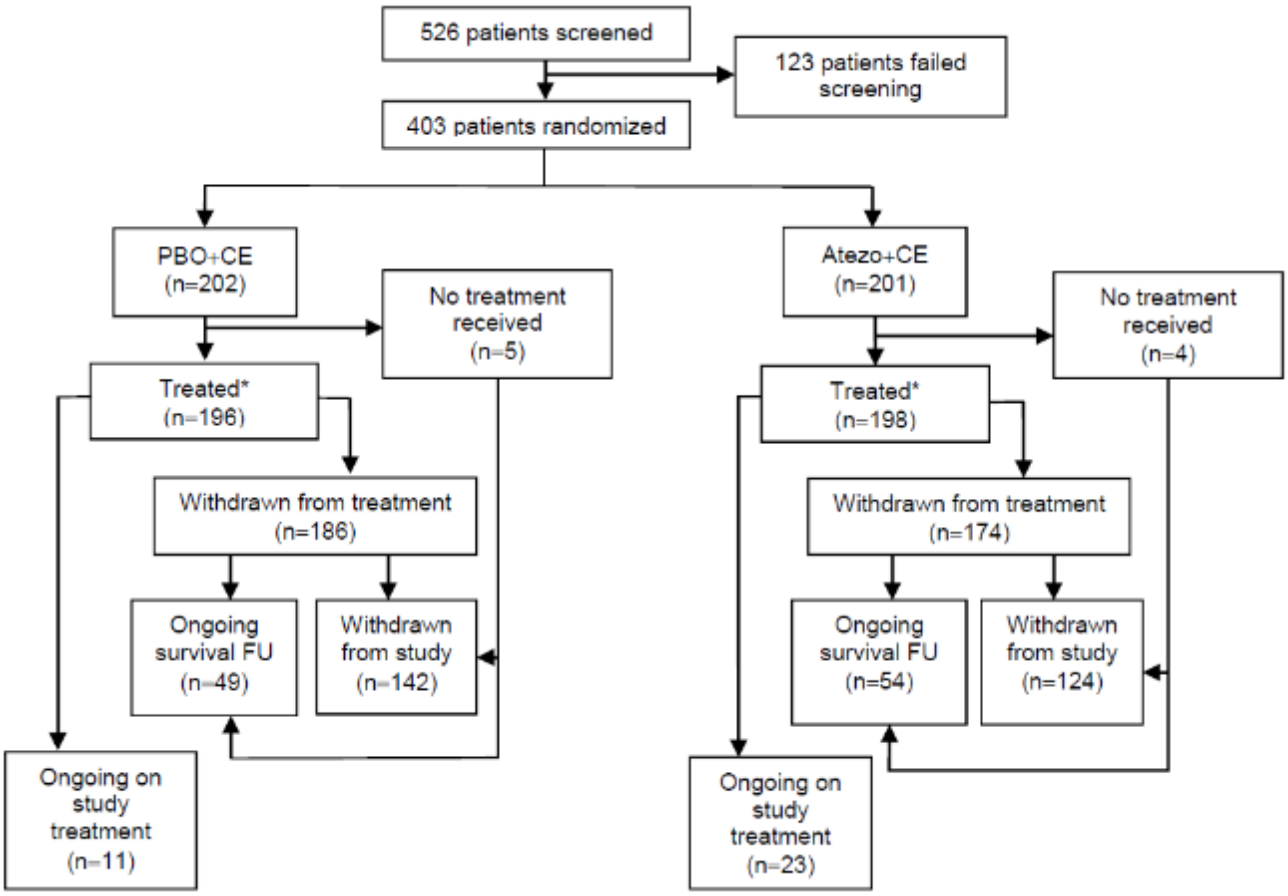
TTD according to the EORTC QLQ-C30 and EORTC QLQ-LC13 measures will be evaluated in each of the following linearly transformed symptom scores: cough, dyspnea (single item), dyspnea (multi-item subscale), chest pain, or arm/shoulder pain. The linear transformation gives each individual symptom subscale a possible score of 0 to 100. For the symptom to be considered "deteriorated," a score increase of $\geq$ 10 points above baseline must be held for at least two consecutive assessments or an initial score increase of $\geq$10 points is followed by death within 3 weeks from the last assessment. A $\geq$ 10-point change in the symptoms subscale score is perceived by patients as clinically significant (Osoba et al. 1998). The methodologies outlined for the analysis of PFS will be used for the analyses of TTD of the pre-specified symptoms of the EORTC QLQ-C30 and EORTC QLQ-LC13 measures. The estimated Kaplan-Meier plots will be provided for each symptom separately.

Subgroup analyses:

The consistency of PFS and OS results was investigated by estimating the treatment effect in predefined subgroups based on key demographics (age, sex, race/ethnicity), baseline disease characteristics (ECOG PS, smoking status, brain, liver and other metastases at enrollment), and pre-specified TMB biomarker expression cutoffs ($\geqslant$10 or

<10 and ≥16 or <16).*Results*

Participant flow



*One Safety Population patient randomized to the PBO + CE arm received Atezo and was therefore counted in the Atezo + CE arm.

Table 6: Patient disposition (screened patients)

Failed screening: A total of 123 patients failed screening based on information collected in the IxRS system. The most common reasons for screen failure were active or untreated CNS metastases (25 patients), withdrawal by subject (13 patients), and lack of evidence of histologically or cytologically confirmed ES-SCLC per the VALG staging system (Inclusion Criterion 4; 10 patients). A listing of all patients who failed screening, including the reason for screening failure, was provided in the appendix of the CSR.

No treatment received: Overall, 9 patients did not receive any study treatment (5 patients in the PBO + CE arm and 4 patients in the Atezo + CE arm). As of the CCOD of 24 April 2018, all 9 untreated patients had discontinued the study due to withdrawal by subject (4 patients), death (4), and physician decision (1).

Patients Unblinded During the Study: At the time of the CCOD, treatment allocation had been unblinded for 4 patients for safety reasons (2 patients in each arm) and for 6 patients for other reasons, for example to inform subsequent treatment decisions after disease progression (2 patients in the Atezo + CE arm and 4 patients in the PBO + CE arm). These were individual patient unblindings that occurred at the site level, and the Sponsor continued to remain blinded to the treatment assignment. Patients who were unblinded were included in the analysis populations.

Table 7: Patient disposition from study (ITT population)

	PBO + CE (Randomized) (N=202)	Atezo + CE (Randomized) (N=201)	All Patients (N=403)
Received Treatment	197 (97.5%)	197 (98.0%)	394 (97.8%)
On-study Status	60 (29.7%)	77 (38.3%)	137 (34.0%)
Alive: On Treatment	11 (5.4%)	23 (11.4%)	34 (8.4%)
Alive: In Follow-Up	49 (24.3%)	54 (26.9%)	103 (25.6%)
Discontinued Study	142 (70.3%)	124 (61.7%)	266 (66.0%)
Death	132 (65.3%)	101 (50.2%)	233 (57.8%)
Lost To Follow-Up	1 (0.5%)	3 (1.5%)	4 (1.0%)
Physician Decision	0	2 (1.0%)	2 (0.5%)
Withdrawal By Subject	9 (4.5%)	18 (9.0%)	27 (6.7%)

Table 8: Patient disposition (safety evaluable population)

	IMpower133			
	PBO+CE (N=196)	Atezo+CE (N=198)	Atezo+Chemo Combo (N=2421)	Atezo Mono (N=3178)
End of Study Status				
n	196 (100%)	198 (100%)	2421 (100%)	3178 (100%)
Discontinued study	137 (69.9%)	120 (60.6%)	1363 (56.3%)	2070 (65.1%)
Ongoing	59 (30.1%)	78 (39.4%)	1058 (43.7%)	1108 (34.9%)
Reason for Study Discontinuation				
All Reasons	137 (69.9%)	120 (60.6%)	1363 (56.3%)	2070 (65.1%)
Death	129 (65.8%)	100 (50.5%)	1251 (51.7%)	1887 (59.4%)
Progressive disease	0	0	0	3 (<0.1%)
Lost to follow-up	1 (0.5%)	3 (1.5%)	10 (0.4%)	70 (2.2%)
Other	0	0	2 (<0.1%)	1 (<0.1%)
Physician decision	0	1 (0.5%)	3 (0.1%)	1 (<0.1%)
Protocol violation	0	0	0	11 (0.3%)
Withdrawal by subject	7 (3.6%)	16 (8.1%)	96 (4.0%)	97 (3.1%)
Non-compliance	0	0	1 (<0.1%)	0
Patients Discontinued from Atezo				
All Reasons	0	175 (88.4%)	1912 (79.0%)	2627 (82.7%)
Adverse event	0	21 (10.6%)	329 (13.6%)	213 (6.7%)
Death	0	8 (4.0%)	69 (2.9%)	15 (0.5%)
Progressive disease	0	126 (63.6%)	1145 (47.3%)	1862 (58.6%)
Progression of disease	0	0	0	371 (11.7%)
Lost to follow-up	0	0	5 (0.2%)	2 (<0.1%)
Other	0	0	12 (0.5%)	10 (0.3%)
Physician decision	0	2 (1.0%)	92 (3.8%)	34 (1.1%)
Protocol violation	0	0	2 (<0.1%)	14 (0.4%)
Protocol Deviation	0	1 (0.5%)	1 (<0.1%)	0
Withdrawal by subject	0	9 (4.5%)	92 (3.8%)	94 (3.0%)
Non-compliance	0	0	3 (0.1%)	8 (0.3%)
Non-compliance with study drug	0	1 (0.5%)	1 (<0.1%)	0
Symptomatic Deterioration	0	7 (3.5%)	161 (6.7%)	4 (0.1%)

Table 9: Patient disposition from study treatment (safety evaluable population)

	PBO + CE (Actual) (N=196)	Atezo + CE (Actual) (N=198)
Received at least one study treatment		
Yes	196 (100.0%)	198 (100.0%)
Treatment Status		
Ongoing	1 (0.5%)	13 (6.6%)
Withdrawn from treatment	195 (99.5%)	185 (93.4%)
Withdrawn from Treatment Reason		
NON-COMPLIANCE WITH STUDY DRUG	0	1 (0.5%)
PROTOCOL DEVIATION	0	1 (0.5%)
DEATH	10 (5.1%)	8 (4.0%)
ADVERSE EVENT	6 (3.1%)	24 (12.1%)
SYMPTOMATIC DETERIORATION	1 (0.5%)	7 (3.5%)
PROGRESSIVE DISEASE	160 (81.6%)	135 (68.2%)
PHYSICIAN DECISION	10 (5.1%)	2 (1.0%)
WITHDRAWAL BY SUBJECT	8 (4.1%)	10 (5.1%)
LOST TO FOLLOW-UP	1 (0.5%)	0

All reasons across study treatments are displayed. Multiple occurrences of the reason within a patient is counted once.

Recruitment

The first patient was randomized on 6 June 2016.

The last patient was randomized on 31 May 2017.

Data cut-off was on 24 April 2018.

The study was conducted across 106 sites in 21 countries. The number of patients randomized per country, followed by the number of centers (in parentheses) was: United States of America 86 (22), Poland 45 (6), Japan 42 (13), Russia 30 (6), Spain 25 (6), Austria 20 (4), Hungary 19 (4), Czech Republic 17 (3), South Korea 17 (4), Italy 15 (6), Serbia 15 (3), Australia 11 (3), Greece 11 (3), United Kingdom 10 (4), Germany 9 (5), Taiwan 9 (3), France 7 (4), Chile 6 (2), Brazil 4 (3), Mexico 4 (1), China 1 (1).

Conduct of the study

Protocol amendments:

The original protocol dated 08 December 2015 was amended on four times (v2, 08 June 2016; v3, 25 August 2016; v4, 29 August 2017; v5, 27 February 2018). Only relevant protocol amendments are included in the following section:

Protocol Amendment 1 (Version 2) – 08 June 2016

- The phase of this study was changed from Phase III to Phase I/III throughout the protocol.
- It was added that in the case of an early termination of the study, patients who were deriving clinical benefit from treatment with atezolizumab would be permitted to continue treatment with atezolizumab at the discretion of the investigator.

Protocol Amendment 2 (Version 3) – 25 August 2016

- The phase of the study was changed from Phase III to Phase I/III where applicable throughout.
- A secondary efficacy objective and corresponding outcome measure were added to evaluate the efficacy of Atezo + CE compared with PBO + CE as measured by investigator-assessed time to response (TTR). TTR will be assessed in the ITT population for patients who had an objective response as determined by the investigator according to RECIST v1.1.
- Clarification was made that during the maintenance phase, prophylactic cranial irradiation was permitted as per local standard-of-care and its use was to be reported on the Prophylactic Cranial Irradiation eCRF page.
- Clarification was made that thoracic radiation with curative intent or the intent to eliminate residual disease was not permitted but that palliative thoracic radiation was allowed.
- The criteria for continuing study treatment beyond radiographic disease progression per RECIST v1.1 was modified to remove the criterion for absence of symptoms and signs including worsening of laboratory vitals indicating unequivocal progression of disease.
- It was added that in the case of an early termination of the study, patients who were deriving clinical benefit from treatment with atezolizumab would be permitted to continue treatment with atezolizumab at the discretion of the investigator.
- Clarification was made that cycles in which no chemotherapy was given did not count toward the total number of induction chemotherapy cycles.

- The screening assessments were revised, clarifying that either a CT or MRI scan of the pelvis was required at screening.
- Clarification was made that biomarker blood samples should not be taken during screening. The baseline biomarker blood sample should be collected on Cycle 1, Day 1, and the samples should be taken prior to administration of any study treatment.
- Revision was made to clarify that a pre-treatment tumor tissue sample could be archival or freshly obtained and should be submitted before or within 4 weeks after randomization. This specimen was expected to be accompanied by the associated pathology report. Additionally, although any available tumor tissue sample could be submitted, preferred sample types were included. It was strongly encouraged that representative tumor specimens in paraffin blocks (preferred) or 10 (or more) serial, freshly cut, unstained slides were submitted for exploratory biomarker analysis, including but not limited to PD-L1 status. NGS may be performed by Foundation Medicine on evaluable pre-treatment tissue if requested by the investigator.
- Clarification was made that pre-treatment tumor tissue samples from patients who were deemed ineligible to enroll into the study were returned no later than 6 weeks after eligibility determination.
- Preferred sample types for optional tumor samples after completion of induction treatment were added. In addition, language was added to specify that NGS may be performed by Foundation Medicine on evaluable tissue if requested by the investigator.
- Revision was made to clarify that if clinically feasible, it was recommended that a tumor biopsy be performed at the time of radiographic progression, preferably within 40 days of radiographic progression or prior to the start of the next anti-cancer treatment, whichever was sooner. Preferred sample types were also added. In addition, language was added to specify that NGS could be performed by Foundation Medicine on evaluable tissue if requested by the investigator.
- The frequency of the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L questionnaires were modified. Patients who discontinued study treatment for any reason other than disease progression per RECIST v1.1 (e.g., toxicity) were to complete these questionnaires at each tumor assessment visit until disease progression per RECIST v1.1, unless the patient withdrew consent or the Sponsor terminated the study, whichever occurred first.
- Revision was made to clarify that if, in the opinion of the investigator, a toxicity was considered to be due solely to one component of the study treatment and the dose or administration of that component was delayed or modified, the dose or administration of the other study treatment components did not require modification and could be administered if there was no contraindication.
- The length of time that atezolizumab could be withheld was clarified to be a maximum of 105 days beyond the last dose of atezolizumab and that exceptions required Medical Monitor's approval.
- Dose modification guidelines for carboplatin and etoposide were revised for clarity and consistency.
- Clarification was made that a hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours were not considered to be SAEs, but should be reported as AEs.
- The requirement for a tumor response assessment at the treatment discontinuation visit was removed.

Protocol Amendment 3 (Version 4) – 29 August 2017

- Modifications were made to the SAP and the timing for the efficacy analyses for PFS and OS in the global study. The OS event-patient ratio for the interim OS analysis was increased from 45% to 55%;

for the final OS analysis, the ratio was reduced from 74% to 70%. Additionally, the second OS interim analysis at the time when 258 OS events had occurred was removed. As a result of the changes, 280 deaths were required for the final OS analysis, estimated to be achieved at approximately first patient randomized plus 31 months, compared to 298 OS events with 37 months under a 74% event-patient ratio. These changes were implemented to be consistent with other studies in the atezolizumab first-line lung cancer program. The multiplicity strategy was adjusted from splitting alpha to a group sequential Holm procedure so that alpha spent on PFS could be recycled to OS when PFS was significant, and vice versa, to most efficiently use alpha and maximize power.

- The secondary objectives and outcome measures regarding investigator-assessed time in response (TIR) and TTR according to RECIST v1.1 were removed to be consistent with other studies in the atezolizumab first line lung cancer program.
- The exploratory objectives and outcome measures regarding disease control rate (DCR), TIR, and TTR according to modified RECIST v1.1, PFS, OS, ORR, DOR, TIR, TTR, and DCR in the PD-L1 selected population, and investigator-assessed DCR according to RECIST v1.1 were removed to be consistent with other studies in the atezolizumab first line lung cancer program.
- The definition of the end of the study was updated. The end of study was to occur when all of the following criteria had been met: the last patient last visit (LPLV) had occurred (i.e., last patient in the global and extended China enrollment phases combined); approximately 280 deaths had been observed among the randomized patients in the global enrollment phase; and there were sufficient OS events in the ITT population enrolled in the China enrollment phase.
- Language was modified to clarify the process for reporting deaths and for reporting events that occurred after the AE reporting period.
- The reporting procedures for death were modified to prohibit use of the term "sudden death" on the AE eCRF unless it was combined with the presumed cause of death (e.g., "sudden cardiac death"), as use of the term "sudden death" required the Sponsor to query the site for clarification on the cause of death.
- The reporting instructions for AEs leading to hospitalization were clarified.
- Language was added to clarify that AE reports were not to be derived from PRO data by the Sponsor and sites were not expected to review the PRO data for AEs.
- PFS defined by additional censoring rule for missed visits was changed to a sensitivity analysis to be consistent with other studies in the atezolizumab first line lung cancer program.
- The impact of non-protocol-specified anti-cancer therapy on OS was to be assessed as a sensitivity analysis by using censoring date cutoff at the date before receipt of non-protocol-specified anti-cancer-therapy to be consistent with other studies in the atezolizumab first line lung cancer program.
- Language was added to clarify that the Sponsor reviewed all protocol deviations, and prospective requests to deviate from the protocol were not allowed.

Protocol Amendment 4 (Version 5) – 27 February 2018

- Protocol GO30081 Version 5 was a country-specific amendment to comply with the Spanish health authority's (Agencia Española de Medicamentos y Productos Sanitarios) requirement to include guidelines on the management of atezolizumab-specific AEs, which were also included in the Atezolizumab Investigator's Brochure, in the protocol.

<u>Protocol deviations:</u>

Table 10: Summary of major protocol deviations (ITT population)

Protocol Deviation Category Protocol Deviation Description	PBO + CE (Randomized) (N=202)	Atezo + CE (Randomized) (N=201)	All Patients (N=403)
Total number of patients with at least one deviation	74 (36.6%)	79 (39.3%)	153 (38.0%)
Overall total number of deviations	104	118	222
Procedural			
Total number of patients with at least one deviation	64 (31.7%)	65 (32.3%)	129 (32.0%)
Total number of events	80	91	171
ICF - Other (e.g. procedural issues)	23 (11.4%)	28 (13.9%)	51 (12.7%)
Other proc. deviation for safety and/or efficacy	19 (9.4%)	19 (9.5%)	38 (9.4%)
Error with stratification	8 (4.0%)	12 (6.0%)	20 (5.0%)
Omission of safety labs required by protocol	9 (4.5%)	9 (4.5%)	18 (4.5%)
Failure to report SAEs or pregnancy per protocol	6 (3.0%)	5 (2.5%)	11 (2.7%)
Tumor assessment significantly out of window	3 (1.5%)	8 (4.0%)	11 (2.7%)
Omission of tumor assessment	4 (2.0%)	4 (2.0%)	8 (2.0%)
No pre-treatment tumor tissue sample submitted	1 (0.5%)	0	1 (0.2%)
Inclusion criteria			
Total number of patients with at least one deviation	9 (4.5%)	15 (7.5%)	24 (6.0%)
Total number of events	9	16	25
Incl/Excl-related test not done/out of window	7 (3.5%)	13 (6.5%)	20 (5.0%)
Ineligible history or current SCLC stage	1 (0.5%)	2 (1.0%)	3 (0.7%)
Inclusion lab values outside allowed limits	1 (0.5%)	0	1 (0.2%)
Received prior treatment for ES-SCLC	0	1 (0.5%)	1 (0.2%)
Medication			
Total number of patients with at least one deviation	9 (4.5%)	7 (3.5%)	16 (4.0%)
Total number of events	10	7	17
Significant deviation from planned study drug dose	7 (3.5%)	5 (2.5%)	12 (3.0%)
Induction treatment not given as per protocol	1 (0.5%)	1 (0.5%)	2 (0.5%)
Received incorrect study drug or wrong dose	1 (0.5%)	1 (0.5%)	2 (0.5%)
Exclusion criteria			
Total number of patients with at least one deviation	5 (2.5%)	4 (2.0%)	9 (2.2%)
Total number of events	5	4	9
Active or untreated CNS metastases	4 (2.0%)	0	4 (1.0%)
Other exclusion criteria	1 (0.5%)	3 (1.5%)	4 (1.0%)
Excluded positive viral test (HIV, HBV, HCV, TB)	0	1 (0.5%)	1 (0.2%)

Baseline data

Table 11: Demographic and baseline disease characteristics (ITT population)

	PBO + CE (Randomized) (N=202)	Atezo + CE (Randomized) (N=201)	All Patients (N=403)
Age (years)			
n	202	201	403
Mean (SD)	63.6 (9.0)	63.8 (8.8)	63.7 (8.9)
Median	64.0	64.0	64.0
Min - Max	26 - 87	28 - 90	26 - 90
Age group (years)			
n	202	201	403
< 65	106 (52.5%)	111 (55.2%)	217 (53.8%)
>= 65	96 (47.5%)	90 (44.8%)	186 (46.2%)
65 - 74	74 (36.6%)	71 (35.3%)	145 (36.0%)
75 - 84	21 (10.4%)	18 (9.0%)	39 (9.7%)
>=85	1 (0.5%)	1 (0.5%)	2 (0.5%)
Sex (eCRF)			
n	202	201	403
Male	132 (65.3%)	129 (64.2%)	261 (64.8%)
Female	70 (34.7%)	72 (35.8%)	142 (35.2%)
Sex (IxRS)			
n	202	201	403
Male	132 (65.3%)	130 (64.7%)	262 (65.0%)
Female	70 (34.7%)	71 (35.3%)	141 (35.0%)
Race			
n	202	201	403
American Indian or Alaska Native	1 (0.5%)	0	1 (0.2%)
Asian	36 (17.8%)	33 (16.4%)	69 (17.1%)
Black or African American	2 (1.0%)	1 (0.5%)	3 (0.7%)
White	159 (78.7%)	163 (81.1%)	322 (79.9%)
Unknown	4 (2.0%)	4 (2.0%)	8 (2.0%)
Ethnicity			
n	202	201	403
Hispanic or Latino	8 (4.0%)	8 (4.0%)	16 (4.0%)
Not Hispanic or Latino	185 (91.6%)	187 (93.0%)	372 (92.3%)
Not Stated	4 (2.0%)	4 (2.0%)	8 (2.0%)
Unknown	5 (2.5%)	2 (1.0%)	7 (1.7%)
Weight (kg) at baseline			
n	196	197	393
Mean (SD)	75.71 (17.81)	75.36 (19.74)	75.53 (18.78)
Median	73.50	73.00	73.00
Min - Max	39.0 - 129.0	45.0 - 181.0	39.0 - 181.0
Baseline ECOG (eCRF)			
n	202	201	403
0	67 (33.2%)	73 (36.3%)	140 (34.7%)
1	135 (66.8%)	128 (63.7%)	263 (65.3%)
Baseline ECOG (IxRS)			
n	202	201	403
0	72 (35.6%)	73 (36.3%)	145 (36.0%)
1	130 (64.4%)	128 (63.7%)	258 (64.0%)
Tobacco Use History			
n	202	201	403
Never	3 (1.5%)	9 (4.5%)	12 (3.0%)
Current	75 (37.1%)	74 (36.8%)	149 (37.0%)
Previous	124 (61.4%)	118 (58.7%)	242 (60.0%)
Brain Metastases (eCRF)			
n	202	201	403
Yes	18 (8.9%)	17 (8.5%)	35 (8.7%)
No	184 (91.1%)	184 (91.5%)	368 (91.3%)
Brain Metastases (IxRS)			
n	202	201	403
Yes	16 (7.9%)	16 (8.0%)	32 (7.9%)
No	186 (92.1%)	185 (92.0%)	371 (92.1%)
bTMB Biomarker Expression			
n	178	173	351
<10	68 (38.2%)	71 (41.0%)	139 (39.6%)
>=10	110 (61.8%)	102 (59.0%)	212 (60.4%)
bTMB Biomarker Expression			
n	178	173	351
<16	138 (77.5%)	133 (76.9%)	271 (77.2%)
>=16	40 (22.5%)	40 (23.1%)	80 (22.8%)
SLD at Baseline			
n	202	201	403
Mean (SD)	116.58 (58.28)	120.90 (58.88)	118.73 (58.55)
Median	105.50	113.00	111.00
Min - Max	15.0 - 353.0	12.0 - 325.0	12.0 - 353.0

Atezo=Atezolizumab, CE=Carboplatin + Etoposide, PBO=Placebo
Data Cutoff: 24APR2018

Table 12: SCLC History, Intent-to-Treat Patients

	PBO + CE (Randomized) (N=202)	Atezo + CE (Randomized) (N=201)	All Patients (N=403)
Initially diagnosed with Limited Stage SCLC prior to progressing to Extensive stage SCLC			
n	202	200	402
Yes	14 (6.9%)	13 (6.5%)	27 (6.7%)
No	188 (93.1%)	187 (93.0%)	375 (93.1%)
Current Disease Status			
n	202	200	402
Limited Stage SCLC	0	1 (0.5%)	1 (0.2%)
Extensive Stage SCLC	202 (100.0%)	199 (99.0%)	401 (99.5%)
Time since Limited Stage SCLC Diagnosis (months)			
n	14	13	27
Mean (SD)	15.74 (9.39)	16.33 (19.81)	16.02 (15.01)
Median	13.83	13.34	13.63
Min - Max	0.9 - 33.7	0.5 - 76.0	0.5 - 76.0
Time since Extensive Stage SCLC Diagnosis (months)			
n	202	199	401
Mean (SD)	0.76 (0.46)	1.00 (1.34)	0.88 (1.00)
Median	0.66	0.72	0.69
Min - Max	0.1 - 2.8	0.1 - 12.4	0.1 - 12.4
Brain Metastasis at Enrollment (per eCRF)			
n	202	201	403
Yes	18 (8.9%)	17 (8.5%)	35 (8.7%)
No	184 (91.1%)	184 (91.5%)	368 (91.3%)
Location of brain metastases			
Supratentorial	16 (7.9%)	9 (4.5%)	25 (6.2%)
Cerebellum	6 (3.0%)	8 (4.0%)	14 (3.5%)
Non-cerebellar Infratentorial	1 (0.5%)	0	1 (0.2%)
Number of brain metastases			
n	18	17	35
Mean (SD)	1.28 (0.46)	1.00 (0.00)	1.14 (0.36)
Median	1.00	1.00	1.00
Min - Max	1.0 - 2.0	1.0 - 1.0	1.0 - 2.0
Brain Metastasis Treatment			
Whole Brain Radiation	12 (5.9%)	13 (6.5%)	25 (6.2%)
SBRT/Gamma Knife	3 (1.5%)	2 (1.0%)	5 (1.2%)
Surgical Resection	1 (0.5%)	3 (1.5%)	4 (1.0%)
Metastatic Site at Enrollment			
Liver	72 (35.6%)	77 (38.3%)	149 (37.0%)
Adrenal Gland	35 (17.3%)	37 (18.4%)	72 (17.9%)
Lung	172 (85.1%)	177 (88.1%)	349 (86.6%)
Lymph Nodes	168 (83.2%)	160 (79.6%)	328 (81.4%)
Breast	1 (0.5%)	0	1 (0.2%)
Bone	42 (20.8%)	39 (19.4%)	81 (20.1%)
Bronchus	1 (0.5%)	0	1 (0.2%)
Chest	10 (5.0%)	6 (3.0%)	16 (4.0%)
Esophagus	1 (0.5%)	0	1 (0.2%)
Head	0	0	0
Kidney	4 (2.0%)	6 (3.0%)	10 (2.5%)
Bone Marrow	0	0	0
Mediastinum	16 (7.9%)	15 (7.5%)	31 (7.7%)
Neck	2 (1.0%)	0	2 (0.5%)
Ovary	0	1 (0.5%)	1 (0.2%)
Pancreas	9 (4.5%)	8 (4.0%)	17 (4.2%)
Pelvis	0	1 (0.5%)	1 (0.2%)
Pericardial Cavity	5 (2.5%)	9 (4.5%)	14 (3.5%)
Peritoneum	3 (1.5%)	4 (2.0%)	7 (1.7%)
Pleura	53 (26.2%)	52 (25.9%)	105 (26.1%)
Skin	2 (1.0%)	1 (0.5%)	3 (0.7%)
Soft Tissue	2 (1.0%)	4 (2.0%)	6 (1.5%)
Stomach	0	0	0
Trachea	0	3 (1.5%)	3 (0.7%)
Other	11 (5.4%)	20 (10.0%)	31 (7.7%)

Subject 10042 had squamous cell carcinoma and was randomized into the study without meeting disease eligibility criteria, therefore no SCLC history is available for this subject.
Subject 10300 had Non-cerebellar Infratentorial brain metastasis and was randomized into the study without meeting eligibility criteria.
Subject 10365 had limited-stage SCLC and was randomized into the study without meeting eligibility criteria, therefore no ES-SCLC history is available for this subject.
Partial Diagnosis date is imputed with 1st of the month if the day is missing in the calculations of time since Limited Stage or Extensive Stage.
Atezo=Atezolizumab, CE=Carboplatin + Etoposide, PBO=Placebo
Data Cutoff: 24APR2018

Table 13: Prior cancer therapy (Intent-to-Treat patients)

Therapy Setting	PBO + CE (Randomized) (N=202)	Atezo + CE (Randomized) (N=201)	All Patients (N=403)
Limited-Stage			
Line of Therapy			
1ST LINE	12 (5.9%)	8 (4.0%)	20 (5.0%)
2ND LINE	1 (0.5%)	0	1 (0.2%)
Therapy Type			
Total number of patients with at least one treatment	12 (5.9%)	8 (4.0%)	20 (5.0%)
Total number of treatments	13	8	21
CHEMOTHERAPY/NON-ANTHRACYCLINE	12 (5.9%)	8 (4.0%)	20 (5.0%)
Regimen Name			
Total number of patients with at least one treatment	12 (5.9%)	8 (4.0%)	20 (5.0%)
Total number of treatments	13	8	21
CISPLATIN, ETOPOSIDE, PLUS CONCURRENT RADIATION	7 (3.5%)	6 (3.0%)	13 (3.2%)
CARBOPLATIN, ETOPOSIDE, PLUS CONCURRENT RADIATION	6 (3.0%)	2 (1.0%)	8 (2.0%)
Other			
1ST LINE	0	1 (0.5%)	1 (0.2%)

Multiple cases within a specific therapy setting for a patient were counted once in the frequency for the therapy setting
A patient was counted more than once if received more than one therapy types under each line and regimen.
Subject 10242 received a dose of etoposide for the first-line treatment of ES-SCLC prior to being randomized into the study.
Atezo=Atezolizumab, CE=Carboplatin + Etoposide, PBO=Placebo
Data Cutoff: 24APR2018

Numbers analysed

Table 14: Overview of analysis populations

	PBO + CE	Atezo + CE	All Patients
All Randomized Intent-to-Treat Patients	202	201	403
Measurable Disease at Baseline per Investigator in Intent-to-Treat Patients	202	201	403
All Safety Evaluable Patients	196	198	394
ADA Evaluable Atezo Patients	0	188	188
PRO Evaluable Patients for EORTC QLQ-C30	177	170	347
PRO Evaluable Patients for EORTC QLQ-LC13	169	166	335
PRO Evaluable Patients for EQ-5D-5L	169	165	334
All PK Evaluable Atezolizumab Treated Patients	0	192	192

ATA = anti-therapeutic antibodies; PRO = patient reported outcome, PK=Pharmacokinetic. Safety, ATA and PK Evaluable populations are actual treatment received. All other populations are randomized treatment.
Atezo=Atezolizumab, CE=Carboplatin + Etoposide, PBO=Placebo
Data Cutoff: 24APR2018

Outcomes and estimation

Co-primary efficacy endpoints:

OS in ITT

At the time of the primary analysis(data cutoff 24 April 2018), patients had a median survival follow up time of 13.9 months. At the final analysis (data cutoff 24 January 2019), median survival follow up time was 22.9 months.

Table 15: Duration of survival follow-up (ITT population)

Time to Event Summary for Duration of Survival Follow-up, Intent-to-Treat Patients
Protocol: GO30081

	PBO + CE (Randomized) (N=202)	Atezo + CE (Randomized) (N=201)	All Patients (N=403)
Patients with event (%)	68 (33.7%)	97 (48.3%)	165 (40.9%)
Earliest contributing event			
Last Alive Date	68	97	165
Patients without event (%)	134 (66.3%)	104 (51.7%)	238 (59.1%)
Time to Event (Months)			
Median	13.2	13.9	13.9
95% CI	(12.9, 14.8)	(13.1, 14.4)	(13.1, 14.4)
25% and 75%-ile	12.2, 16.1	11.8, 16.1	11.9, 16.1
Range	0.0 to 21.4	0.0 to 21.1	0.0 to 21.4

* Censored, ^ Censored and event, NE = Not estimable.

Table 16: Overview of overall survival results (ITT population)

Parameter	Interim OS Analysis (CCOD 24 April 2018)		Updated OS Analysis (CCOD 24 January 2019)	
	PBO+CE	Atezo+CE	PBO+CE	Atezo+CE
Co-Primary Efficacy Objective: Overall Survival				
ITT Population	N=202	N=201	N = 202	N = 201
Patients with event (%)	134 (66.3)	104 (51.7)	160 (79.2)	142 (70.6)
Median duration of survival - months (95% CI)	10.3 (9.3, 11.3)	12.3 (10.8, 15.9)	10.3 (9.3, 11.3)	12.3 (10.8, 15.8)
Stratified Hazard Ratio (95% CI) p-value (log-rank)	0.701 (0.541, 0.909) 0.0069[a]		0.755 (0.601, 0.949) 0.0154[b]	
Patients remaining at risk	59	74	74	93
12-month event-free rate - % (95% CI)	38.2 (31.2, 45.3)	51.7 (44.4, 59.0)	39.0 (32.1, 45.9)	51.9 (44.6, 59.1)
Patients remaining at risk	3	5	39	61
18-month event-free rate - % (95% CI)	20.2 (11.1, 29.4)	25.0 (11.2, 38.7)	21.0 (15.2, 26.8)	34.0 (27.1, 40.9)
Patients remaining at risk	NE	NE	8	21
24-month event-free rate - % (95% CI)	NE (NE, NE)	NE (NE, NE)	16.8 (11.3, 22.2)	22.0 (15.7, 28.3)

Atezo = atezolizumab; CCOD = clinical cut-off date; CE = carboplatin + etoposide; CI = confidence interval; DOR = duration of response; ITT = intent-to-treat; OS = overall survival; NE = not estimable; PBO = placebo.

[a] Interim Analysis OS was tested at two-sided α of 0.0193 (with 238 observed OS events at CCOD) to control the overall two-sided type I error for OS at 0.045 by Lan DeMets function approximating O'Brien-Fleming boundary.

[b] Descriptive purposes only

Source: Table 17 Primary CSR, and t_ef_ttet01_IT_os_24JAN2019

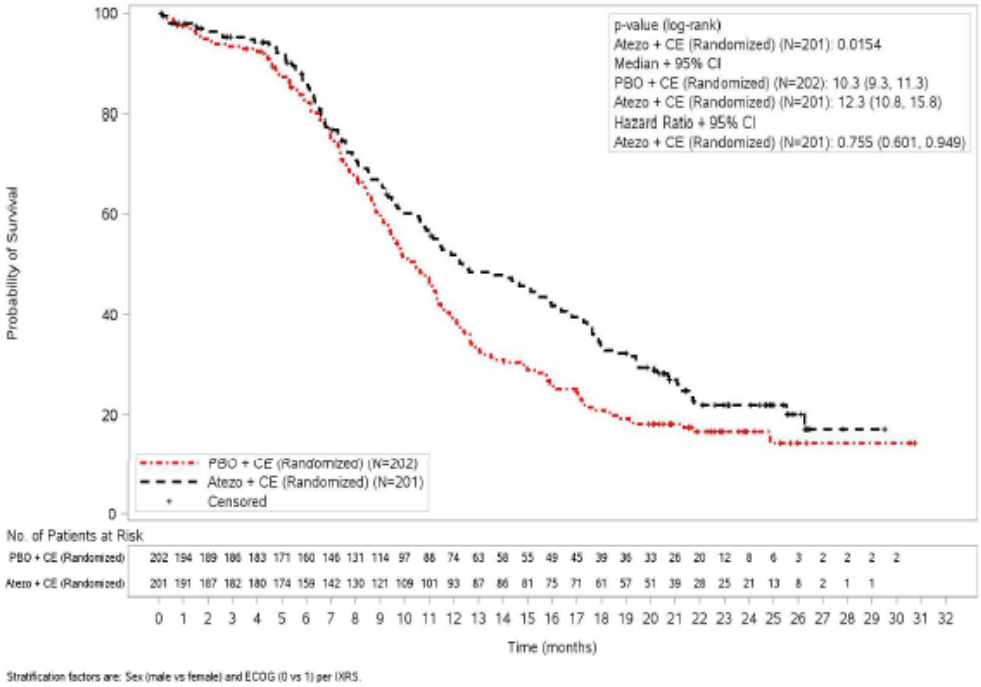


Figure 7: Kaplan-Meier curves for overall survival – final analysis (ITT population)

INV-PFS in ITT

Data from the primary analysis with cutoff on 24 April 2018.

Table 17: Time to event summary for progression free survival per RECIST v1.1 – Investigator (Intent-to-treat patients)

	PBO + CE (Randomized) (N=202)		Atezo + CE (Randomized) (N=201)
Patients with event (%)	189 (93.6%)		171 (85.1%)
Earliest contributing event			
Death	20		19
Disease Progression	169		152
Patients without event (%)	13 (6.4%)		30 (14.9%)
Time to Event (Months)			
Median	4.3		5.2
95% CI	(4.2, 4.5)		(4.4, 5.6)
25% and 75%-ile	4.0, 5.7		4.1, 7.2
Range	0.0* to 17.3^		0.0* to 21.1
Stratified Analysis			
p-value (log-rank)		0.0170	
Hazard Ratio		0.772	
95% CI		(0.624, 0.955)	
Unstratified Analysis			
p-value (log-rank)		0.0100	
Hazard Ratio		0.759	
95% CI		(0.615, 0.937)	
Time Point Analysis			
6 Months			
Patients remaining at risk	44		58
Event Free Rate (%)	22.39		30.86
95% CI	(16.56, 28.22)		(24.26, 37.45)
Difference in Event Free Rate		8.47	
95% CI		(-0.33, 17.27)	
p-value (Z-test)		0.0593	
12 Months			
Patients remaining at risk	9		21
Event Free Rate (%)	5.35		12.62
95% CI	(2.14, 8.56)		(7.85, 17.40)
Difference in Event Free Rate		7.27	
95% CI		(1.52, 13.02)	
p-value (Z-test)		0.0133	

* Censored, ^ Censored and event, NE = Not estimable.
Summaries of Time-to-Event (median, percentiles) are 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) per IXRS.
Atezo=Atezolizumab, CE=Carboplatin + Etoposide, PBO=Placebo
Data Cutoff: 24APR2018

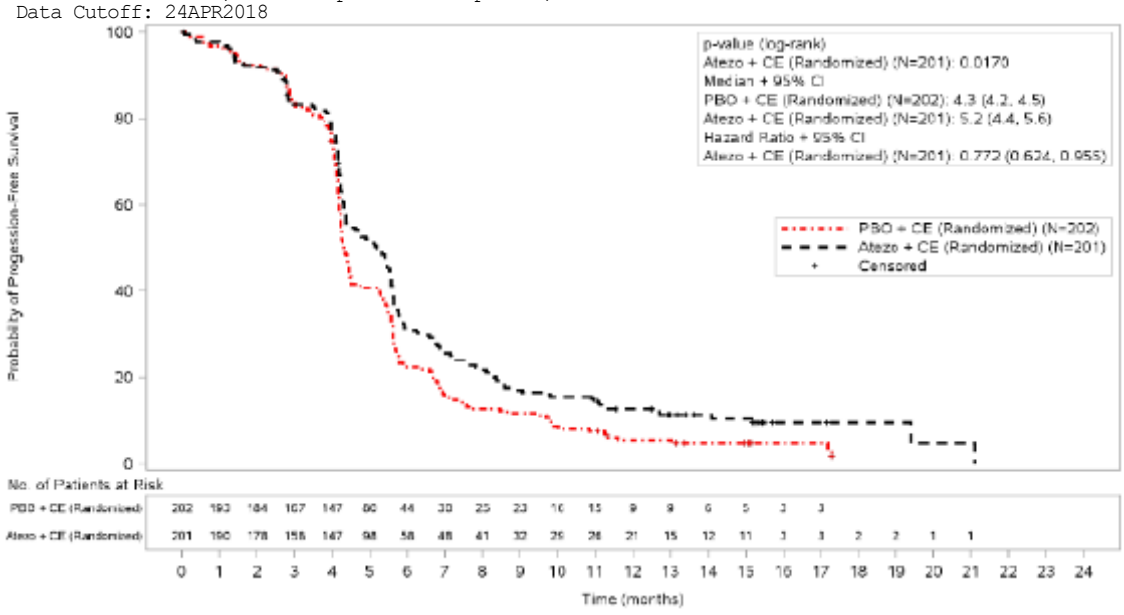


Figure 8: Kaplan-Meier plot of progression free survival with stratified analysis (Intent-to-treat patients)

Secondary efficacy endpoints:

Unconfirmed ORR

Table 18: Summary of ORR (ITT population patients with unconfirmed response assessed by investigator per RECIST v1.1)

	PBO + CE (Randomized) (N=202)	Atezo + CE (Randomized) (N=201)
Responders	155 (76.7%)	149 (74.1%)
Non-Responders	47 (23.3%)	52 (25.9%)
95% CI for Response Rate (Clopper-Pearson)	(70.29, 82.38)	(67.50, 80.03)
Difference in Response Rates	-2.60	
95% CI for Difference in Response Rates (Wald with Continuity Correction)	(-11.50, 6.30)	
p-Value* (Cochran-Mantel-Haenszel)	0.5412	
Odds Ratio*	0.87	
95% CI for Odds Ratio*	(0.55, 1.37)	
Complete Response (CR)	3 (1.5%)	5 (2.5%)
95% CI	(0.31, 4.28)	(0.81, 5.71)
Partial Response (PR)	152 (75.2%)	144 (71.6%)
95% CI	(68.70, 81.04)	(64.87, 77.76)
Stable Disease (SD)	22 (10.9%)	24 (11.9%)
95% CI	(6.95, 16.02)	(7.80, 17.24)
Progressive Disease (PD)	11 (5.4%)	15 (7.5%)
95% CI	(2.75, 9.53)	(4.24, 12.01)
Missing or unevaluable	14 (6.9%)	13 (6.5%)

Patients were classified as missing or unevaluable if no post-baseline response assessments were available or all post-baseline response baseline assessments were unevaluable. Responders refer to patients with <CR/PR>.
95% CI for rates were constructed using the Clopper Pearson method.Wald is the normal approximation for 95% CI of difference in rates. * Stratification factors are Sex and ECOG per IxRS.
Atezo=Atezolizumab, CE=Carboplatin + Etoposide, PBO=Placebo
Data Cutoff: 24APR2018

Unconfirmed DoR

Table 19: Summary of DOR (ITT population patients with unconfirmed response assessed by investigator per RECIST v1.1)

	PBO + CE (Randomized) (N=155)		Atezo + CE (Randomized) (N=149)
Patients with event (%)	148 (95.5%)		129 (86.6%)
Earliest contributing event			
Death	9		8
Disease Progression	139		121
Patients without event (%)	7 (4.5%)		20 (13.4%)
Time to Event (Months)			
Median	3.1		4.1
95% CI	(2.9, 3.9)		(3.5, 4.2)
25% and 75%-ile	2.8, 4.5		2.8, 6.6
Range	0.3 to 16.1*		0.0* to 19.5
Stratified Analysis			
p-value (log-rank)		0.0125	
Hazard Ratio		0.731	
95% CI		(0.571, 0.935)	
Unstratified Analysis			
p-value (log-rank)		0.0063	
Hazard Ratio		0.715	
95% CI		(0.562, 0.911)	
Time Point Analysis			
6 Months			
Patients remaining at risk	22		39
Event Free Rate (%)	14.34		27.13
95% CI	(8.80, 19.89)		(19.87, 34.40)

* Censored, ^ Censored and event, NE = Not estimable.
Summaries of Time-to-Event (median, percentiles) are 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) per IXRS.
Atezo=Atezolizumab, CE=Carboplatin + Etoposide, PBO=Placebo
Data Cutoff: 24APR2018

PROs

Table 20: Baseline patient-reported outcome scores

	PBO + CE (N=202)	Atezo + CE (N=201)
	Mean scores (SD)	
Select EORTC QLQ-LC13 scales	**n = 168**	**n = 176**
Coughing	42.9 (29.2)	42.2 (27.7)
Pain in chest	22.2 (25.7)	22.9 (26.6)
Dyspnea	29.6 (25.9)	34.3 (25.9)
Pain in arm or shoulder	19.4 (27.4)	22.2 (30.6)
Select EORTC QLQ-C30 scales	**n = 175**	**n = 179**
Fatigue	38.7 (26.9)	42.0 (26.4)
Appetite loss	27.4 (31.9)	28.9 (32.3)
Physical functioning	71.9 (23.5)	70.7 (22.7)
Role functioning	66.4 (32.9)	67.1 (31.3)
Social functioning	73.3 (28.8)	71.1 (29.1)
Emotional functioning	69.9 (24.0)	68.6 (23.9)
Cognitive functioning	83.3 (20.6)	81.8 (21.1)
Global health status or HRQoL	53.7 (23.4)	51.6 (22.4)

Atezo – atezolizumab, CE – carboplatin and etoposide, HRQoL – health-related quality of life, PBO = placebo; PRO = patient-reported outcome, SD = standard deviation

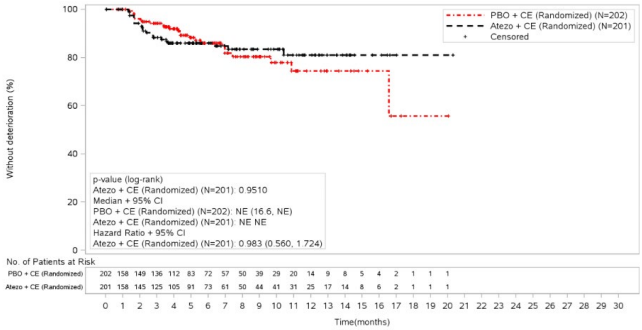


Figure 9: Kaplan-Meier plot of time to confirmed deterioration of cough with stratified analysis (ITT patients)

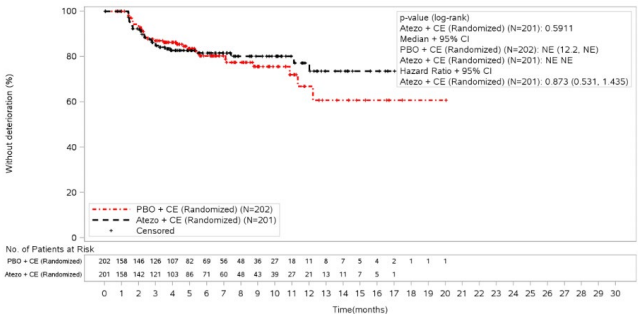


Figure 10: Kaplan-Meier plot of time to confirmed deterioration of pain in chest with stratified analysis (ITT patients)

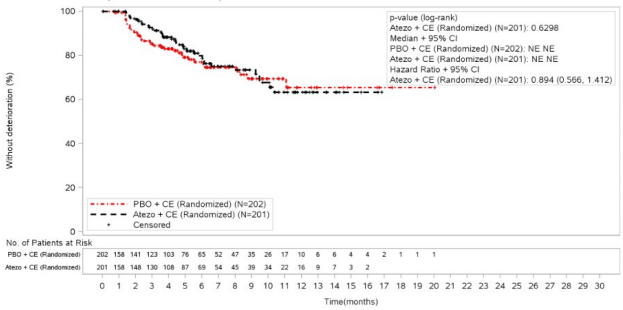


Figure 11: Kaplan-Meier plot of time to confirmed deterioration of pain in arm or shoulder with stratified analysis (ITT patients)

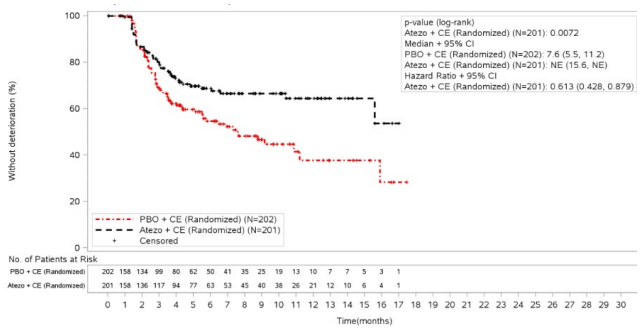


Figure 12: Kaplan-Meier plot of time to confirmed deterioration of dyspnoea with stratified analysis (ITT patients)

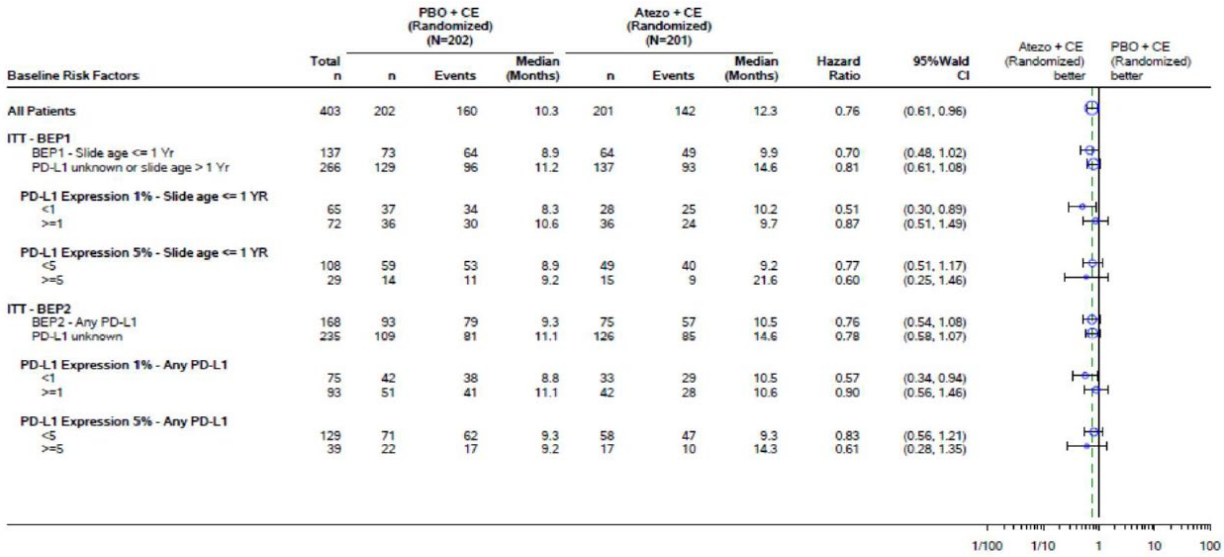
Ancillary analyses

Efficacy according to PD-L1 IHC status

Table 21: IMpower133 PD-L1 IHC (SP263) prevalence from patients with available tissue (ITT patients)

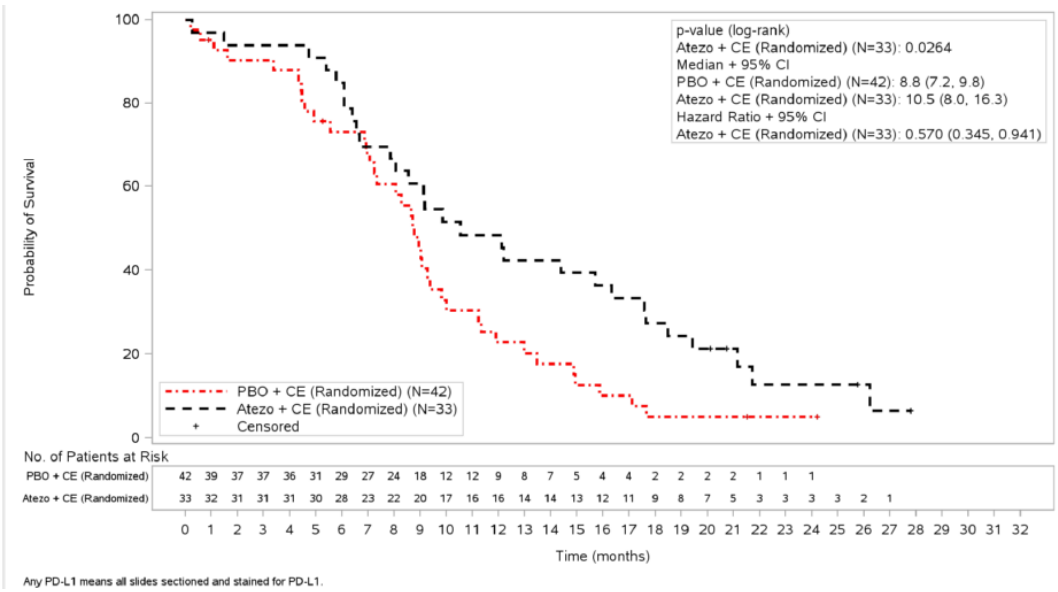
	PBO + CE (Randomized) (N=202)	Atezo + CE (Randomized) (N=201)	All Patients (N=403)
BEP1 (Section age <=1YR)			
n	73 (36.1%)	64 (31.8%)	137 (34.0%)
TC>=50% or IC>=50%	0	0	0
TC>=25% or IC>=25%	0	1 (1.6%)	1 (0.7%)
TC>=5% or IC>=5%	14 (19.2%)	15 (23.4%)	29 (21.2%)
TC>=1% or IC>=1%	36 (49.3%)	36 (56.3%)	72 (52.6%)
TC<1% and IC<1%	37 (50.7%)	28 (43.8%)	65 (47.4%)
BEP2 (Any PD-L1)			
n	93 (46.0%)	75 (37.3%)	168 (41.7%)
TC>=50% or IC>=50%	0	0	0
TC>=25% or IC>=25%	0	1 (1.3%)	1 (0.6%)
TC>=5% or IC>=5%	22 (23.7%)	17 (22.7%)	39 (23.2%)
TC>=1% or IC>=1%	51 (54.8%)	42 (56.0%)	93 (55.4%)
TC<1% and IC<1%	42 (45.2%)	33 (44.0%)	75 (44.6%)

BEP1 (Biomarker Evaluable Population 1) = ITT patients with a valid PD-L1 IHC result from a tumor tissue slide sectioned <= 1 year prior to IHC staining.
BEP2 (Biomarker Evaluable Population 2) = ITT patients with a valid PD-L1 IHC result from a tumor tissue slide, regardless of slide age at IHC staining.
Percentages in the Biomarker Evaluable Population rows are based on the treatment column N. Percentages in the TCIC expression rows are based on the Biomarker Evaluable Population row total n.



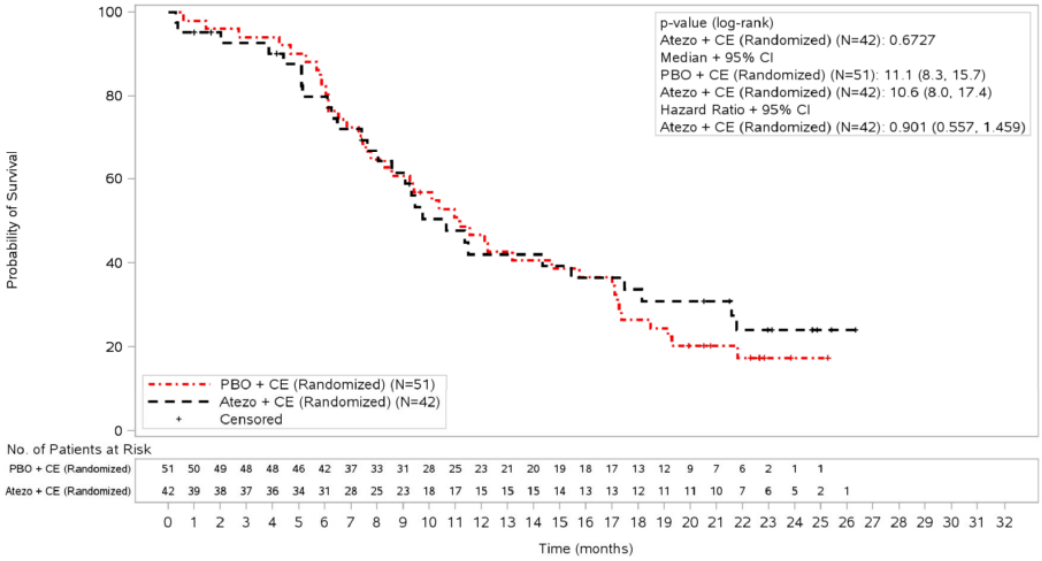
BEP1 (Biomarker Evaluable Population 1) = ITT patients with a valid PD-L1 IHC result from a tumor tissue slide sectioned <= 1 year prior to IHC staining.
BEP2 (Biomarker Evaluable Population 2) = ITT patients with a valid PD-L1 IHC result from a tumor tissue slide, regardless of slide age at IHC staining.
Medians were estimated from Kaplan-Meier method. NE = Not estimable.
Hazard ratios relative to PBO + CE and the associated confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.

Figure 13: Forest plot – subgroup analysis of OS by PD-L1 status in BEP1 and BEP2 (ITT population)



Any PD-L1 means all slides sectioned and stained for PD-L1.

Figure 14: Kaplan-Meier curves for overall survival in PD-L1 negative subgroup (<1% TC or <1% IC) of BEP2 (ITT population)



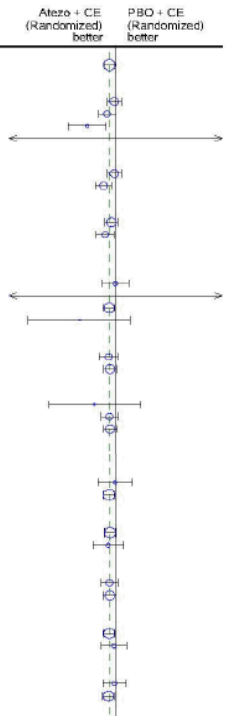
Any PD-L1 means all slides sectioned and stained for PD-L1.

Figure 15: Kaplan-Meier curves for overall survival in PD-L1 positive subgroup (≥1% TC or ≥1% IC) of BEP2 (ITT population)

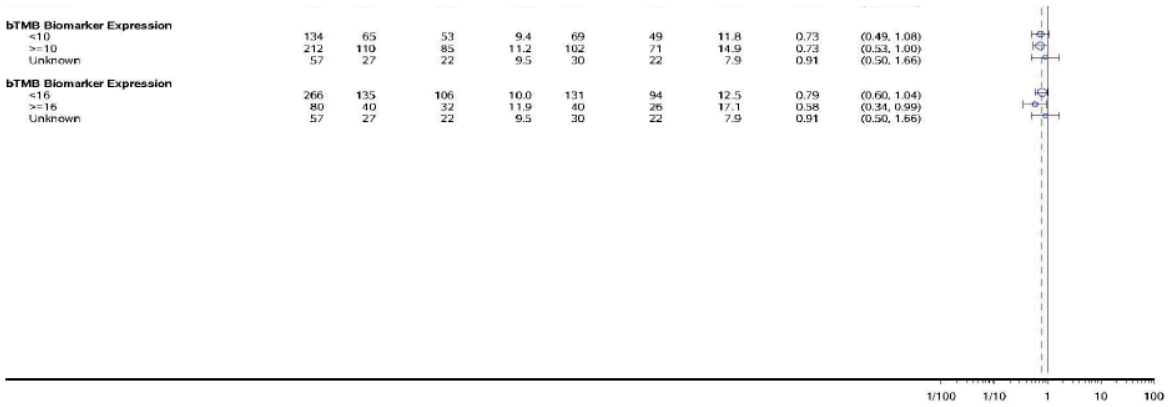
Subgroup analyses by selected demographics and baseline disease characteristics

Updated subgroup analysis of OS, 24-JAN-2019

Baseline Risk Factors	Total n	PBO + CE (Randomized) (N=202) n	Events	Median (Months)	Atezo + CE (Randomized) (N=201) n	Events	Median (Months)	Hazard Ratio	95%Wald CI
All Patients	403	202	160	10.3	201	142	12.3	0.76	(0.61, 0.96)
Age Group 4 Categories (yr)									
<65	217	106	79	11.5	111	78	12.1	0.94	(0.68, 1.28)
65 - 74	145	74	61	9.7	71	53	12.3	0.69	(0.47, 1.00)
75 - 84	39	21	19	9.6	18	10	17.9	0.29	(0.13, 0.66)
>=85	2	1	1	0.5	1	1	5.4	<0.01	(0.00, NE)
Age Group 2 Categories (yr)									
< 65	217	106	79	11.5	111	78	12.1	0.94	(0.68, 1.28)
>= 65	186	96	81	9.6	90	64	14.4	0.59	(0.42, 0.82)
Sex (eCRF)									
Male	261	132	103	10.9	129	95	12.2	0.83	(0.63, 1.10)
Female	142	70	57	9.5	72	47	13.6	0.64	(0.43, 0.94)
Race									
American Indian or Alaska Native	1	1	1	7.7				NE	(NE , NE)
Asian	69	36	24	13.2	33	22	15.4	0.98	(0.55, 1.74)
Black or African American	3	2	2	12.9	1	0	NE	<0.01	(0.00, NE)
White	322	159	129	9.9	163	118	12.1	0.75	(0.59, 0.97)
Unknown	8	4	4	7.6	4	2	10.8	0.21	(0.02, 1.88)
Baseline ECOG (eCRF)									
0	140	67	49	12.6	73	43	16.8	0.73	(0.48, 1.10)
1	263	135	111	9.3	128	99	11.3	0.78	(0.60, 1.03)
Tobacco Use									
Never	12	3	2	15.8	9	3	21.7	0.40	(0.05, 2.98)
Current	149	75	57	9.7	74	53	11.4	0.76	(0.52, 1.11)
Previous	242	124	101	10.9	118	86	12.6	0.79	(0.59, 1.05)
Brain Metastases (eCRF)									
Yes	35	18	14	9.7	17	15	8.5	0.96	(0.46, 2.01)
No	368	184	146	10.4	184	127	12.6	0.74	(0.58, 0.94)
Lung Metastasis at Enrollment									
Yes	349	172	139	10.3	177	127	12.6	0.77	(0.61, 0.99)
No	54	30	21	10.4	24	15	10.9	0.70	(0.36, 1.36)
Liver Metastasis at Enrollment									
Yes	149	72	63	7.8	77	58	9.3	0.75	(0.52, 1.07)
No	254	130	97	11.2	124	84	16.3	0.76	(0.56, 1.01)
Lymph Node Metastasis at Enrollment									
Yes	328	168	136	10.0	160	115	12.1	0.74	(0.57, 0.95)
No	75	34	24	11.2	41	27	14.4	0.91	(0.53, 1.58)
Adrenal Gland Metastasis at Enrollment									
Yes	72	35	30	8.8	37	34	9.1	0.93	(0.57, 1.53)
No	331	167	130	10.9	164	108	14.9	0.72	(0.56, 0.93)



bTMB Biomarker Expression									
<10	134	65	53	9.4	69	49	11.8	0.73	(0.49, 1.08)
>=10	212	110	85	11.2	102	71	14.9	0.73	(0.53, 1.00)
Unknown	57	27	22	9.5	30	22	7.9	0.91	(0.50, 1.66)
bTMB Biomarker Expression									
<16	266	135	106	10.0	131	94	12.5	0.79	(0.60, 1.04)
>=16	80	40	32	11.9	40	26	17.1	0.58	(0.34, 0.99)
Unknown	57	27	22	9.5	30	22	7.9	0.91	(0.50, 1.66)

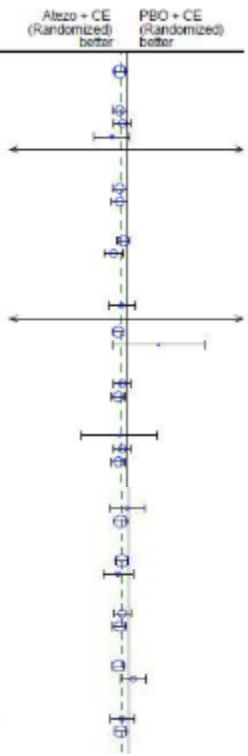


Medians were estimated from Kaplan-Meier method. NE = Not estimable.
Hazard ratios relative to PBO + CE and the associated confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.

Figure 16: Forest plot – subgroup analysis of OS by selected demographics and baseline disease characteristics – updated analysis (ITT population)

<u>Subgroup analysis of PFS, 24-APR-2018</u>

Baseline Risk Factors	Total n	PBO + CE (Randomized) (N=202) n	Events	Median (Months)	Atezo + CE (Randomized) (N=201) n	Events	Median (Months)	Hazard Ratio	95%Wald CI
All Patients	403	202	189	4.3	201	171	5.2	0.76	(0.61, 0.94)
Age Group 4 Categories (yr)									
<65	217	106	98	4.3	111	93	5.1	0.76	(0.57, 1.01)
65 - 74	145	74	69	5.3	71	64	5.3	0.85	(0.60, 1.20)
75 - 84	39	21	21	4.2	18	13	5.7	0.56	(0.28, 1.14)
>=85	2	1	1	0.5	1	1	4.2	<0.01	(0.00, NE)
Age Group 2 Categories (yr)									
< 65	217	106	98	4.3	111	93	5.1	0.76	(0.57, 1.01)
>= 65	186	96	91	4.6	90	78	5.3	0.76	(0.56, 1.03)
Sex (eCRF)									
Male	261	132	123	4.4	129	112	4.4	0.87	(0.67, 1.13)
Female	142	70	66	4.2	72	59	5.6	0.59	(0.41, 0.85)
Race									
American Indian or Alaska Native	1	1	1	5.6				NE	(NE , NE)
Asian	69	36	32	4.3	33	28	4.3	0.83	(0.49, 1.38)
Black or African American	3	2	2	4.2	1	1	8.3	<0.01	(0.00, NE)
White	322	159	150	4.3	163	139	5.4	0.72	(0.57, 0.91)
Unknown	8	4	4	6.5	4	3	4.2	3.49	(0.57, 21.55)
Baseline ECOG (eCRF)									
0	140	67	64	4.3	73	64	4.9	0.84	(0.59, 1.20)
1	263	135	125	4.3	128	107	5.4	0.72	(0.55, 0.94)
Tobacco Use									
Never	12	3	3	4.1	9	4	3.9	0.74	(0.16, 3.33)
Current	149	75	66	4.4	74	63	5.6	0.84	(0.59, 1.19)
Previous	242	124	120	4.2	118	104	5.2	0.73	(0.56, 0.95)
Brain Metastases (eCRF)									
Yes	35	18	18	4.4	17	15	4.2	0.98	(0.49, 2.00)
No	368	184	171	4.3	184	156	5.3	0.75	(0.60, 0.93)
Lung Metastasis at Enrollment									
Yes	349	172	162	4.4	177	152	5.2	0.78	(0.62, 0.97)
No	54	30	27	4.1	24	19	5.4	0.67	(0.37, 1.23)
Liver Metastasis at Enrollment									
Yes	149	72	69	4.2	77	69	4.3	0.80	(0.57, 1.13)
No	254	130	120	4.4	124	102	5.6	0.72	(0.55, 0.94)
Lymph Node Metastasis at Enrollment									
Yes	328	168	158	4.2	160	137	5.4	0.69	(0.54, 0.87)
No	75	34	31	5.5	41	34	4.5	1.23	(0.75, 2.02)
Adrenal Gland Metastasis at Enrollment									
Yes	72	35	33	4.2	37	34	4.5	0.80	(0.49, 1.31)
No	331	167	156	4.3	164	137	5.3	0.75	(0.59, 0.94)



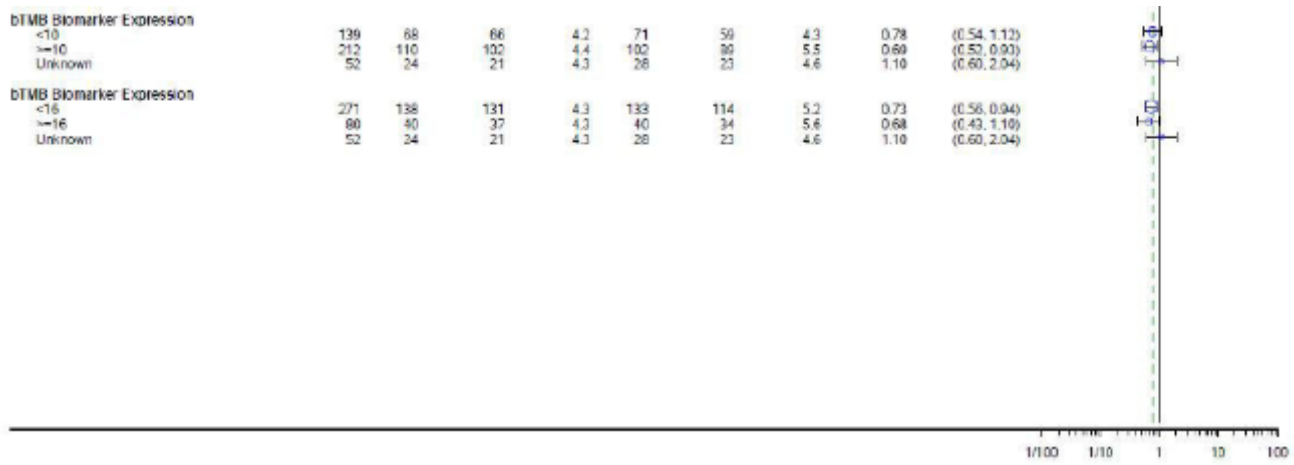


Figure 17: Forest plot – subgroup analysis of PFS per RECIST v1.1 – investigator (ITT patients)

Sensitivity analyses

Table 22: Time to event summary for investigator PFS censored for missing visits (ITT patients)

	PBO + CE (Randomized) (N=202)		Atezo + CE (Randomized) (N=201)
Patients with event (%)	185 (91.6%)		166 (82.6%)
Earliest contributing event			
Death	19		16
Disease Progression	166		150
Patients without event (%)	17 (8.4%)		35 (17.4%)
Time to Event (Months)			
Median	4.3		5.1
95% CI	(4.2, 4.5)		(4.3, 5.6)
25% and 75%-ile	4.0, 5.7		4.1, 7.1
Range	0.0* to 17.3^		0.0* to 21.1
Stratified Analysis			
p-value (log-rank)		0.0209	
Hazard Ratio		0.777	
95% CI		(0.626, 0.963)	
Unstratified Analysis			
p-value (log-rank)		0.0126	
Hazard Ratio		0.763	
95% CI		(0.616, 0.944)	

* Censored, ^ Censored and event, NE = Not estimable.
Summaries of Time-to-Event (median, percentiles) are 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) per IXRS.
Atezo=Atezolizumab, CE=Carboplatin + Etoposide, PBO=Placebo
Data Cutoff: 24APR2018

Table 23: Subsequent non-protocol anti-cancer treatments (ITT patients)

	PBO + CE (Randomized) (N=202)	Atezo + CE (Randomized) (N=201)	All Patients (N=403)
Line of Therapy			
MAINTENANCE	0	2 (1.0%)	2 (0.5%)
2ND LINE	116 (57.4%)	101 (50.2%)	217 (53.8%)
3RD LINE	38 (18.8%)	29 (14.4%)	67 (16.6%)
4TH LINE	15 (7.4%)	3 (1.5%)	18 (4.5%)
MISSING	1 (0.5%)	0	1 (0.2%)
Therapy Type			
Total number of patients with at least one treatment	116 (57.4%)	104 (51.7%)	220 (54.6%)
Total number of treatments	176	138	314
CHEMOTHERAPY/NON-ANTHRACYCLINE	88 (43.6%)	81 (40.3%)	169 (41.9%)
CHEMOTHERAPY/ANTHRACYCLINE	46 (22.8%)	31 (15.4%)	77 (19.1%)
IMMUNOTHERAPY	15 (7.4%)	6 (3.0%)	21 (5.2%)
OTHER	2 (1.0%)	2 (1.0%)	4 (1.0%)
TARGETED THERAPY	1 (0.5%)	2 (1.0%)	3 (0.7%)

Multiple cases within a specific line of therapy and regimen for a patient were counted once for the frequency of line of therapy or regimen name.
A patient was counted more than once if received more than one therapy types under each line and regimen.
Atezo=Atezolizumab, CE=Carboplatin + Etoposide, PBO=Placebo
Data Cutoff: 24APR2018

Table 24: Time to event summary for PFS censoring for NPT (ITT patients)

Time to Event Summary for Investigator Progression-Free Survival Censored at NPT, Intent-to-Treat Patients
Protocol: GO30081

	PBO + CE (Randomized) (N=202)		Atezo + CE (Randomized) (N=201)
Patients with event (%)	186 (92.1%)		170 (84.6%)
Earliest contributing event			
Death	20		19
Disease Progression	166		151
Patients without event (%)	16 (7.9%)		31 (15.4%)
Time to Event (Months)			
Median	4.3		5.2
95% CI	(4.2, 4.5)		(4.4, 5.6)
25% and 75%-ile	4.0, 5.7		4.1, 7.1
Range	0.0* to 17.3^		0.0* to 21.1
Stratified Analysis			
p-value (log-rank)		0.0212	
Hazard Ratio		0.778	
95% CI		(0.628, 0.964)	
Unstratified Analysis			
p-value (log-rank)		0.0136	
Hazard Ratio		0.767	
95% CI		(0.621, 0.947)	
Time Point Analysis			
6 Months			
Patients remaining at risk	43		57
Event Free Rate (%)	22.37		30.68
95% CI	(16.49, 28.25)		(24.08, 37.28)

* Censored, ^ Censored and event, NE = Not estimable.
Summaries of Time-to-Event (median, percentiles) are 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) per IXRS.
Atezo=Atezolizumab, CE=Carboplatin + Etoposide, PBO=Placebo
Data Cutoff: 24APR2018

Table 25: Time to event summary for OS censoring for NPT (ITT patients)

	Overall Survival Stratified Hazard Ratio (95% CI)
Discounting for NPT with 10% Benefit Reduction	0.690 (0.533, 0.895)
Discounting for NPT with 20% Benefit Reduction	0.691 (0.533, 0.896)
Discounting for NPT with 30% Benefit Reduction	0.694 (0.536, 0.899)

Exploratory analyses:

Confirmed ORR and DOR

Table 26: Summary of ORR per RECIST v1.1 by Investigator (ITT Population Patients with Confirmed Response)

+ CE	PBO + CE (Randomized) (N=202)	Atezo (Randomized) (N=201)
Responders (60.2%)	130 (64.4%)	121
Non-Responders (39.8%)	72 (35.6%)	80
95% CI for Response Rate (Clopper-Pearson)	(57.33, 70.95)	(53.07, 67.02)
Difference in Response Rates	-4.16	
95% CI for Difference in Response Rates (Wald with Continuity Correctio	(-14.11, 5.79)	
p-Value* (Cochran-Mantel-Haenszel)	0.3839	
Odds Ratio*	0.84	
95% CI for Odds Ratio*	(0.56, 1.25)	
Complete Response (CR)	2 (1.0%)	5 (2.5%)
95% CI	(0.12, 3.53)	(0.81, 5.71)
Partial Response (PR)	128 (63.4%)	116 (57.7%)
95% CI	(56.32, 70.02)	(50.56, 64.63)
Stable Disease (SD)	43 (21.3%)	42 (20.9%)
95% CI	(15.85, 27.58)	(15.49, 27.18)
Progressive Disease (PD)	14 (6.9%)	22 (10.9%)
95% CI	(3.84, 11.36)	(6.99, 16.10)
Missing or unevaluable	15 (7.4%)	16 (8.0%)

Patients were classified as missing or unevaluable if no post-baseline response assessments were available or all post-baseline response baseline assessments were unevaluable. Responders refer to patients with <CR/PR>.
95% CI for rates were constructed using the Clopper Pearson method.Wald is the normal approximation for 95% CI of difference in rates. *Stratification factors are Sex and ECOG per IxRS.
Atezo=Atezolizumab, CE=Carboplatin + Etoposide, PBO=Placebo
Data Cutoff: 24APR2018

Table 27: Summary of DOR (ITT Population Patients with Confirmed Response Assessed by Investigator per RECIST v1.1)

	PBO + CE (Randomized) (N=130)	Atezo + CE (Randomized) (N=121)
Patients with event (%)	123 (94.6%)	103 (85.1%)
Earliest contributing event		
Death	7	4
Disease Progression	116	99
Patients without event (%)	7 (5.4%)	18 (14.9%)
Time to Event (Months)		
Median	3.9	4.2
95% CI	(3.1, 4.2)	(4.1, 4.5)

25% and 75%-ile	2.8, 5.3		3.0, 7.2
Range	2.0 to 16.1*		1.4* to 19.5
Stratified Analysis			
p-value (log-rank)		0.0109	
Hazard Ratio		0.700	
95% CI		(0.532, 0.922)	
Unstratified Analysis			
p-value (log-rank)		0.0055	
Hazard Ratio		0.685	
95% CI		(0.524, 0.896)	

* Censored, ^ Censored and event, NE = Not estimable.
Summaries of Time-to-Event (median, percentiles) are 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) per IXRS.
Atezo=Atezolizumab, CE=Carboplatin + Etoposide, PBO=Placebo
Data Cutoff: 24APR2018

PFS by modified RECIST

The median duration of PFS by modified RECIST (5.6 months [95% CI: 5.5, 6.0]) was similar with RECIST v1.1 (5.2 months [95% CI: 4.4, 5.6]).

Anti-drug antibodies (ADA)

Table 28: Baseline Prevalence and Post-Baseline Incidence of Anti-Drug Antibodies (ADA) to Atezolizumab

	Atezo+CE (N=198)
Baseline evaluable patients	n=196
No. of patients positive for ADA	4 (2.0%)
No. of patients negative for ADA	192
Post-baseline evaluable patients	n=188
No. of patients positive for ADA	35 (18.6%)
Treatment-induced ADA [a]	35
Treatment-enhanced ADA [b]	0
No. of patients negative for ADA	153
Treatment-unaffected ADA [c]	4

Table 29: PFS by Investigator and OS by Atezolizumab Treatment- Emergent ADA status (ADA-Evaluable Atezolizumab Patients in Safety Evaluable Population)

	PBO + CE (N=202)	Atezo + CE (N=188)	
	All patients	Atezo ADA-Negative	Atezo ADA-Positive
Progression Free Survival per Investigator			
N	n = 202	n = 153	n = 35
Patients with event (%)	189 (93.6%)	135 (88.2%)	30 (85.7%)
Median time to event (months) 95% CI	4.3 (4.2, 4.5)	5.1 (4.3, 5.6)	5.5 (5.2, 5.6)
6 Months			
Patients remaining at risk	44	49	9
Event Free Rate (%)	22.4	32.7	27.6
95% CI	(16.6, 28.2)	(25.2, 40.2)	(12.3, 42.9)
1 year			
Patients remaining at risk	9	18	3
Event Free Rate (%)	5.4	13.2	12.3
95% CI	(2.1, 8.6)	(7.7, 18.7)	(1.0, 23.5)
Overall Survival			
N	n = 202	n = 153	n = 35
Patients with event (%)	134 (66.3%)	82 (53.6%)	17 (48.6%)
Median time to event (months) 95% CI	10.3 (9.3, 11.3)	12.6 (11.1, 16.6)	10.9 (9.1, NE)
1 year			
Patients remaining at risk	59	63	11
Event Free Rate (%)	38.2	53.7	49.1
95% CI	(31.2, 45.3)	(45.5, 61.9)	(31.6, 66.7)
2 year			
Patients remaining at risk	NE	NE	NE
Event Free Rate (%)	NE	NE	NE
95% CI	NE	NE	NE

ADA = anti-drug antibodies; Atezo + CE = atezolizumab in combination with carboplatin and etoposide; CI = confidence interval; NE = not estimable; OS = overall survival; PFS = progression-free survival; PBO + CE = placebo in combination with carboplatin and etoposide;

Table 30: IMpower133: OS hazard ratios in ADA-positive and ADA-negative patients for IPW and PSM based on original CCOD

ADA Status	IPW HR (95% CI)	PSM HR (95% CI)
ADA-positive	0.696 (0.381, 1.269)	0.667 (0.277, 1.604)
ADA-negative	0.687 (0.516, 0.914)	0.590 (0.389, 0.895)

ADA = anti-drug antibody; HR = hazard ratio; IPW = inverse probability weighting; PSM propensity score matching.

Table 31: IMpower133: OS hazard ratios in ADA-positive and ADA-negative patients for IPW and PSM based on updated CCOD

ADA Status	IPW HR (95% CI)	PSM HR (95% CI)
ADA-positive	0.841 (0.528, 1.340)	1.231 (0.547, 2.770)
ADA-negative	0.735 (0.572, 0.945)	0.600 (0.420, 0.857)

ADA = anti-drug antibody; HR = hazard ratio; IPW = inverse probability weighting; PSM propensity score matching.

Table 32: Sensitivity analysis: OS hazard ratios in ADA-positive and ADA-negative patients for IPW and PSM – original CCOD for OS but using updated covariate information

ADA Status	IPW HR (95% CI)	PSM HR (95% CI)
ADA-positive	0.708 (0.382, 1.311)	0.944 (0.395, 2.253)
ADA-negative	0.685 (0.515, 0.911)	0.557 (0.377, 0.824)

ADA = anti-drug antibody; HR = hazard ratio; IPW = inverse probability weighting; PSM propensity score matching.

Table 33: IMpower133: PFS hazard ratios in ADA-positive and ADA-negative patients for IPW and PSM based on original CCOD

ADA Status	IPW HR (95% CI)	PSM HR (95% CI)
ADA-positive	0.724 (0.453, 1.158)	0.604 (0.296, 1.234)
ADA-negative	0.743 (0.588, 0.938)	0.760 (0.549, 1.051)

ADA = anti-drug antibody; HR = hazard ratio; IPW = inverse probability weighting; PSM propensity score matching.

Treatment beyond progressive disease

Table 34: Summary of disease progression by induction and maintenance phase (safety evaluable population)

	PBO + CE (Actual) (N=196)	Atezo + CE (Actual) (N=198)	All Patients (N=394)
PD during induction			
n	16	21	37
Chose to continue treatment	9 (56.3%)	11 (52.4%)	20 (54.1%)
Other 2L anti-cancer drug	4 (25.0%)	4 (19.0%)	8 (21.6%)
No ulterior treatment	3 (18.8%)	6 (28.6%)	9 (24.3%)
Completed 4 cycles of induction			
n	196	198	394
Completed 4 cycles	176 (89.8%)	162 (81.8%)	338 (85.8%)
Did not complete 4 cycles	20 (10.2%)	36 (18.2%)	56 (14.2%)
PD after 4 cycles of induction			
n	154	134	288
Chose to continue treatment	42 (27.3%)	45 (33.6%)	87 (30.2%)
Other 2L anti-cancer drug	83 (53.9%)	60 (44.8%)	143 (49.7%)
No ulterior treatment	29 (18.8%)	29 (21.6%)	58 (20.1%)
Underwent maintenance treatment			
n	163	155	318
1-2 doses	67 (41.1%)	51 (32.9%)	118 (37.1%)
3-4 doses	50 (30.7%)	37 (23.9%)	87 (27.4%)
5-6 doses	19 (11.7%)	14 (9.0%)	33 (10.4%)
>= 7 doses	27 (16.6%)	53 (34.2%)	80 (25.2%)
PD during maintenance treatment			
n	152	132	284
Chose to continue treatment	38 (25.0%)	38 (28.8%)	76 (26.8%)
Other 2L anti-cancer drug	84 (55.3%)	65 (49.2%)	149 (52.5%)
No ulterior treatment	30 (19.7%)	29 (22.0%)	59 (20.8%)
Ongoing Treatment			
n	196	198	394
Ongoing Treatment	11 (5.6%)	23 (11.6%)	34 (8.6%)
Not Still on Treatment	185 (94.4%)	175 (88.4%)	360 (91.4%)

Atezo=Atezolizumab, CE=Carboplatin + Etoposide, PBO=Placebo

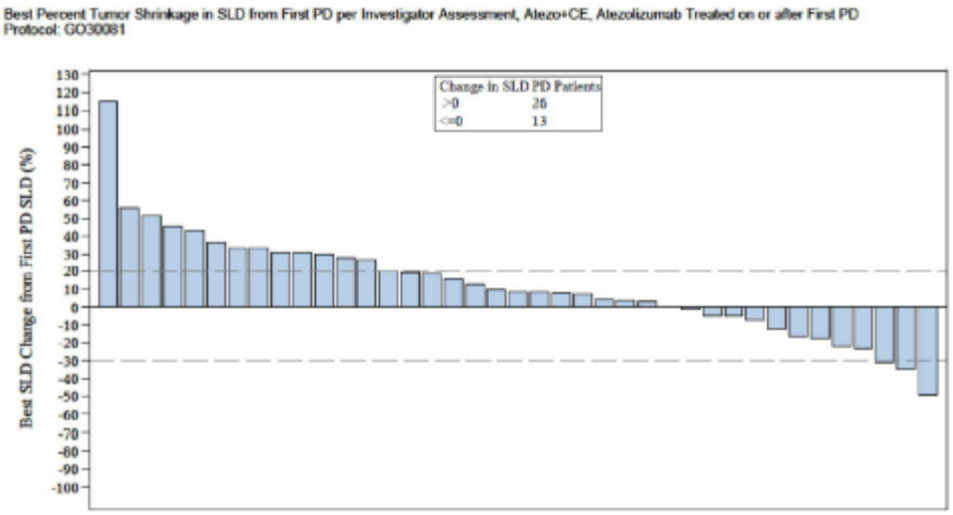
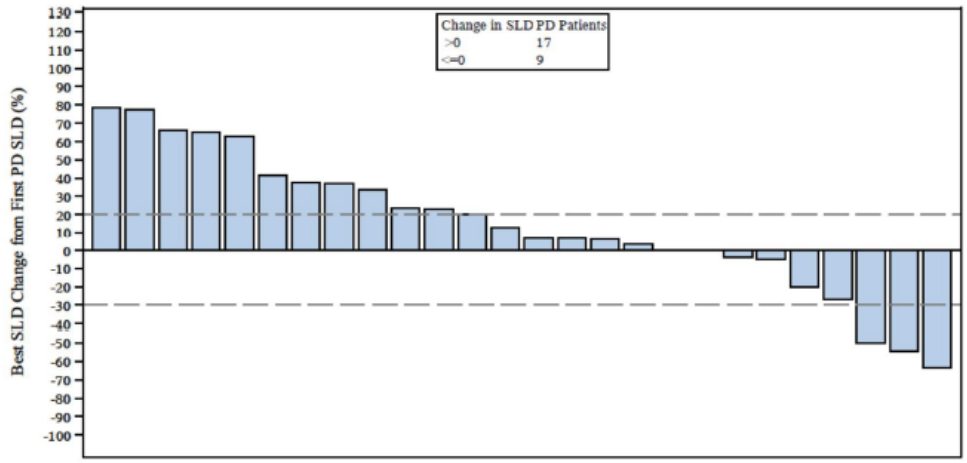


Figure 35: Maximum Percent Post-PD Tumor Shrinkage in SLD from Disease Progression by Investigator Assessment, ATZ+CE arm, ATZ treated on or After First PD



PD: Progression of Disease. SLD: Sum of Longest Diameters.
CE=Carboplatin + Etoposide, PBO=Placebo
Data Cutoff: 24APR2018

Figure 36: Maximum Percent Post-PD Tumour Shrinkage in SLD from Disease Progression by Investigator Assessment, PBO + CE, Placebo Treated on or After First PD

Table 35: Time to Event Summary for Overall Survival on or after First PD, atezo treated (intent to treat patients)

Time to Event Summary for Overall Survival on or after First PD, Intent-to-Treat Patients
Protocol: GO30081

	Atezo Treated on or after First PD (N=49)	Other Anti-cancer Therapy Excludes Atezo on or after First PD (N=69)	No Treatment on or after First PD (N=35)	All Patients (N=153)
Patients with event (%)	23 (46.9%)	38 (55.1%)	24 (68.6%)	85 (55.6%)
Earliest contributing event				
Death	23	38	24	85
Patients without event (%)	26 (53.1%)	31 (44.9%)	11 (31.4%)	68 (44.4%)
Time Since First PD to Event (Months)				
Median	9.6	7.7	1.9	6.7
95% CI	(6.6, 16.3)	(6.4, 10.0)	(1.7, 3.9)	(5.2, 8.5)
25% and 75%-ile	4.4, 16.3	4.2, 12.6	1.2, 5.0	3.4, 11.9
Range	1.0+ to 16.0+	0.1+ to 13.6	0.0+ to 9.9+	0.0+ to 16.0+

Table 36: Time to Event Summary for Overall Survival on or after First PD, Placebo Treated (safety evaluable population)

	Placebo Treated on or after First PD (N=47)	Other Anti-cancer Therapy excluding Placebo on or after First PD (N=88)	No Treatment on or after First PD (N=33)	All Patients (N=168)
Patients with event (%)	24 (51.1%)	63 (71.6%)	27 (81.8%)	114 (67.9%)
Earliest contributing event				
Death	24	63	27	114
Patients without event (%)	23 (48.9%)	25 (28.4%)	6 (18.2%)	54 (32.1%)
Time Since First PD to Event (Months)				
Median	6.5	6.0	2.0	5.2
95% CI	(4.8, 12.8)	(4.9, 7.4)	(1.1, 3.1)	(4.5, 6.2)
25% and 75%-ile	3.1, 12.8	3.6, 8.5	0.6, 3.3	2.9, 8.6
Range	0.1* to 12.8	0.7 to 17.0*	0.1* to 8.1*	0.1* to 17.0*

Atezo=Atezolizumab, CE=Carboplatin + Etoposide, PBO=Placebo
PD = Progression of Disease
* = Censored value; ^ = Censored and Event.
NE = Not estimable.
Summaries of duration (median and percentiles) are Kaplan-Meier estimates. 95% CIs for the median are computed using the method of Brookmeyer and Crowley.

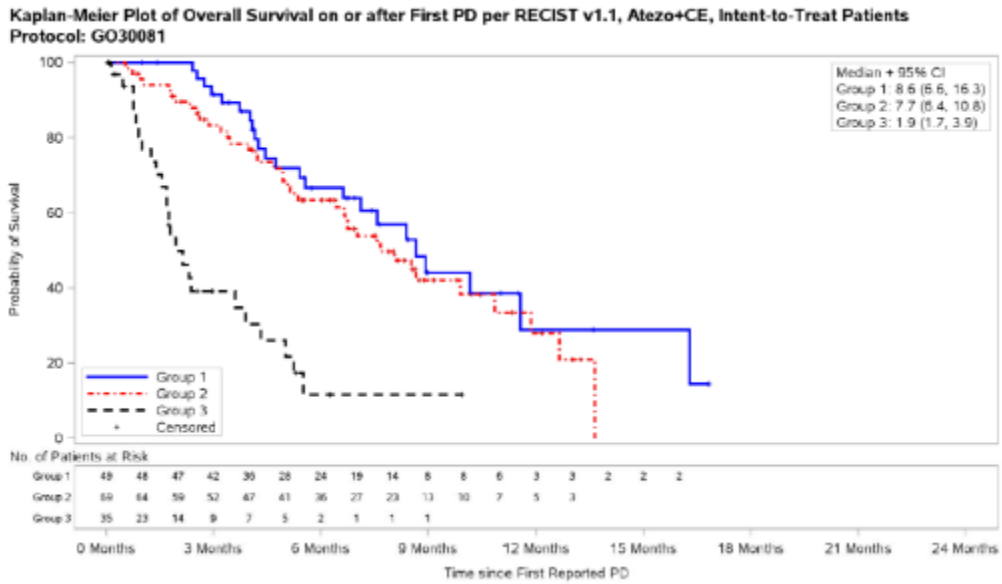


Figure 37: Kaplan-Meier Plot of Overall Survival on or after First PD (Intent to-Treat Population)

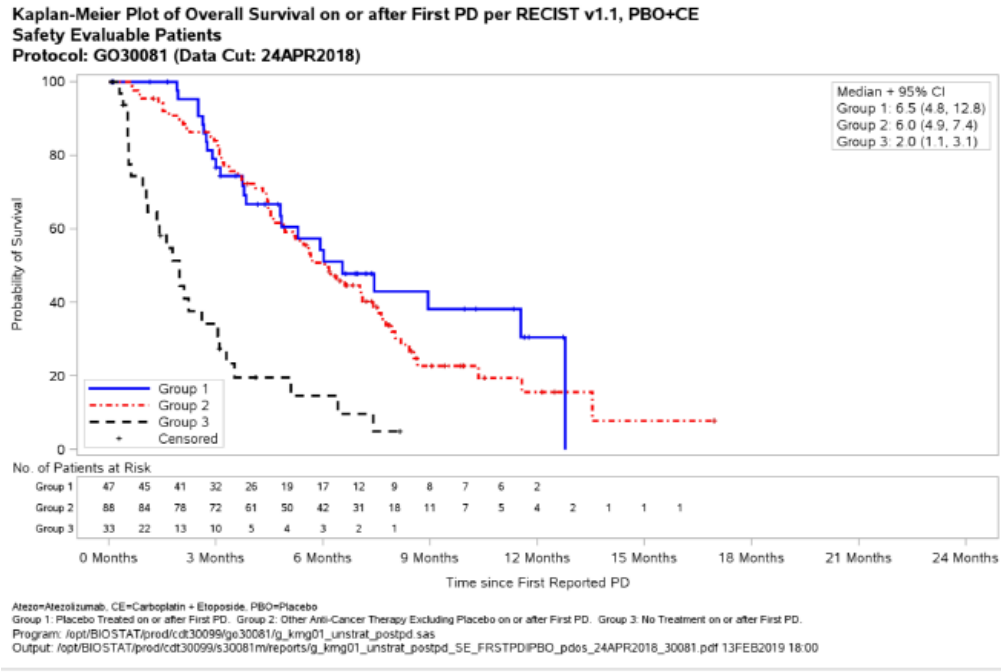


Figure 38: Kaplan-Meier Plot of Overall Survival on or after First PD (Intent to-Treat Population)

Summary of main study

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

Table 37: Summary of Efficacy for trial IMpower133

Title: A Phase I/III, randomised, double-blind, placebo-controlled study of carboplatin plus etoposide with or without atezolizumab (anti-PD-L1 antibody) in patients with untreated extensive-stage small cell lung cancer (IMpower133).			
Study identifier	GO30081		
Design	Phase I/III, randomised, double-blind, placebo-controlled, two-arm		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Not applicable, event-driven Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Arm A (ATZ+CE)		Atezolizumab+carboplatin+etoposide until loss of clinical benefit, n=201
	Arm B (PBO+CE)		Placebo+carboplatin+etoposide until loss of clinical benefit, n=202
Endpoints and definitions	Co-Primary endpoint	INV-PFS ITT	Investigator-assessed progression free survival according to RECIST v1.1 in intention-to-treat population
	Co-Primary endpoint	OS ITT	Overall survival in intention-to-treat population
	Secondary endpoint	ORR and DoR in ITT	Overall response rate and duration of response per RECIST v1.1 in intention-to-treat population
Database lock	24 April 2018 final PFS analysis, 24 January 2019 final OS analysis		
Results and Analysis			
Analysis description	**Primary Analysis of PFS, ORR and DOR; final analysis of OS**		
Analysis population and time point description	Intent-to-treat=403, when 360 INV-PFS (89%, final PFS analysis) and 302 OS events (75%, final OS analysis) have occurred		
Descriptive statistics and estimate variability	Treatment group	Arm A (ATZ+CE)	Arm B (PBO+CE)
	Number of subjects	201	202
	Median OS, months	12.3	10.3
	95% CI	10.8, 15.8	9.3, 11.3
	Median PFS, months	5.2	4.3

	95% CI	4.4, 5.6	4.2, 4.5
	Unconfirmed INV-ORR, number of responders (%)	149 (74.1)	155 (76.7%)
	95% CI	67.5, 80.0	70.3, 82.4
	Median unconfirmed INV-DOR, months	4.1	3.1
	95% CI	3.5, 4.2	2.9, 3.9
Effect estimate per comparison	OS ITT	Comparison groups	ATZ+CE vs. PBO+CE
		Stratified Hazard Ratio	0.76
		95% CI	0.60, 0.95
		p-value (log-rank)	0.0154
	INV- PFS ITT	Comparison groups	ATZ+CE vs. PBO+CE
		Stratified Hazard Ratio	0.77
		95% CI	0.62, 0.96
		p-value (log-rank)	0.0170
	Unconfirmed INV-ORR ITT confirmed response	Comparison groups	ATZ+CE vs. PBO+CE
		Odds Ratio	0.87
		95% CI	0.55, 1.37
		p-value (Cochran-Mantel-Haenszel)	0.5412
	Unconfirmed INV-DOR ITT	Comparison groups	ATZ+CE vs. PBO+CE
		Stratified Hazar Ratio	0.73
		95% CI	0.57, 0.94
		p-value (log-rank)	0.0125
Notes	Both co-primary endpoints have been met		

Clinical studies in special populations

Table 38 Number of elderly patients investigated in IMpower133

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	145/403	39/403	2/403

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH has provided data from the final PFS analysis and interim OS analysis (24-APR-2018) and the final OS analysis (24-JAN-2019) of IMpower133, a pivotal phase I/III, randomised, double-blind, placebo (PBO) controlled study of carboplatin plus etoposide (CE) with or without atezolizumab (ATZ) in patients with untreated extensive-stage small cell lung cancer (ES-SCLC). Co-primary objectives were PFS and OS assessed in the ITT population, hypothesis was superiority of ATZ+CE over PBO+CE.

For sample size calculation, a considerable PFS benefit was assumed (HR of 0.68 and 0.55 for OS and PFS, respectively), planning to recruit 400 all-comer patients. Eligible subjects were stratified by sex (male vs. female), ECOG PS (0 vs. 1), and presence of brain metastases (yes vs. no) and then randomised 1:1 to receive 4 cycles of either ATZ+CE or PBO+CE. After induction, patients continued maintenance therapy with ATZ or PBO, respectively. Treatment continued until disease progression per RECIST v1.1, but patients could be considered for treatment beyond radiographic disease progression if they had evidence of clinical benefit. During the maintenance phase, prophylactic cranial irradiation and palliative thoracic radiation was permitted per local standard-of-care. Dose and scheduling of all drugs was based in previously approved indications.

The main challenges in relation to the design of the study include maintenance (treatment effect cannot be differentiated from induction); treatment beyond progressive disease (considering patients on the PBO+CE arm would continue on PBO+/-CE); not allowing consolidation thoracic radiotherapy; and not considering the choice between cisplatin and carboplatin for the backbone chemotherapy regimen.

INV-assessed PFS is an acceptable co-primary endpoint because the study is double-blinded and OS was the other co-primary objective. The definitions of primary and secondary objectives were also endorsed.

Out of 526 screened patients, 403 were randomised into both arms of the trial. The distribution of major protocol deviations between arms is balanced. The proportion of patients with brain metastases (8%) is about half of that in clinical practice (15%), but this was explained as due to the specific inclusion requirements for these patients. The proportion of patients in each of the analysis subpopulations is acceptable and balanced between arms.

Overall, the main issue upon the design and conduct of this study is failing to enforce the established tissue requirement, leading to retrospective biomarker availability for less than half of the ITT population.

Efficacy data and additional analyses

At first data cutoff on 24 April 2018, 238 death events (59%) and 360 PFS events (89%) had occurred, satisfying the predefined data-driven criteria for performing the interim analysis of OS and the final analysis of PFS. Median duration of survival follow-up was 13.9 months in the ITT population.

Both co-primary endpoints of the study had been met. OS data showed significant statistical benefit from ATZ+CE (mOS 12.3 months) over PBO+CE (mOS 10.3 months), as indicated by a stratified HR of 0.701 (95% CI 0.54-0.91, p=0.0069). OS results from PBO+CE are comparable to data from most published studies of platinum + etoposide. The MAH has provided results from the exploratory final OS analysis after a median follow-up of 22.9 months (data cutoff 24 January 2019, 302 out of 403 OS events = 75%). The data seem overall consistent with the first interim analysis. Median OS in both arms is unchanged (12.3 months in the ATZ+CE arm and 10.3 months in the PBO+CE arm), although the statistical parameters differ slightly: HR 0.76 (95%CI 0.60, 0.95), p-value=0.0154.

PFS was statistically significant (only) after alpha was recycled from the significant OS analysis ("recycling" was introduced with protocol amendment 3). However, the difference in PFS between ATZ+CE (mPFS 5.2 months) and PBO+CE (mPFS 4.3 months) is not striking and hence of only marginal clinical relevance, observing a stratified HR of 0.772 (95% CI 0.62-0.96, p=0.0170).

The benefit of adding atezolizumab was not substantially supported by secondary endpoints. Both confirmed and unconfirmed ORR were numerically higher in the PBO+CE arm. DoR was similar in both arms. PRO data "time to deterioration of lung cancer-related symptoms" did not demonstrate clinically meaningful consistent differences. Forest plots on PFS and OS (including bTMB biomarker) did not identify any particular –appropriately sized– subgroup with considerably higher or lower benefit from ATZ+CE over PBO+CE. The limited number of patients with CNS metastases in the trial limits conclusions regarding efficacy of adding ATZ to CE in this subgroup, so a clarification has been inserted in the SmPC. The practiced sensitivity analyses do not alter the modest statistical benefit indicated from the primary endpoints.

IHC as a biomarker to select patients who benefit from immunotherapy across cancers is well established. PD-L1 IHC (Ventana SP263) results are available for 168 patients (42% from ITT), 93 in the PBO+CE arm and 75 in the ATZ+CE arm. PD-L1 positivity, defined as staining of ≥1% of tumour cells, was 55% in the PBO+CE arm and 56% in the ATZ+CE arm. In PD-L1 positive patients (n=93), median OS is 10.6 in ATZ+CE and 11.1 in PBO+CE. In PD-L1 negative patients (n=75), median OS is 10.5 in ATZ+CE and 8.8 in PBO+CE. The addition of atezolizumab to CE demonstrated a greater OS benefit in the PD-L1 negative

subgroups compared to the PD-L1 positive subgroups when regarding the lower PD-L1 cutoff of 1%, which lacks any biological rationale. Overall, the provided retrospective OS results are considered inconclusive (see Benefit-Risk section).

95% of the 198 patients who received ATZ were evaluable for anti-drug antibodies (ADAs). Updated analyses of OS by treatment-emergent ADA status based on the 24 January 2019 cutoff analyses reported an even larger difference for the median OS values between both ADA subgroups (mOS 14.1 months in ADA- subgroup and 10.9 months in the ADA+ subgroup), but the data are limited due to the small sample size of the ADA+ (n=35) subgroup.

Concerning treatment beyond progression, the benefit of maintaining ATZ is not established: 3 out of 49 patients who continued atezolizumab beyond progression exhibited a partial response.

2.4.4. Conclusions on the clinical efficacy

IMpower133 has met both its co-primary endpoints (superior OS and INV-assessed PFS from ATZ+CE vs. PBO+CE in ITT), but whether this translates into a compelling clinical benefit to all patients regardless of PD-L1 IHC status is unknown. Overall, in patients with ES-SCLC, a net gain of roughly 1 month in median PFS and 2 months in median OS must be weighed against the known safety risks from combining immunotherapy with chemotherapy.

2.5. Clinical safety

Introduction

As of 17 May 2018, an estimated 16,815 patients have been exposed to atezolizumab either as a single agent or in combination with chemotherapy, immunotherapy, or targeted therapy in ongoing clinical studies.

The safety of atezolizumab monotherapy is based on pooled data in 3,178 patients with multiple tumour types. The most common adverse reactions were fatigue (35.9%), decreased appetite (25.5%), nausea (23.5%), cough (20.8%), dyspnoea (20.5%), pyrexia (20.1%), diarrhoea (19.7%), rash (19.5%), back pain (15.3%), vomiting (15.0%), asthenia (14.5%), arthralgia (13.9%), musculoskeletal pain (13.0%), pruritus (12.6%) and urinary tract infection (11.6%).

Safety data for the use of ATZ+CE in patients with chemotherapy-naïve ES-SCLC in the IMpower133 study are presented versus the standard of care control arm (PBO+CE). Safety analyses included all treated patients (defined as all randomized patients who received any amount of any component of study treatment) according to actual treatment received: 198 patients treated with ATZ+CE and 196 patients treated with PBO+CE. Patients who received any amount of atezolizumab were analyzed as part of the ATZ+CE arm even if atezolizumab was given in error.

In addition, safety data from atezolizumab-treated safety evaluable patients (all patients who received any amount of atezolizumab) were pooled and are presented as follows:

- Atezolizumab in combination with platinum-based doublet chemotherapy as 1L treatment in lung cancer, hereinafter referred to as Atezo + Chemo Combo population. The safety analyses for this population are based on safety data from a total of 2421 atezolizumab-treated, safety evaluable patients from IMpower133 (n=198 with SCLC), IMpower130 (n=473 with NSCLC), IMpower131 (n=666 with NSCLC), IMpower132 (n=291 with NSCLC), and IMpower150 (n=793 with NSCLC).
- Single-agent atezolizumab regardless of tumor type, hereinafter referred to as Atezo Mono population. The safety analyses for this population are based on safety data from a total of 3178 atezolizumab-treated, safety evaluable patients from OAK (n=609 with NSCLC), POPLAR (n=142

with NSCLC), BIRCH (n=659 with NSCLC), FIR (n=137 with NSCLC), IMvigor211 (n=459 with UC), IMvigor210 (n=429 with UC), IMmotion150 (n=103 with RCC), and PCD4989g (n=89 with NSCLC, n=95 with UC, n=17 with SCLC, n=439 with other tumor types).

The severity of all adverse events (AEs) was graded according to the National Cancer Institute Common Terminology Criteria for AEs, Version 4.0 (NCI-CTCAE v4.0) and reported in detail in the electronic Case Report Form (eCRF). Multiple occurrences of the same event in the same patient are counted once at the maximum severity (worst grade) in summary tables.

Verbatim descriptions of AEs were mapped to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms. MedDRA Version 21.0 was used for the individual study of IMpower133, the pooled analysis of Atezo + Chemo Combo studies, and the pooled analysis of Atezo Mono studies.

Patient exposure

Table 39: Exposure to atezolizumab in patients receiving 1200 mg Q3W (safety evaluable population)

	IMpower133		
	Atezo+CE (N=198)	Atezo+Chemo Combo (N=2421)	Atezo Mono (N=2748)
Number of doses			
n	198	2421	2748
Mean (SD)	8.5 (5.9)	12.3 (9.6)	9.4 (9.0)
Median	7.0	10.0	6.0
Min - Max	1 - 30	1 - 48	1 - 49
Treatment duration (M)			
n	198	2421	2748
Mean (SD)	5.7 (4.4)	8.4 (6.9)	6.1 (6.4)
Median	4.7	6.5	3.5
Min - Max	0 - 21	0 - 33	0 - 33
Treatment duration (M)			
n	198	2421	2748
<=3	47 (23.7%)	587 (24.2%)	1305 (47.5%)
>3-6	87 (43.9%)	543 (22.4%)	479 (17.4%)
>6-12	41 (20.7%)	578 (23.9%)	411 (15.0%)
>12-18	20 (10.1%)	456 (18.8%)	335 (12.2%)
>18-24	3 (1.5%)	176 (7.3%)	194 (7.1%)
>24	0	81 (3.3%)	24 (0.9%)

Table 40: Exposure to placebo (safety evaluable population)

	IMpower133 PBO + CE
	N = 196
Treatment duration (M)	
n	196
Mean (SD)	5.0 (3.5)
Median	4.1
Min – Max	0 - 21
Treatment duration (M)	
n	196
0 to ≤3 months	41 (20.9%)
> 3 months to ≤ 6 months	113 (57.7%)
> 6 months to ≤ 12 months	30 (15.3%)
> 12 months	12 (6.1%)
Dose intensity (%)	
n	196
Mean (SD)	92.9 (7.2)
Median	94.7
Min – Max	60 - 102
Number of doses received	
n	196
Mean (SD)	7.7 (4.8)
Median	6.0
Min – Max	1 - 30
Total cumulative dose (mg)	
n	196
Mean (SD)	0.0 (0.0)
Median	0.0
Min - Max	0 - 0

Table 41: Exposure to Carboplatin and etoposide treatment (safety evaluable population)

Treatment:	CARBOPLATIN		ETOPOSIDE	
	PBO + CE (Actual) (N=196)	Atezo + CE (Actual) (N=198)	PBO + CE (Actual) (N=196)	Atezo + CE (Actual) (N=198)
Treatment duration (months)				
n	196	198	196	198
Mean (SD)	2.2 (0.6)	2.1 (0.7)	2.2 (0.6)	2.2 (0.7)
Median	2.2	2.3	2.2	2.3
Min - Max	0 - 4	0 - 4	0 - 4	0 - 4
Treatment duration				
n	196	198	196	198
0 to <= 3 months	191 (97.4%)	193 (97.5%)	191 (97.4%)	191 (96.5%)
>3 months to <= 6 months	5 (2.6%)	5 (2.5%)	5 (2.6%)	7 (3.5%)
Dose Intensity (%)				
n	196	198	196	198
Mean (SD)	92.0 (8.0)	91.0 (7.9)	89.6 (8.0)	88.1 (8.6)
Median	93.3	92.3	90.3	89.4
Min - Max	60 - 102	48 - 101	59 - 99	32 - 99
Number of doses received				
n	196	198	196	198
Mean (SD)	3.8 (0.6)	3.7 (0.8)	11.4 (2.0)	11.1 (2.5)
Median	4.0	4.0	12.0	12.0
Min - Max	1 - 5	1 - 6	2 - 15	1 - 18
Total cumulative dose (mg)				
n	196	198	196	198
Mean (SD)	2145.7 (645.0)	2019.2 (642.2)	2034.5 (477.2)	1965.8 (539.8)
Median	2175.0	2062.5	2131.7	2055.2
Min - Max	341 - 3691	360 - 3670	294 - 3240	8 - 3492

Adverse events

AE summary across IMpower133, Atezo+Chemo and Atezo Mono populations:

Table 42: Safety summary (safety evaluable population)

	PBO + CE (Actual) (N=196)	Atezo + CE (Actual) (N=198)	All Patients (N=394)
Total number of patients with at least one adverse event	189 (96.4%)	198 (100.0%)	387 (98.2%)
Total number of events	1861	2166	4027
Total number of patients with at least one			
Treatment-related AE	181 (92.3%)	188 (94.9%)	369 (93.7%)
Any Treatment	181 (92.3%)	188 (94.9%)	369 (93.7%)
Atezolizumab/Placebo	98 (50.0%)	128 (64.6%)	226 (57.4%)
Grade 3-4 AE	125 (63.8%)	133 (67.2%)	258 (65.5%)
Treatment-related Grade 3-4 AE	110 (56.1%)	112 (56.6%)	222 (56.3%)
Grade 5 AE	11 (5.6%)	4 (2.0%)	15 (3.8%)
Treatment-related Grade 5 AE	3 (1.5%)	3 (1.5%)	6 (1.5%)
Serious AE	68 (34.7%)	74 (37.4%)	142 (36.0%)
AE leading to withdrawal from treatment	6 (3.1%)	22 (11.1%)	28 (7.1%)
Any Treatment	6 (3.1%)	22 (11.1%)	28 (7.1%)
Atezolizumab/Placebo	5 (2.6%)	21 (10.6%)	26 (6.6%)
Carboplatin	1 (0.5%)	5 (2.5%)	6 (1.5%)
Etoposide	2 (1.0%)	8 (4.0%)	10 (2.5%)
AE leading to any dose modification/interruption	119 (60.7%)	138 (69.7%)	257 (65.2%)
Any Treatment	119 (60.7%)	138 (69.7%)	257 (65.2%)
Atezolizumab/Placebo	102 (52.0%)	117 (59.1%)	219 (55.6%)
Carboplatin	96 (49.0%)	111 (56.1%)	207 (52.5%)
Etoposide	95 (48.5%)	113 (57.1%)	208 (52.8%)

Investigator text for AEs encoded using MedDRA version 21.0.
Includes adverse events occurring on or after the start date of treatment.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" row, multiple occurrences of the same AE in an individual are counted separately. For "Grade 3-4 AE" and "Treatment-related Grade 3-4 AE", multiple occurrences of the same AE within Grade 3-4 is counted at the highest grade for an individual.
Atezo=Atezolizumab, CE=Carboplatin + Etoposide, PBO=Placebo
Data Cutoff: 24APR2018

Common AEs reported in ≥10% patients:

Table 43: Adverse Events by Preferred Term with Incidence Rate of at Least 10% in either Arm/Population (Safety Evaluable Population)

	IMpower133			
MedDRA Preferred Term	PBO+CE (N=196)	Atezo+CE (N=198)	Atezo+Chemo Combo (N=2421)	Atezo Mono (N=3178)
Total number of patients with at least one adverse event	189 (96.4%)	198 (100%)	2388 (98.6%)	3051 (96.0%)
Total number of events	1861	2166	35088	33365
ANAEMIA	69 (35.2%)	86 (43.4%)	1063 (43.9%)	505 (15.9%)
NAUSEA	64 (32.7%)	75 (37.9%)	914 (37.8%)	747 (23.5%)
NEUTROPENIA	69 (35.2%)	74 (37.4%)	642 (26.5%)	36 (1.1%)
ALOPECIA	68 (34.7%)	73 (36.9%)	843 (34.8%)	37 (1.2%)
DECREASED APPETITE	36 (18.4%)	54 (27.3%)	655 (27.1%)	810 (25.5%)
FATIGUE	49 (25.0%)	54 (27.3%)	778 (32.1%)	1142 (35.9%)
CONSTIPATION	58 (29.6%)	51 (25.8%)	698 (28.8%)	652 (20.5%)
VOMITING	33 (16.8%)	39 (19.7%)	477 (19.7%)	480 (15.1%)
NEUTROPHIL COUNT DECREASED	46 (23.5%)	37 (18.7%)	336 (13.9%)	5 (0.2%)
DIARRHOEA	31 (15.8%)	35 (17.7%)	685 (28.3%)	624 (19.6%)
THROMBOCYTOPENIA	31 (15.8%)	33 (16.7%)	451 (18.6%)	82 (2.6%)
ASTHENIA	20 (10.2%)	25 (12.6%)	478 (19.7%)	461 (14.5%)
LEUKOPENIA	19 (9.7%)	25 (12.6%)	171 (7.1%)	9 (0.3%)
PLATELET COUNT DECREASED	29 (14.8%)	25 (12.6%)	366 (15.1%)	37 (1.2%)
HEADACHE	23 (11.7%)	24 (12.1%)	297 (12.3%)	352 (11.1%)
DYSPNOEA	18 (9.2%)	20 (10.1%)	464 (19.2%)	653 (20.5%)
HYPOTHYROIDISM	1 (0.5%)	20 (10.1%)	218 (9.0%)	137 (4.3%)
PYREXIA	16 (8.2%)	20 (10.1%)	385 (15.9%)	638 (20.1%)
WEIGHT DECREASED	10 (5.1%)	20 (10.1%)	222 (9.2%)	277 (8.7%)
ARTHRALGIA	13 (6.6%)	18 (9.1%)	406 (16.8%)	442 (13.9%)
COUGH	25 (12.8%)	18 (9.1%)	444 (18.3%)	660 (20.8%)
WHITE BLOOD CELL COUNT DECREASED	25 (12.8%)	18 (9.1%)	178 (7.4%)	25 (0.8%)
BACK PAIN	19 (9.7%)	17 (8.6%)	283 (11.7%)	487 (15.3%)
INSOMNIA	13 (6.6%)	15 (7.6%)	250 (10.3%)	281 (8.8%)
RASH	12 (6.1%)	14 (7.1%)	335 (13.8%)	358 (11.3%)
OEDEMA PERIPHERAL	7 (3.6%)	13 (6.6%)	216 (8.9%)	332 (10.4%)
URINARY TRACT INFECTION	6 (3.1%)	13 (6.6%)	201 (8.3%)	338 (10.6%)
HYPOMAGNESAEMIA	9 (4.6%)	12 (6.1%)	301 (12.4%)	131 (4.1%)
PRURITUS	9 (4.6%)	12 (6.1%)	233 (9.6%)	401 (12.6%)
MYALGIA	8 (4.1%)	8 (4.0%)	254 (10.5%)	194 (6.1%)
NEUROPATHY PERIPHERAL	5 (2.6%)	8 (4.0%)	368 (15.2%)	101 (3.2%)
PERIPHERAL SENSORY NEUROPATHY	2 (1.0%)	8 (4.0%)	302 (12.5%)	43 (1.4%)

Grade 5 AEs due to PD are excluded for studies GO27831 and GO28625.
Investigator text for AEs encoded using MedDRA v21.0. 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. All treatment emergent AEs are included. Sort order is by decreasing frequency in Atezo+CE treatment arm.
Atezo=Atezolizumab, PBO=Placebo, CE=Carboplatin+Etoposide. Atezo+Chemo Combo: GO29537 (IMPOWER130) Arm A + GO29437 (IMPOWER131) Arm A+B + GO29436 (IMPOWER150) Arm A+B + GO29438 (IMPOWER132) Arm A + GO30081 (IMPOWER133) Arm A. Atezo Mono: GO28915 (OAK) + GO28753 (POPLAR) + GO28754 (BIRCH) + GO28625 (FIR) + GO27831 (PCD4989g - All Cohorts) + GO29293 (IMVIGOR210) + GO29294 (IMVIGOR211) + WO29074 (IMMOTION150 Arm B). Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO29293:04JUL2016, GO28915:07JUL2016, GO29294:13MAR2017, GO29436:22JAN2018, GO29437:20APR2018, GO29438:22MAY2018, GO29537:15MAR2018, GO30081:24APR2018, WO29074:17OCT2016.

Table 39: Adverse Events with a Difference of at Least 5% between the PBO + CE and Atezo + CE arms (Safety Population)

MedDRA Preferred Term	PBO + CE (Actual) (N=196)	Atezo + CE (Actual) (N=198)	All Patients (N=394)
Total number of patients with at least one adverse event	189 (96.4%)	198 (100.0%)	387 (98.2%)
Total number of events	1861	2166	4027
ANAEMIA	69 (35.2%)	86 (43.4%)	155 (39.3%)
NAUSEA	64 (32.7%)	75 (37.9%)	139 (35.3%)
DECREASED APPETITE	36 (18.4%)	54 (27.3%)	90 (22.8%)
HYPOKALAEMIA	18 (9.2%)	8 (4.0%)	26 (6.6%)
HYPOTHYROIDISM	1 (0.5%)	20 (10.1%)	21 (5.3%)

Investigator text for AEs encoded using MedDRA version 21.0.
Includes adverse events occurring on or after the start date of treatment.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
Atezo=Atezolizumab, CE=Carboplatin + Etoposide, PBO=Placebo
Data Cutoff: 24APR2018

Table 45 Adverse Events by Preferred Term, Difference of at Least 5% between IMpower133 Arm A and atezo+Chemo Combo Patients (Safety Evaluable Population)

MedDRA Preferred Term	IMpower133 Atezo+CE (N=198)	IMpower133 Atezo+Chemo Combo (N=2421)
Total number of patients with at least one adverse event	198 (100%)	2388 (98.6%)
Total number of events	2166	35088
NEUTROPENIA	74 (37.4%)	642 (26.5%)
DIARRHOEA	35 (17.7%)	685 (28.3%)
ASTHENIA	25 (12.6%)	478 (19.7%)
LEUKOPENIA	25 (12.6%)	171 (7.1%)
DYSPNOEA	20 (10.1%)	464 (19.2%)
PYREXIA	20 (10.1%)	385 (15.9%)
ARTHRALGIA	18 (9.1%)	406 (16.8%)
COUGH	18 (9.1%)	444 (18.3%)
RASH	14 (7.1%)	335 (13.8%)
HYPOMAGNESAEMIA	12 (6.1%)	301 (12.4%)
MYALGIA	8 (4.0%)	254 (10.5%)
NEUROPATHY PERIPHERAL	8 (4.0%)	368 (15.2%)
PERIPHERAL SENSORY NEUROPATHY	8 (4.0%)	302 (12.5%)
ALANINE AMINOTRANSFERASE INCREASED	7 (3.5%)	207 (8.6%)
EPISTAXIS	3 (1.5%)	209 (8.6%)

Investigator text for AEs encoded using MedDRA v21.0. 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. All treatment emergent AEs are included. Sort order is by decreasing frequency in Atezo+CE treatment arm.
Atezo=Atezolizumab, CE=Carboplatin+Etoposide. Atezo+Chemo Combo: GO29537 (IMPOWER130) Arm A + GO29437 (IMPOWER131) Arm A+B + GO29436 (IMPOWER150) Arm A+B + GO29438 (IMPOWER132) Arm A + GO30081 (IMPOWER133) Arm A. Clinical cut-off dates: GO29436:22JAN2018, GO29437:20APR2018, GO29438:22MAY2018, GO29537:15MAR2018, GO30081:24APR2018.

Table 46: Treatment-Related Adverse Events Reported as Related to Any Treatment in ≥20% of Patients in Either Arm/Population (Safety Evaluable Population)

MedDRA Preferred Term	IMpower133 Atezo + CE (N = 198)	Atezo + Chemo Combo (N = 2421)
Total number of patients with at least one AE	188 (94.9%)	2279 (94.1%)
Anaemia	77 (38.9%)	946 (39.1%)
Neutropenia	72 (36.4%)	625 (25.8%)
Nausea	63 (31.8%)	794 (32.8%)
Alopecia	69 (34.8%)	821 (33.9%)
Fatigue	42 (21.2%)	628 (25.9%)
Decreased appetite	41 (20.7%)	495 (20.4%)
Diarrhoea	19 (9.6%)	484 (20.0%)

AE = adverse event, Atezo = Atezolizumab, CE = carboplatin + etoposide, MedDRA = Medical Dictionary for Regulatory Activities

G3-4 AEs:

Table 47: Grade 3-4 adverse events reported in ≥5% of patients in any treatment arm (safety evaluable population)

MedDRA Preferred Term	PBO + CE (Actual) (N=196)	Atezo + CE (Actual) (N=198)	All Patients (N=394)
NEUTROPENIA	49 (25.0%)	45 (22.7%)	94 (23.9%)
NEUTROPHIL COUNT DECREASED	33 (16.8%)	31 (15.7%)	64 (16.2%)
ANAEMIA	26 (13.3%)	31 (15.7%)	57 (14.5%)
THROMBOCYTOPENIA	17 (8.7%)	20 (10.1%)	37 (9.4%)
HYPONATRAEMIA	13 (6.6%)	9 (4.5%)	22 (5.6%)
FEBRILE NEUTROPENIA	12 (6.1%)	7 (3.5%)	19 (4.8%)
LEUKOPENIA	8 (4.1%)	10 (5.1%)	18 (4.6%)

Table 48: Grade 3-4 adverse events with incidence rate of at least 2% in either arm/population (safety evaluable population)

	IMpower133			
MedDRA System Organ Class MedDRA Preferred Term	PBO+CE (N=196)	Atezo+CE (N=198)	Atezo+Chemo Combo (N=2421)	Atezo Mono (N=3178)
Total number of patients with at least one adverse event	136 (69.4%)	136 (68.7%)	1702 (70.3%)	1564 (49.2%)
Overall total number of events	345	375	5073	3366
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
Total number of patients with at least one adverse event	80 (40.8%)	81 (40.9%)	880 (36.3%)	218 (6.9%)
Total number of events	150	152	1573	257
NEUTROPENIA	49 (25.0%)	45 (22.7%)	414 (17.1%)	11 (0.3%)
ANAEMIA	26 (13.3%)	31 (15.7%)	415 (17.1%)	160 (5.0%)
THROMBOCYTOPENIA	17 (8.7%)	20 (10.1%)	162 (6.7%)	21 (0.7%)
LEUKOPENIA	8 (4.1%)	10 (5.1%)	70 (2.9%)	0
FEBRILE NEUTROPENIA	12 (6.1%)	7 (3.5%)	137 (5.7%)	8 (0.3%)
INVESTIGATIONS				
Total number of patients with at least one adverse event	40 (20.4%)	38 (19.2%)	445 (18.4%)	189 (5.9%)
Total number of events	83	85	891	274
NEUTROPHIL COUNT DECREASED	33 (16.8%)	31 (15.7%)	229 (9.5%)	2 (<0.1%)
PLATELET COUNT DECREASED	8 (4.1%)	7 (3.5%)	110 (4.5%)	6 (0.2%)
WHITE BLOOD CELL COUNT DECREASED	9 (4.6%)	7 (3.5%)	90 (3.7%)	5 (0.2%)
GASTROINTESTINAL DISORDERS				
Total number of patients with at least one adverse event	11 (5.6%)	18 (9.1%)	257 (10.6%)	242 (7.6%)
Total number of events	17	22	342	319
DIARRHOEA	2 (1.0%)	4 (2.0%)	85 (3.5%)	36 (1.1%)
VOMITING	5 (2.6%)	3 (1.5%)	43 (1.8%)	26 (0.8%)
NAUSEA	1 (0.5%)	1 (0.5%)	53 (2.2%)	35 (1.1%)
METABOLISM AND NUTRITION DISORDERS				
Total number of patients with at least one adverse event	19 (9.7%)	18 (9.1%)	273 (11.3%)	308 (9.7%)
Total number of events	28	25	367	387
HYPONATRAEMIA	13 (6.6%)	9 (4.5%)	60 (2.5%)	98 (3.1%)
HYPERGLYCAEMIA	1 (0.5%)	4 (2.0%)	39 (1.6%)	32 (1.0%)
DECREASED APPETITE	0	2 (1.0%)	49 (2.0%)	35 (1.1%)
HYPOKALAEMIA	3 (1.5%)	0	51 (2.1%)	32 (1.0%)
INFECTIONS AND INFESTATIONS				
Total number of patients with at least one adverse event	15 (7.7%)	15 (7.6%)	355 (14.7%)	347 (10.9%)
Total number of events	16	19	437	419
PNEUMONIA	5 (2.6%)	6 (3.0%)	132 (5.5%)	89 (2.8%)
URINARY TRACT INFECTION	2 (1.0%)	2 (1.0%)	24 (1.0%)	72 (2.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Total number of patients with at least one adverse event	8 (4.1%)	12 (6.1%)	272 (11.2%)	265 (8.3%)
Total number of events	8	13	308	315
ASTHENIA	4 (2.0%)	5 (2.5%)	78 (3.2%)	63 (2.0%)
FATIGUE	1 (0.5%)	5 (2.5%)	105 (4.3%)	109 (3.4%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Total number of patients with at least one adverse event	16 (8.2%)	12 (6.1%)	242 (10.0%)	323 (10.2%)
Total number of events	20	13	303	415
DYSPNOEA	2 (1.0%)	3 (1.5%)	59 (2.4%)	117 (3.7%)
PULMONARY EMBOLISM	3 (1.5%)	2 (1.0%)	50 (2.1%)	59 (1.9%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
Total number of patients with at least one adverse event	4 (2.0%)	7 (3.5%)	51 (2.1%)	49 (1.5%)
Total number of events	4	8	56	52
INFUSION RELATED REACTION	1 (0.5%)	4 (2.0%)	12 (0.5%)	7 (0.2%)
VASCULAR DISORDERS				
Total number of patients with at least one adverse event	4 (2.0%)	5 (2.5%)	114 (4.7%)	103 (3.2%)
Total number of events	5	5	130	107
HYPERTENSION	3 (1.5%)	3 (1.5%)	61 (2.5%)	42 (1.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Total number of patients with at least one adverse event	8 (4.1%)	12 (6.1%)	272 (11.2%)	265 (8.3%)
Total number of events	8	13	308	315
ASTHENIA	4 (2.0%)	5 (2.5%)	78 (3.2%)	63 (2.0%)
FATIGUE	1 (0.5%)	5 (2.5%)	105 (4.3%)	109 (3.4%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Total number of patients with at least one adverse event	16 (8.2%)	12 (6.1%)	242 (10.0%)	323 (10.2%)
Total number of events	20	13	303	415
DYSPNOEA	2 (1.0%)	3 (1.5%)	59 (2.4%)	117 (3.7%)
PULMONARY EMBOLISM	3 (1.5%)	2 (1.0%)	50 (2.1%)	59 (1.9%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
Total number of patients with at least one adverse event	4 (2.0%)	7 (3.5%)	51 (2.1%)	49 (1.5%)
Total number of events	4	8	56	52
INFUSION RELATED REACTION	1 (0.5%)	4 (2.0%)	12 (0.5%)	7 (0.2%)
VASCULAR DISORDERS				
Total number of patients with at least one adverse event	4 (2.0%)	5 (2.5%)	114 (4.7%)	103 (3.2%)
Total number of events	5	5	130	107
HYPERTENSION	3 (1.5%)	3 (1.5%)	61 (2.5%)	42 (1.3%)

Investigator text for AEs encoded using MedDRA v21.0. Percentages are based on N in the column headings. Patients with one AE of highest grade 5 and other AEs of highest grade 3-4 are included in the overall and SOC total number rows counting for grade 3-4 in this table. 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. All treatment emergent AEs are included. Sort order is by decreasing frequency in Atezo+CE treatment arm.
Atezo=Atezolizumab, PBO=Placebo, CE=Carboplatin+Etoposide. Atezo+Chemo Combo: GO29537 (IMPOWER130) Arm A + GO29437 (IMPOWER131) Arm A+B + GO29436 (IMPOWER150) Arm A+B + GO29438 (IMPOWER132) Arm A + GO30081 (IMPOWER133) Arm A. Atezo Mono: GO28915 (OAK) + GO28753 (POPLAR) + GO28754 (BIRCH) + GO28625 (FIR) + GO27831 (PCD4989g - All Cohorts) + GO29293 (IMVIGOR210) + GO29294 (IMVIGOR211) + WO29074 (IMMOTION150 Arm B). Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO29293:04JUL2016, GO28915:07JUL2016, GO29294:13MAR2017, GO29436:22JAN2018, GO29437:20APR2018, GO29438:22MAY2018, GO29537:15MAR2018, GO30081:24APR2018, WO29074:17OCT2016.

Adverse drug reactions

The MAH has submitted a table with the pooled adverse drug reactions from atezolizumab in monotherapy (n=3178) and in combination therapy (n=2759).

Table 49: Data from combination therapy comes from the following studies:

Study	Description
GO29436 (IMpower150)	Atezolizumab in Combination With Carboplatin + Paclitaxel With or Without Bevacizumab Compared With Carboplatin + Paclitaxel + Bevacizumab in Participants With Stage IV Non-Squamous Non-Small Cell Lung Cancer (NSCLC)
GO29438 (IMpower132)	Atezolizumab in Combination With Carboplatin or Cisplatin + Pemetrexed Compared With Carboplatin or Cisplatin + Pemetrexed in Participants Who Are Chemotherapy-Naive and Have Stage IV Non-Squamous Non-Small Cell Lung Cancer (NSCLC)
GO29537 (IMpower130)	Atezolizumab in Combination With Carboplatin + Nab-Paclitaxel Compared With Carboplatin + Nab-Paclitaxel in Participants With Stage IV Non-Squamous Non-Small Cell Lung Cancer (NSCLC)
GO30081 (IMpower133)	Carboplatin + Etoposide With or Without Atezolizumab in Participants With Untreated Extensive-Stage (ES) Small Cell Lung Cancer (SCLC)
WO29074 (IMmotion150)	Atezolizumab as monotherapy or in combination with Bevacizumab compared to Sunitinib (Sutent®) in Participants With Untreated Advanced Renal Cell Carcinoma
WO29637 (IMmotion151)	Atezolizumab in Combination With Bevacizumab Versus Sunitinib in Participants With Untreated Advanced Renal Cell Carcinoma (RCC)
WO29522(IMpassion130)	Atezolizumab in Combination With Nab-Paclitaxel Compared With Placebo With Nab-Paclitaxel for Participants With Previously Untreated Metastatic Triple-Negative Breast Cancer

The table below reflects the ADRs from the pooled safety data for atezolizumab including study IMpower133.

Table 50: Frequency of ADRs reported with atezolizumab based on a pooled safety data set

Atezolizumab monotherapy (n=3178)		**System Organ Class ADR**	Atezolizumab in combination therapy* (n=2759)	
Frequency (All Grades)	Incidence % (All Grades)		Frequency (All Grades)	Incidence % (All Grades)
Infections and infestations				
very common	368 (11.6%)	Urinary tract infection [a]	-	-
-	-	Lung infection[b]	very common	377 (13.7%)
Blood and Lymphatic System Disorders				
-	-	Anaemia	very common	916 (33.2%)
-	-	Neutropenia [d]	very common	930 (33.7%)
common	116 (3.7%)	Thrombocytopenia [c]	very common	586 (21.2%)
-	-	Leukopenia[e]	very common	322 (11.7%)
-	-	Lymphocyte count decreased	common	55 (2.0%)
Immune System Disorders				
common	51 (1.6%)	Infusion related reaction [f]	-	-
Endocrine Disorders				
uncommon	11 (0.3%)	Adrenal insufficiency[j]	-	-

uncommon	10 (0.3%)	Diabetes mellitus[i]	-	-
uncommon	30 (0.9%)	Hyperthyroidism[h]	-	-
rare	2 (<0.1%)	Hypophysitis[k]	-	-
common	164 (5.2%)	Hypothyroidism[g]	very common	420 (15.2%)
Metabolism and nutrition disorders				
very common	810 (25.5%)	Decreased appetite	very common	678 (24.6%)
common	138 (4.3%)	Hypokalemia	common	202 (7.3%)
-	-	Hypomagnesaemia	common	259 (9.4%)
common	169 (5.3%)	Hyponatremia	common	145 (5.3%)
common	103 (3.2%)	Hyperglycaemia	-	-
Nervous System Disorders				
-	-	Dizziness	very common	292 (10.6%)
-	-	Syncope	common	46 (1.7%)
uncommon	5 (0.2%)	Guillain-Barré syndrome [m]	-	-
uncommon	14 (0.4%)	Meningoencephalitis [n]	-	-
rare	1 (<0.1%)	Myasthenic syndrome [o]	-	-
-	-	Peripheral neuropathy[l]	very common	740 (26.8%)
-	-	Headache	very common	469 (17.0%)
Cardiac Disorders				
rare	2 (<0.1%)	Myocarditis[p]	-	-
Vascular Disorders				
common	102 (3.2%)	Hypotension	-	-
Respiratory, Thoracic, and Mediastinal Disorders				
very common	660 (20.8%)	Cough	very common	554 (20.1%)
very common	651 (20.5%)	Dyspnoea	very common	481 (17.4%)
common	73 (2.3%)	Hypoxia	-	-
common	101 (3.2%)	Nasal congestion	-	-
common	87 (2.7%)	Pneumonitis[q]	-	-
common	141 (4.4%)	Nasopharyngitis	-	-
-	-	Dysphonia	common	155 (5.6%)
Gastrointestinal Disorders				
common	268 (8.4%)	Abdominal pain	-	-
common	34 (1.1%)	Colitis[s]	-	-
-	-	Constipation	very common	745 (27.0%)
very common	626 (19.7%)	Diarrhoea[r]	very common	814 (29.5%)
common	82 (2.6%)	Dysphagia	-	-
very common	747 (23.5%)	Nausea	very common	1031 (37.4%)
uncommon	18 (0.6%)	Pancreatitis[u]	-	-
-	-	Stomatitis	common	259 (9.4%)
very common	477 (15.0%)	Vomiting	very common	527 (19.1%)
common	131 (4.1%)	Oropharyngeal pain[t]	-	-
-	-	Dysgeusia	common	199 (7.2%)
Hepatobiliary Disorders				
common	167 (5.3%)	ALT increased	common	219 (7.9%)
common	180 (5.7%)	AST increased	common	203 (7.4%)
common	62 (2.0%)	Hepatitis[v]	-	-
Skin and Subcutaneous Tissue Disorders				
very common	400 (12.6%)	Pruritus	very common	363 (13.2%)
very common	619 (19.5%)	Rash[w]	very common	785 (28.5%)
Musculoskeletal and Connective Tissue Disorders				
very common	441 (13.9%)	Arthralgia	very common	535 (19.4%)
very common	487 (15.3%)	Back pain	very common	373 (13.5%)
very common	414 (13.0%)	Musculoskeletal pain[x]	very common	510 (18.5%)
Uncommon	13 (0.4%)	Myositis[y]	-	-
Renal Disorders				
-	-	Proteinuria[z]	common	215 (7.8%)
rare	3 (<0.1%)	Nephritis[aa]	-	-
General Disorders and Administration				
very common	461 (14.5%)	Asthenia	very common	487 (17.7%)
common	207 (6.5%)	Chills	-	-
very common	1142 (35.9%)	Fatigue	very common	1003 (36.4%)
common	186 (5.9%)	Influenza like illness	-	-
very common	638 (20.1%)	Pyrexia	very common	473 (17.1%)

[a] Includes reports of urinary tract infection, cystitis, pyelonephritis, escherichia urinary tract infection, urinary tract infection bacterial, kidney infection, pyelonephritis acute, urinary tract infection fungal, urinary tract infection pseudomonal.

[b] Includes reports of pneumonia, bronchitis, lung infection, lower respiratory tract infection, infective exacerbation of COPD, infectious pleural effusion, tracheobronchitis, atypical pneumonia, lung abscess, pyopneumothorax.

[c] Includes reports of thrombocytopenia and platelet count decreased.
[d] Includes reports of neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic sepsis, granulocytopenia.
[e] Includes reports of white blood cell count decreased and leukopenia.
[f] Includes reports of cytokine release syndrome, hypersensitivity, anaphylaxis.
[g] 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, myxoedema, 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.
[h] Includes reports of hyperthyroidism, Basedow's disease, endocrine ophthalmopathy, exophthalmos.
[i] Includes reports of diabetes mellitus, type 1 diabetes mellitus, diabetic ketoacidosis, ketoacidosis.
[j] Includes reports of adrenal insufficiency and primary adrenal insufficiency.
[ak] Incudes reports of hypophysitis and temperature regulation disorder.
[l] Includes reports of neuropathy peripheral, autoimmune neuropathy, peripheral sensory neuropathy, polyneuropathy, herpes zoster, peripheral motor neuropathy, neuralgic amyotrophy, peripheral sensorimotor neuropathy, toxic neuropathy, axonal neuropathy, lumbosacral plexopathy, neuropathic arthropathy, peripheral nerve infection.
[m] Includes reports of Guillain-Barré syndrome and demyelinating polyneuropathy.
[n] Includes reports of encephalitis, meningitis, photophobia.
[ao] Incudes reports of myasthenia gravis.
[p] Reported in studies outside the pooled dataset. The frequency is based on the program wide exposure.
[q] Includes reports of pneumonitis, lung infiltration, bronchiolitis, interstitial lung disease, radiation pneumonitis.
[r] Includes reports of diarrhoea, defaecation urgency, frequent bowel movements, and gastrointestinal hypermotility.
[s] Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic, colitis ulcerative.
[t] Includes reports of oropharyngeal pain, oropharyngeal discomfort and throat irritation.
[u] Includes reports of autoimmune pancreatitis, pancreatitis, pancreatitis acute, lipase increased, amylase increased.
[v] 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.
[w] Includes reports of acne, acne pustular, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis exfoliative generalised, drug eruption, eczema, eczema infected, erythema, erythema multiforme, erythema of eyelid, exfoliative rash, eyelid rash, fixed eruption, folliculitis, furuncle, generalised erythema, palmar-plantar erythrodysaesthesia syndrome, rash , rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash papulosquamous, rash pruritic, rash pustular, rash vesicular, seborrhoeic dermatitis, skin exfoliation, skin toxicity, skin ulcer, toxic epidermal necrolysis, toxic skin eruption.
[x] Includes reports of musculoskeletal pain and myalgia.
[y] Includes reports of myositis, rhabdomyolysis, polymyalgia rheumatica, dermatomyositis, muscle abscess, myoglobin urine present.
[z] Includes reports of proteinuria, protein urine present, haemoglobinurea, nephrotic syndrome.
[aa] Includes report of nephritis, Henoch-Schonlein Purpura nephritis.

– *includes studies GO29436, GO29438, GO29537, GO30081, WO29074, WO29637, WO29522.

Serious adverse event/deaths/other significant events

Serious AEs:

Table 51: Serious adverse events reported in ≥2% of patients in either treatment arm (safety evaluable patients)

MedDRA System Organ Class MedDRA Preferred Term	PBO + CE (Actual) (N=196)	Atezo + CE (Actual) (N=198)	All Patients (N=394)
Total number of patients with at least one adverse event	68 (34.7%)	74 (37.4%)	142 (36.0%)
Overall total number of events	113	129	242
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Total number of patients with at least one adverse event	27 (13.8%)	17 (8.6%)	44 (11.2%)
Total number of events	30	23	53
NEUTROPENIA	8 (4.1%)	7 (3.5%)	15 (3.8%)
FEBRILE NEUTROPENIA	9 (4.6%)	5 (2.5%)	14 (3.6%)
THROMBOCYTOPENIA	4 (2.0%)	5 (2.5%)	9 (2.3%)
PANCYTOPENIA	4 (2.0%)	0	4 (1.0%)
INFECTIONS AND INFESTATIONS			
Total number of patients with at least one adverse event	20 (10.2%)	16 (8.1%)	36 (9.1%)
Total number of events	22	21	43
PNEUMONIA	7 (3.6%)	9 (4.5%)	16 (4.1%)
METABOLISM AND NUTRITION DISORDERS			
Total number of patients with at least one adverse event	5 (2.6%)	4 (2.0%)	9 (2.3%)
Total number of events	6	4	10
HYPONATRAEMIA	4 (2.0%)	1 (0.5%)	5 (1.3%)

Investigator text for AEs encoded using MedDRA version 21.0.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
Atezo=Atezolizumab, CE=Carboplatin + Etoposide, PBO=Placebo
Data Cutoff: 24APR2018

Table 40: Serious adverse events by preferred term occurring in ≥1% in either arm/population (safety evaluable population)

MedDRA Preferred Term	IMpower133			
	PBO+CE (N=196)	Atezo+CE (N=198)	Atezo+Chemo Combo (N=2421)	Atezo Mono (N=3178)
Total number of patients with at least one adverse event	68 (34.7%)	74 (37.4%)	1073 (44.3%)	1309 (41.2%)
Total number of events	113	129	2023	2267
PNEUMONIA	7 (3.6%)	9 (4.5%)	144 (5.9%)	98 (3.1%)
NEUTROPENIA	8 (4.1%)	7 (3.5%)	34 (1.4%)	0
FEBRILE NEUTROPENIA	9 (4.6%)	5 (2.5%)	93 (3.8%)	7 (0.2%)
THROMBOCYTOPENIA	4 (2.0%)	5 (2.5%)	31 (1.3%)	6 (0.2%)
ANAEMIA	2 (1.0%)	3 (1.5%)	49 (2.0%)	29 (0.9%)
DIARRHOEA	1 (0.5%)	3 (1.5%)	52 (2.1%)	21 (0.7%)
FATIGUE	0	3 (1.5%)	11 (0.5%)	21 (0.7%)
SYNCOPE	0	3 (1.5%)	10 (0.4%)	12 (0.4%)
VOMITING	3 (1.5%)	3 (1.5%)	27 (1.1%)	19 (0.6%)
ACUTE KIDNEY INJURY	0	2 (1.0%)	20 (0.8%)	37 (1.2%)
ASTHENIA	1 (0.5%)	2 (1.0%)	11 (0.5%)	13 (0.4%)
AUTOIMMUNE THYROIDITIS	0	2 (1.0%)	2 (<0.1%)	0
BRONCHITIS	0	2 (1.0%)	19 (0.8%)	7 (0.2%)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	2 (1.0%)	2 (1.0%)	35 (1.4%)	10 (0.3%)
COLITIS	0	2 (1.0%)	17 (0.7%)	16 (0.5%)
GENERAL PHYSICAL HEALTH DETERIORATION	1 (0.5%)	2 (1.0%)	11 (0.5%)	11 (0.3%)
HAEMOPTYSIS	1 (0.5%)	2 (1.0%)	28 (1.2%)	20 (0.6%)
HYPERGLYCAEMIA	0	2 (1.0%)	5 (0.2%)	5 (0.2%)
LEUKOPENIA	1 (0.5%)	2 (1.0%)	5 (0.2%)	0
LOWER RESPIRATORY TRACT INFECTION	0	2 (1.0%)	5 (0.2%)	15 (0.5%)
PLEURAL EFFUSION	1 (0.5%)	2 (1.0%)	16 (0.7%)	40 (1.3%)
PYREXIA	0	2 (1.0%)	45 (1.9%)	79 (2.5%)
URINARY TRACT INFECTION	2 (1.0%)	2 (1.0%)	20 (0.8%)	61 (1.9%)
ATRIAL FIBRILLATION	2 (1.0%)	1 (0.5%)	17 (0.7%)	9 (0.3%)
DYSPNOEA	2 (1.0%)	1 (0.5%)	32 (1.3%)	89 (2.8%)
HYPONATRAEMIA	4 (2.0%)	1 (0.5%)	12 (0.5%)	20 (0.6%)
INFUSION RELATED REACTION	2 (1.0%)	1 (0.5%)	11 (0.5%)	7 (0.2%)
PNEUMONITIS	2 (1.0%)	1 (0.5%)	51 (2.1%)	35 (1.1%)
ACUTE RESPIRATORY FAILURE	2 (1.0%)	0	5 (0.2%)	3 (<0.1%)
BACK PAIN	0	0	11 (0.5%)	35 (1.1%)
LUNG INFECTION	3 (1.5%)	0	28 (1.2%)	15 (0.5%)
PANCYTOPENIA	4 (2.0%)	0	7 (0.3%)	0
PLATELET COUNT DECREASED	2 (1.0%)	0	6 (0.2%)	2 (<0.1%)
PULMONARY EMBOLISM	2 (1.0%)	0	40 (1.7%)	42 (1.3%)
SEPSIS	1 (0.5%)	0	27 (1.1%)	41 (1.3%)

Grade 5 AEs due to PD are excluded for studies GO27831 and GO28625.
Investigator text for AEs encoded using MedDRA v21.0. 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. All treatment emergent AEs are included. Sort order is by decreasing frequency in Atezo+CE treatment arm.
Atezo=Atezolizumab, PBO=Placebo, CE=Carboplatin+Etoposide. Atezo+Chemo Combo: GO29537 (IMPOWER130) Arm A + GO29437 (IMPOWER131) Arm A+B + GO29436 (IMPOWER150) Arm A+B + GO29438 (IMPOWER132) Arm A + GO30081 (IMPOWER133) Arm A. Atezo Mono: GO28915 (OAK) + GO28753 (POPLAR) + GO28754 (BIRCH) + GO28625 (FIR) + GO27831 (PCD4989g - All Cohorts) + GO29293 (IMVIGOR210) + GO29294 (IMVIGOR211) + WO29074 (IMMOTION150 Arm B). Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO29293:04JUL2016, GO28915:07JUL2016, GO29294:13MAR2017, GO29436:22JAN2018, GO29437:20APR2018, GO29438:22MAY2018, GO29537:15MAR2018, GO30081:24APR2018, WO29074:17OCT2016.

Deaths and primary cause of deaths:

Table 41: All deaths and primary cause of death (safety evaluable population)

	IMpower133			
	PBO+CE (N=196)	Atezo+CE (N=198)	Atezo+Chemo Combo (N=2421)	Atezo Mono (N=3178)
All death				
n	130 (66.3%)	103 (52.0%)	1277 (52.7%)	1884 (59.3%)
<=30 days from last study drug administration	13 (6.6%)	8 (4.0%)	235 (9.7%)	352 (11.1%)
>30 days from last study drug administration	117 (59.7%)	95 (48.0%)	1042 (43.0%)	1532 (48.2%)
Primary cause of death				
n	130 (66.3%)	103 (52.0%)	1277 (52.7%)	1884 (59.3%)
ADVERSE EVENT	11 (5.6%)	4 (2.0%)	143 (5.9%)	120 (3.8%)
PROGRESSIVE DISEASE	115 (58.7%)	90 (45.5%)	1062 (43.9%)	1463 (46.0%)
OTHER	4 (2.0%)	9 (4.5%)	72 (3.0%)	301 (9.5%)

Deaths due to other includes unrelated adverse events outside of reporting window. Other Cause of Death is displayed verbatim.
Patient GO29293-268804-1310 in Atezo Mono group has missing data for Other Cause of Death.
Atezo=Atezolizumab, PBO=Placebo, CE=Carboplatin+Etoposide. Atezo+Chemo Combo: GO29537 (IMPOWER130) Arm A + GO29437 (IMPOWER131) Arm A+B + GO29436 (IMPOWER150) Arm A+B + GO29438 (IMPOWER132) Arm A + GO30081 (IMPOWER133) Arm A. Atezo Mono: GO28915 (OAK) + GO28753 (POPLAR) + GO28754 (BIRCH) + GO28625 (FIR) + GO27831 (PCD4989g - All Cohorts) + GO29293 (IMVIGOR210) + GO29294 (IMVIGOR211) + WO29074 (IMMOTION150 Arm B). Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO29293:04JUL2016, GO28915:07JUL2016, GO29294:13MAR2017, GO29436:22JAN2018, GO29437:20APR2018, GO29438:22MAY2018, GO29537:15MAR2018, GO30081:24APR2018, WO29074:17OCT2016.

G5 AEs across IMpower133, Atezo+Chemo and Atezo Mono populations:

Table 42: Grade 5 events by preferred term (safety evaluable population)

	IMpower133			
MedDRA SOC/Preferred Term	PBO+CE (N=196)	Atezo+CE (N=198)	Atezo+Chemo Combo (N=2421)	Atezo Mono (N=3178)
Total number of deaths	11 (5.6%)	4 (2.0%)	144 (5.9%)	120 (3.8%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS / NEUTROPENIA	0	1 (0.5%)	1 (<0.1%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS / DEATH	0	1 (0.5%)	15 (0.6%)	19 (0.6%)
INFECTIONS AND INFESTATIONS / PNEUMONIA	3 (1.5%)	1 (0.5%)	19 (0.8%)	12 (0.4%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / RESPIRATORY FAILURE	0	1 (0.5%)	3 (0.1%)	5 (0.2%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS / DISSEMINATED INTRAVASCULAR COAGULATION	0	0	0	1 (<0.1%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS / FEBRILE NEUTROPENIA	0	0	3 (0.1%)	1 (<0.1%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS / HISTIOCYTOSIS HAEMATOPHAGIC	0	0	0	1 (<0.1%)
CARDIAC DISORDERS / ACUTE CORONARY SYNDROME	0	0	0	1 (<0.1%)
CARDIAC DISORDERS / ACUTE MYOCARDIAL INFARCTION	0	0	0	1 (<0.1%)
CARDIAC DISORDERS / CARDIAC ARREST	0	0	7 (0.3%)	5 (0.2%)
CARDIAC DISORDERS / CARDIAC FAILURE	0	0	0	3 (<0.1%)
CARDIAC DISORDERS / CARDIAC FAILURE ACUTE	0	0	1 (<0.1%)	0
CARDIAC DISORDERS / CARDIAC TAMPONADE	0	0	0	1 (<0.1%)
CARDIAC DISORDERS / CARDIO-RESPIRATORY ARREST	0	0	2 (<0.1%)	0
CARDIAC DISORDERS / CARDIOPULMONARY FAILURE	1 (0.5%)	0	0	0
CARDIAC DISORDERS / MYOCARDIAL INFARCTION	0	0	4 (0.2%)	2 (<0.1%)
CARDIAC DISORDERS / MYOCARDIAL ISCHAEMIA	0	0	0	1 (<0.1%)
CARDIAC DISORDERS / PERICARDIAL EFFUSION	1 (0.5%)	0	0	0
CARDIAC DISORDERS / PERICARDITIS CONSTRICTIVE	0	0	0	1 (<0.1%)
CARDIAC DISORDERS / VENTRICULAR TACHYCARDIA	0	0	1 (<0.1%)	0
GASTROINTESTINAL DISORDERS / ENTEROCOLITIS	0	0	1 (<0.1%)	0
GASTROINTESTINAL DISORDERS / ENTEROVESICAL FISTULA	0	0	0	1 (<0.1%)
GASTROINTESTINAL DISORDERS / GASTRIC PERFORATION	0	0	0	1 (<0.1%)
GASTROINTESTINAL DISORDERS / GASTROINTESTINAL HAEMORRHAGE	0	0	1 (<0.1%)	1 (<0.1%)
GASTROINTESTINAL DISORDERS / INTESTINAL ANGINA	0	0	1 (<0.1%)	0
GASTROINTESTINAL DISORDERS / INTESTINAL ISCHAEMIA	0	0	1 (<0.1%)	0
GASTROINTESTINAL DISORDERS / INTESTINAL OBSTRUCTION	0	0	1 (<0.1%)	0
GASTROINTESTINAL DISORDERS / INTESTINAL PERFORATION	0	0	0	1 (<0.1%)
GASTROINTESTINAL DISORDERS / LARGE INTESTINAL OBSTRUCTION	0	0	0	1 (<0.1%)
GASTROINTESTINAL DISORDERS / LARGE INTESTINE PERFORATION	0	0	1 (<0.1%)	1 (<0.1%)
GASTROINTESTINAL DISORDERS / PROCTITIS ULCERATIVE	0	0	1 (<0.1%)	0
GASTROINTESTINAL DISORDERS / SMALL INTESTINAL PERFORATION	0	0	1 (<0.1%)	0
GASTROINTESTINAL DISORDERS / SUBILEUS	0	0	0	1 (<0.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS / GENERAL PHYSICAL HEALTH DETERIORATION	1 (0.5%)	0	0	1 (<0.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS / SUDDEN DEATH	0	0	0	3 (<0.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS / ULCER HAEMORRHAGE	0	0	0	1 (<0.1%)
HEPATOBILIARY DISORDERS / HEPATIC CIRRHOSIS	0	0	1 (<0.1%)	0
HEPATOBILIARY DISORDERS / HEPATIC FAILURE	0	0	0	2 (<0.1%)
HEPATOBILIARY DISORDERS / HEPATIC FUNCTION ABNORMAL	0	0	1 (<0.1%)	0
HEPATOBILIARY DISORDERS / HEPATIC HAEMATOMA	0	0	0	1 (<0.1%)
HEPATOBILIARY DISORDERS / HEPATITIS ACUTE	0	0	1 (<0.1%)	0
HEPATOBILIARY DISORDERS / HEPATOTOXICITY	0	0	1 (<0.1%)	0
INFECTIONS AND INFESTATIONS / EMPYEMA	0	0	0	1 (<0.1%)
INFECTIONS AND INFESTATIONS / INFLUENZA	0	0	2 (<0.1%)	0
INFECTIONS AND INFESTATIONS / LOWER RESPIRATORY TRACT INFECTION	0	0	0	1 (<0.1%)
INFECTIONS AND INFESTATIONS / LUNG INFECTION	0	0	1 (<0.1%)	2 (<0.1%)

INFECTIONS AND INFESTATIONS / NEUTROPENIC SEPSIS	0	0	1 (<0.1%)	0
INFECTIONS AND INFESTATIONS / PULMONARY SEPSIS	1 (0.5%)	0	0	2 (<0.1%)
INFECTIONS AND INFESTATIONS / RESPIRATORY TRACT INFECTION	0	0	0	1 (<0.1%)
INFECTIONS AND INFESTATIONS / SEPSIS	1 (0.5%)	0	6 (0.2%)	8 (0.3%)
INFECTIONS AND INFESTATIONS / SEPTIC SHOCK	1 (0.5%)	0	4 (0.2%)	5 (0.2%)
INFECTIONS AND INFESTATIONS / STAPHYLOCOCCAL SEPSIS	0	0	1 (<0.1%)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS / HEAD INJURY	0	0	0	1 (<0.1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS / HIP FRACTURE	0	0	1 (<0.1%)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS / OVERDOSE	0	0	0	1 (<0.1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS / SUBDURAL HAEMATOMA	0	0	1 (<0.1%)	0
INVESTIGATIONS / GENERAL PHYSICAL CONDITION ABNORMAL	0	0	0	1 (<0.1%)
METABOLISM AND NUTRITION DISORDERS / DECREASED APPETITE	0	0	1 (<0.1%)	0
METABOLISM AND NUTRITION DISORDERS / FAILURE TO THRIVE	0	0	0	1 (<0.1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) / TUMOUR EMBOLISM	0	0	2 (<0.1%)	0
NERVOUS SYSTEM DISORDERS / CEREBRAL ARTERY EMBOLISM	0	0	0	1 (<0.1%)
NERVOUS SYSTEM DISORDERS / CEREBRAL HAEMORRHAGE	0	0	0	2 (<0.1%)
NERVOUS SYSTEM DISORDERS / CEREBRAL INFARCTION	0	0	0	1 (<0.1%)
NERVOUS SYSTEM DISORDERS / CEREBROVASCULAR ACCIDENT	0	0	3 (0.1%)	2 (<0.1%)
NERVOUS SYSTEM DISORDERS / GUILLAIN-BARRE SYNDROME	0	0	1 (<0.1%)	0
NERVOUS SYSTEM DISORDERS / HAEMORRHAGE INTRACRANIAL	0	0	2 (<0.1%)	0
NERVOUS SYSTEM DISORDERS / ISCHAEMIC STROKE	0	0	0	2 (<0.1%)
NERVOUS SYSTEM DISORDERS / SEIZURE	0	0	1 (<0.1%)	0
PSYCHIATRIC DISORDERS / ASSISTED SUICIDE	0	0	0	1 (<0.1%)
PSYCHIATRIC DISORDERS / COMPLETED SUICIDE	0	0	3 (0.1%)	1 (<0.1%)
RENAL AND URINARY DISORDERS / ACUTE KIDNEY INJURY	0	0	1 (<0.1%)	0
RENAL AND URINARY DISORDERS / RENAL FAILURE	0	0	0	1 (<0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / ACUTE RESPIRATORY FAILURE	1 (0.5%)	0	1 (<0.1%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / ASPIRATION	0	0	3 (0.1%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	0	5 (0.2%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / DYSPNOEA	0	0	1 (<0.1%)	1 (<0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / HAEMOPTYSIS	1 (0.5%)	0	8 (0.3%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / INTERSTITIAL LUNG DISEASE	0	0	2 (<0.1%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / PNEUMONIA ASPIRATION	0	0	1 (<0.1%)	2 (<0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / PNEUMONITIS	0	0	4 (0.2%)	1 (<0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / PNEUMOTHORAX	0	0	0	1 (<0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / PULMONARY EMBOLISM	0	0	12 (0.5%)	2 (<0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / PULMONARY HAEMORRHAGE	0	0	2 (<0.1%)	1 (<0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / PULMONARY HYPERTENSION	0	0	0	1 (<0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / PULMONARY OEDEMA	0	0	1 (<0.1%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / RESPIRATORY DISORDER	0	0	0	1 (<0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / RESPIRATORY DISTRESS	0	0	1 (<0.1%)	2 (<0.1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS / TOXIC EPIDERMAL NECROLYSIS	0	0	0	1 (<0.1%)
VASCULAR DISORDERS / AORTIC DISSECTION	0	0	1 (<0.1%)	0
VASCULAR DISORDERS / EMBOLISM	0	0	1 (<0.1%)	2 (<0.1%)
VASCULAR DISORDERS / HAEMODYNAMIC INSTABILITY	0	0	1 (<0.1%)	0
VASCULAR DISORDERS / INTERNAL HAEMORRHAGE	0	0	0	1 (<0.1%)
VASCULAR DISORDERS / JUGULAR VEIN THROMBOSIS	0	0	0	1 (<0.1%)
VASCULAR DISORDERS / SUPERIOR VENA CAVA SYNDROME	0	0	1 (<0.1%)	0

Grade 5 AEs due to PD are excluded for studies GO27831 and GO28625.
Investigator text for AEs encoded using MedDRA v21.0. 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 deaths" rows, the multiple occurrences of the same AE in an individual are counted separately. All treatment emergent AEs are included. Sort order is by decreasing frequency in Atezo+CE treatment arm.
Atezo=Atezolizumab, PBO=Placebo, CE=Carboplatin+Etoposide. Atezo+Chemo Combo: GO29537 (IMPOWER130) Arm A + GO29437 (IMPOWER131) Arm A+B + GO29436 (IMPOWER150) Arm A+B + GO29438 (IMPOWER132) Arm A + GO30081 (IMPOWER133) Arm A. Atezo Mono: GO28915 (OAK) + GO28753 (POPLAR) + GO28754 (BIRCH) + GO28625 (FIR) + GO27831 (PCD4989g - All Cohorts) + GO29293 (IMVIGOR210) + GO29294 (IMVIGOR211) + WO29074 (IMMOTION150 Arm B). Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO29293:04JUL2016, GO28915:07JUL2016, GO29294:13MAR2017, GO29436:22JAN2018, GO29437:20APR2018, GO29438:22MAY2018, GO29537:15MAR2018, GO30081:24APR2018, WO29074:17OCT2016.

AESIs to atezolizumab across IMpower133, Atezo+Chemo Combo and Atezo Mono populations:

Table 43: Summary of AESIs for atezolizumab (safety evaluable population)

	IMpower133			
	PBO+CE (N=196)	Atezo+CE (N=198)	Atezo+Chemo Combo (N=2421)	Atezo Mono (N=3178)
Total number of patients with at least one AESI	48 (24.5%)	79 (39.9%)	1164 (48.1%)	1098 (34.6%)
Total number of AESI events	71	146	2395	2186
Total number of patients with at least one				
Treatment-related AESI	36 (18.4%)	64 (32.3%)	975 (40.3%)	794 (25.0%)
Atezo-related AESI	0	61 (30.8%)	880 (36.3%)	794 (25.0%)
Grade 3-4 AESI	5 (2.6%)	16 (8.1%)	250 (10.3%)	248 (7.8%)
Treatment-related Grade 3-4 AESI	4 (2.0%)	14 (7.1%)	213 (8.8%)	173 (5.4%)
Atezo-related Grade 3-4 AESI	0	14 (7.1%)	194 (8.0%)	173 (5.4%)
Grade 5 AESI	0	0	11 (0.5%)	4 (0.1%)
Treatment-related Grade 5 AESI	0	0	11 (0.5%)	2 (<0.1%)
Atezo-related Grade 5 AESI	0	0	10 (0.4%)	2 (<0.1%)
Serious AESI	7 (3.6%)	13 (6.6%)	173 (7.1%)	151 (4.8%)
Treatment-related serious AESI	5 (2.6%)	11 (5.6%)	155 (6.4%)	127 (4.0%)
Atezo-related serious AESI	0	11 (5.6%)	149 (6.2%)	127 (4.0%)
AESI leading to any Treatment withdrawal	2 (1.0%)	8 (4.0%)	134 (5.5%)	58 (1.8%)
AESI leading to Atezo withdrawal	0	7 (3.5%)	122 (5.0%)	58 (1.8%)
AESI leading to Treatment modification/interruption	11 (5.6%)	22 (11.1%)	299 (12.4%)	210 (6.6%)
AESI Treated with Systemic Corticosteroids	9 (4.6%)	21 (10.6%)	373 (15.4%)	247 (7.8%)

Immune-Related Rash	20 (10.2%)	37 (18.7%)	616 (25.4%)	620 (19.5%)
Immune-Related Hypothyroidism	1 (0.5%)	25 (12.6%)	277 (11.4%)	164 (5.2%)
Immune-Related Hepatitis (Diagnosis and Lab Abnormalities)	9 (4.6%)	14 (7.1%)	345 (14.3%)	343 (10.8%)
Immune-Related Hepatitis (Lab Abnormalities)	9 (4.6%)	14 (7.1%)	315 (13.0%)	315 (9.9%)
Immune-Related Hyperthyroidism	5 (2.6%)	11 (5.6%)	91 (3.8%)	30 (0.9%)
Infusion-Related Reactions	10 (5.1%)	11 (5.6%)	70 (2.9%)	34 (1.1%)
Immune-Related Pneumonitis	5 (2.6%)	4 (2.0%)	134 (5.5%)	87 (2.7%)
Immune-Related Colitis	0	3 (1.5%)	38 (1.6%)	34 (1.1%)
Immune-Related Severe Cutaneous Reactions	0	2 (1.0%)	19 (0.8%)	22 (0.7%)
Rhabdomyolysis	0	2 (1.0%)	5 (0.2%)	5 (0.2%)
Immune-Related Diabetes Mellitus	0	1 (0.5%)	16 (0.7%)	11 (0.3%)
Immune-Related Guillain-Barre Syndrome	0	1 (0.5%)	2 (<0.1%)	5 (0.2%)
Immune-Related Hypophysitis	0	1 (0.5%)	7 (0.3%)	2 (<0.1%)
Immune-Related Nephritis	1 (0.5%)	1 (0.5%)	12 (0.5%)	3 (<0.1%)
Immune-Related Pancreatitis	2 (1.0%)	1 (0.5%)	17 (0.7%)	18 (0.6%)
Autoimmune Hemolytic Anemia	0	0	6 (0.2%)	4 (0.1%)
Immune-Related Adrenal Insufficiency	2 (1.0%)	0	18 (0.7%)	12 (0.4%)
Immune-Related Encephalitis	0	0	3 (0.1%)	2 (<0.1%)
Immune-Related Hepatitis (Diagnosis)	0	0	44 (1.8%)	62 (2.0%)
Immune-Related Meningitis	0	0	7 (0.3%)	11 (0.3%)
Immune-Related Meningoencephalitis	0	0	10 (0.4%)	13 (0.4%)
Immune-Related Myasthenia Gravis	0	0	0	1 (<0.1%)
Immune-Related Myocarditis	0	0	1 (<0.1%)	0
Immune-Related Myositis	0	0	6 (0.2%)	8 (0.3%)
Immune-Related Ocular Inflammatory Toxicity	0	0	7 (0.3%)	16 (0.5%)
Immune-Related Vasculitis	1 (0.5%)	0	6 (0.2%)	7 (0.2%)
Systemic Immune Activation	0	0	1 (<0.1%)	2 (<0.1%)

Table 56: Summary of safety information for important AESIs for atezolizumab (IMpower 133 safety evaluable population)

Important AESI (Atezo +CE N=198) (39.9%)	Severity			Resolved All Grades *	Median time to onset All Grades (months) (range)	Median duration All Grades (months) (range)	All Grades AESIs leading to atezolizumab withdrawal	All Grades AESIs requiring the use of corticosteroids (imAEs)
	All Grades	Grade 3-4	Grade 5					
	Atezo +CE	Atezo +CE	Atezo +CE	Atezo +CE	Atezo +CE	Atezo +CE	Atezo +CE	Atezo +CE
Immune-Related								
Hypothyroidism	25 (12.8%)	0	0	8 (32.0%)	4.21 (1.7-11.3)	NE (0-12*)	0	1 (0.5%)
Hepatitis (Diagnosis & Laboratory Abnormality)	14 (7.1%)	3 (1.5%)	0	10 (71.4%)	1.49 (0.2-6.5)	0.7 (0*-4)	1 (0.5%)	6 (3.0%)
Hepatitis (Diagnosis)	0	0	0	0	NE (NE,NE)	NE (NE)	0	0
Hepatitis (Laboratory Abnormality)	14 (7.1%)	3 (1.5%)	0	10 (71.4%)	1.49 (0.2-6.5)	0.7 (0*-4)	1 (0.5%)	6 (3.0%)
Hyperthyroidism	11 (5.6%)	0	0	10 (90.9%)	2.10 (0.3-4.6)	4.7 (0-10*)	0	1 (0.5%)
Infusion-Related Reactions	11 (5.6%)	4 (2.0%)	0	11 (100%)	0.72 (0.0-3.3)	0.0 (0-0)	4 (2.0%)	5 (2.5%)
Pneumonitis	4 (2.0%)	1 (0.5%)	0	2 (50.0%)	2.18 (0.5-4.0)	NE (0-9*)	0	2 (1.0%)
Colitis	3 (1.5%)	2 (1.0%)	0	3 (100%)	0.95 (0.3-1.6)	0.7 (0-1)	0	3 (1.5%)
Guillain-Barré Syndrome	1 (0.5%)	1 (0.5%)	0	0	3.65 (3.6-3.6)	NE (4*-4*)	0	0
Pancreatitis	1 (0.5%)	1 (0.5%)	0	1 (100%)	0.13 (0.1-0.1)	0.6 (1-1)	0	0
Diabetes Mellitus	1 (0.5%)	0	0	0	2.76 (2.8-2.8)	NE (18*-18*)	0	1 (0.5%)
Hypophysitis	1 (0.5%)	0	0	1 (100%)	17.54 (17.5-17.5)	0.5 (0-0)	0	0
Nephritis	1 (0.5%)	1 (0.5%)	0	1 (100%)	9.40 (9.4-9.4)	0.6 (1-1)	1 (0.5%)	1 (0.5%)
Adrenal Insufficiency	0	0	0	0	NE (NE,NE)	NE (NE)	0	0

Immune-related AEs

Immune-related hypothyroidism across IMpower133, Atezo+Chemo Combo and Atezo Mono Populations:

Table 57: Summary of immune-related hypothyroidism (safety evaluable population)

AE of Special Interest Medical Concept MedDRA Preferred Term	Grade	Impower133 PBO+CE (N=196)	Impower133 Atezo+CE (N=198)	Atezo+Chemo Combo (N=2421)	Atezo Mono (N=3178)
EUTHYROID SICK SYNDROME	- Any Grade -	0	0	1 (<0.1%)	1 (<0.1%)
	1 or 2	0	0	1 (<0.1%)	1 (<0.1%)
GOITRE	- Any Grade -	0	0	2 (<0.1%)	0
	1 or 2	0	0	2 (<0.1%)	0
MYXOEDEMA	- Any Grade -	0	0	0	1 (<0.1%)
	1 or 2	0	0	0	1 (<0.1%)
MYXOEDEMA COMA	- Any Grade -	0	0	1 (<0.1%)	0
	3 or 4	0	0	1 (<0.1%)	0
THYROID FUNCTION TEST ABNORMAL	- Any Grade -	0	0	0	1 (<0.1%)
	1 or 2	0	0	0	1 (<0.1%)
THYROIDITIS ACUTE	- Any Grade -	0	0	0	1 (<0.1%)
	1 or 2	0	0	0	1 (<0.1%)
THYROXINE DECREASED	- Any Grade -	0	0	0	1 (<0.1%)
	1 or 2	0	0	0	1 (<0.1%)
THYROXINE FREE DECREASED	- Any Grade -	0	0	2 (<0.1%)	0
	1 or 2	0	0	2 (<0.1%)	0
THYROXINE INCREASED	- Any Grade -	0	0	2 (<0.1%)	0
	1 or 2	0	0	2 (<0.1%)	0
TRI-IODOTHYRONINE ABNORMAL	- Any Grade -	0	0	1 (<0.1%)	0
	1 or 2	0	0	1 (<0.1%)	0
TRI-IODOTHYRONINE DECREASED	- Any Grade -	0	0	1 (<0.1%)	0
	1 or 2	0	0	1 (<0.1%)	0
TRI-IODOTHYRONINE FREE DECREASED	- Any Grade -	0	0	1 (<0.1%)	0
	1 or 2	0	0	1 (<0.1%)	0

Grade 5 Aes due to PD are excluded for studies GO27831 and GO28625.
Investigator text for Aes encoded using MedDRA v21.0. 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 'AE of Special Interest Medical Concept' 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. All treatment emergent Aes are included. Adverse events with missing grade are not included. Sort order is by decreasing frequency in Atezo+CE treatment arm.
Atezo=Atezolizumab, PBO=Placebo, CE=Carboplatin+Etoposide. Atezo+Chemo Combo: GO29537 (IMPOWER130) Arm A + GO29437 (IMPOWER131) Arm A+B + GO29436 (IMPOWER150) Arm A+B + GO29438 (IMPOWER132) Arm A + GO30081 (IMPOWER133) Arm A. Atezo Mono: GO28915 (OAK) + GO28753 (POPLAR) + GO28754 (BIRCH) + GO28625 (FIR) + GO27831 (PCD4989g – All Cohorts) + GO29293 (IMVIGOR210) + GO29294 (IMVIGOR211) + WO29074 (IMMOTION150 Arm B). Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO29293:04JUL2016, GO28915:07JUL2016, GO29294:13MAR2017, GO29436:22JAN2018, GO29437:20APR2018, GO29438:22MAY2018, GO29537:15MAR2018, GO30081:24APR2018, WO29074:17OCT2016.

Immune-related hepatitis across IMpower133, Atezo+Chemo Combo and Atezo Mono Populations:

Table 58: Summary of immune-related hepatitis (safety evaluable population)

AE of Special Interest Medical Concept MedDRA Preferred Term	Grade	IMpower133 PBO+CE (N=196)	IMpower133 Atezo+CE (N=198)	Atezo+Chemo Combo (N=2421)	Atezo Mono (N=3178)
IMMUNE-RELATED HEPATITIS (DIAGNOSIS)					
- Overall -	- Any Grade -	0	0	44 (1.8%)	62 (2.0%)
	1 or 2	0	0	24 (1.0%)	35 (1.1%)
	3 or 4	0	0	17 (0.7%)	25 (0.8%)
	5	0	0	3 (0.1%)	2 (<0.1%)
IMMUNE-RELATED HEPATITIS (LAB ABNORMALITIES)					
- Overall -	- Any Grade -	9 (4.6%)	14 (7.1%)	315 (13.0%)	315 (9.9%)
	1 or 2	9 (4.6%)	11 (5.6%)	228 (9.4%)	204 (6.4%)
	3 or 4	0	3 (1.5%)	86 (3.6%)	111 (3.5%)
	5	0	0	1 (<0.1%)	0
IMMUNE-RELATED HEPATITIS (DIAGNOSIS AND LAB ABNORMALITIES)					
- Overall -	- Any Grade -	9 (4.6%)	14 (7.1%)	345 (14.3%)	343 (10.8%)
	1 or 2	9 (4.6%)	11 (5.6%)	241 (10.0%)	213 (6.7%)
	3 or 4	0	3 (1.5%)	100 (4.1%)	128 (4.0%)
	5	0	0	4 (0.2%)	2 (<0.1%)

Grade 5 AEs due to PD are excluded for studies GO27831 and GO28625. Investigator text for AEs encoded using MedDRA v21.0. 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 'AE of Special Interest Medical Concept' 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. All treatment emergent AEs are included. Adverse events with missing grade are not included. Sort order is by decreasing frequency in Atezo+CE treatment arm. Atezo=Atezolizumab, PBO=Placebo, CE=Carboplatin+Etoposide. Atezo+Chemo Combo: GO29537 (IMPOWER130) Arm A + GO29437 (IMPOWER131) Arm A+B + GO29436 (IMPOWER150) Arm A+B + GO29438 (IMPOWER132) Arm A + GO30081 (IMPOWER133) Arm A. Atezo Mono: GO28915 (OAK) + GO28753 (POPLAR) + GO28754 (BIRCH) + GO28625 (FIR) + GO27831 (PCD4989g – All Cohorts) + GO29293 (IMVIGOR210) + GO29294 (IMVIGOR211) + WO29074 (IMMOTION150 Arm B). Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO29293:04JUL2016, GO28915:07JUL2016, GO29294:13MAR2017, GO29436:22JAN2018, GO29437:20APR2018, GO29438:22MAY2018, GO29537:15MAR2018, GO30081:24APR2018, WO29074:17OCT2016. Program:

Immune-related hyperthyroidism across IMpower133, Atezo+Chemo Combo and Atezo Mono Populations:

Table 59: Summary of immune-related hyperthyroidism (safety evaluable population)

AE of Special Interest Medical Concept MedDRA Preferred Term	Grade	IMpower133 PBO+CE (N=196)	IMpower133 Atezo+CE (N=198)	Atezo+Chemo Combo (N=2421)	Atezo Mono (N=3178)
IMMUNE-RELATED HYPERTHYROIDISM					
- Overall -	- Any Grade -	5 (2.6%)	11 (5.6%)	91 (3.8%)	30 (0.9%)
	1 or 2	5 (2.6%)	11 (5.6%)	87 (3.6%)	29 (0.9%)
	3 or 4	0	0	4 (0.2%)	1 (<0.1%)
HYPERTHYROIDISM	- Any Grade -	5 (2.6%)	11 (5.6%)	91 (3.8%)	27 (0.8%)
	1 or 2	5 (2.6%)	11 (5.6%)	87 (3.6%)	26 (0.8%)
	3 or 4	0	0	4 (0.2%)	1 (<0.1%)
BASEDOW'S DISEASE	- Any Grade -	0	0	0	1 (<0.1%)
	1 or 2	0	0	0	1 (<0.1%)
ENDOCRINE OPHTHALMOPATHY	- Any Grade -	0	0	0	1 (<0.1%)
	1 or 2	0	0	0	1 (<0.1%)
EXOPHTHALMOS	- Any Grade -	0	0	0	1 (<0.1%)
	1 or 2	0	0	0	1 (<0.1%)

Grade 5 AEs due to PD are excluded for studies GO27831 and GO28625.
Investigator text for AEs encoded using MedDRA v21.0. 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 'AE of Special Interest Medical Concept' 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. All treatment emergent AEs are included. Adverse events with missing grade are not included. Sort order is by decreasing frequency in Atezo+CE treatment arm.
Atezo=Atezolizumab, PBO=Placebo, CE=Carboplatin+Etoposide. Atezo+Chemo Combo: GO29537 (IMPOWER130) Arm A + GO29437 (IMPOWER131) Arm A+B + GO29436 (IMPOWER150) Arm A+B + GO29438 (IMPOWER132) Arm A + GO30081 (IMPOWER133) Arm A. Atezo Mono: GO28915 (OAK) + GO28753 (POPLAR) + GO28754 (BIRCH) + GO28625 (FIR) + GO27831 (PCD4989g - All Cohorts) + GO29293 (IMVIGOR210) + GO29294 (IMVIGOR211) + WO29074 (IMMOTION150 Arm B). Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO29293:04JUL2016, GO28915:07JUL2016, GO29294:13MAR2017, GO29436:22JAN2018, GO29437:20APR2018, GO29438:22MAY2018, GO29537:15MAR2018, GO30081:24APR2018, WO29074:17OCT2016.

Immune-related pneumonitis across IMpower133, Atezo+Chemo Combo and Atezo Mono Populations:

Table 60: Summary of immune-related pneumonitis (safety evaluable population)

AE of Special Interest Medical Concept MedDRA Preferred Term	Grade	IMpower133 PBO+CE (N=196)	IMpower133 Atezo+CE (N=198)	Atezo+Chemo Combo (N=2421)	Atezo Mono (N=3178)
IMMUNE-RELATED PNEUMONITIS					
- Overall -	- Any Grade -	5 (2.6%)	4 (2.0%)	134 (5.5%)	87 (2.7%)
	1 or 2	3 (1.5%)	3 (1.5%)	95 (3.9%)	59 (1.9%)
	3 or 4	2 (1.0%)	1 (0.5%)	33 (1.4%)	27 (0.8%)
	5	0	0	6 (0.2%)	1 (<0.1%)
PNEUMONITIS	- Any Grade -	4 (2.0%)	4 (2.0%)	114 (4.7%)	70 (2.2%)
	1 or 2	2 (1.0%)	3 (1.5%)	80 (3.3%)	44 (1.4%)
	3 or 4	2 (1.0%)	1 (0.5%)	30 (1.2%)	25 (0.8%)
	5	0	0	4 (0.2%)	1 (<0.1%)
ALVEOLAR LUNG DISEASE	- Any Grade -	0	0	1 (<0.1%)	0
	1 or 2	0	0	1 (<0.1%)	0
BRONCHIOLITIS	- Any Grade -	0	0	1 (<0.1%)	2 (<0.1%)
	1 or 2	0	0	1 (<0.1%)	2 (<0.1%)
INTERSTITIAL LUNG DISEASE	- Any Grade -	0	0	8 (0.3%)	4 (0.1%)
	1 or 2	0	0	4 (0.2%)	3 (<0.1%)
	3 or 4	0	0	2 (<0.1%)	1 (<0.1%)
	5	0	0	2 (<0.1%)	0
LUNG INFILTRATION	- Any Grade -	0	0	7 (0.3%)	7 (0.2%)
	1 or 2	0	0	7 (0.3%)	6 (0.2%)
	3 or 4	0	0	0	1 (<0.1%)
PULMONARY FIBROSIS	- Any Grade -	0	0	1 (<0.1%)	0
	1 or 2	0	0	1 (<0.1%)	0
PULMONARY RADIATION INJURY	- Any Grade -	0	0	1 (<0.1%)	0
	1 or 2	0	0	1 (<0.1%)	0
RADIATION PNEUMONITIS	- Any Grade -	1 (0.5%)	0	5 (0.2%)	4 (0.1%)
	1 or 2	1 (0.5%)	0	4 (0.2%)	4 (0.1%)
	3 or 4	0	0	1 (<0.1%)	0

Immune-related colitis across IMpower133, Atezo+Chemo Combo and Atezo Mono Populations:

Table 61: Summary of immune-related colitis (safety evaluable population)

AE of Special Interest Medical Concept MedDRA Preferred Term	Grade	IMpower133 PBO+CE (N=196)	IMpower133 Atezo+CE (N=198)	Atezo+Chemo Combo (N=2421)	Atezo Mono (N=3178)
IMMUNE-RELATED COLITIS					
- Overall -	- Any Grade -	0	3 (1.5%)	38 (1.6%)	34 (1.1%)
	1 or 2	0	1 (0.5%)	14 (0.6%)	16 (0.5%)
	3 or 4	0	2 (1.0%)	24 (1.0%)	18 (0.6%)
COLITIS	- Any Grade -	0	2 (1.0%)	31 (1.3%)	30 (0.9%)
	1 or 2	0	0	11 (0.5%)	15 (0.5%)
	3 or 4	0	2 (1.0%)	20 (0.8%)	15 (0.5%)
AUTOIMMUNE COLITIS	- Any Grade -	0	1 (0.5%)	5 (0.2%)	2 (<0.1%)
	1 or 2	0	1 (0.5%)	2 (<0.1%)	0
	3 or 4	0	0	3 (0.1%)	2 (<0.1%)
COLITIS ISCHAEMIC	- Any Grade -	0	0	0	1 (<0.1%)
	3 or 4	0	0	0	1 (<0.1%)
COLITIS MICROSCOPIC	- Any Grade -	0	0	2 (<0.1%)	1 (<0.1%)
	1 or 2	0	0	1 (<0.1%)	1 (<0.1%)
	3 or 4	0	0	1 (<0.1%)	0
COLITIS ULCERATIVE	- Any Grade -	0	0	0	1 (<0.1%)
	3 or 4	0	0	0	1 (<0.1%)

Grade 5 AEs due to PD are excluded for studies GO27831 and GO28625.
Investigator text for AEs encoded using MedDRA v21.0. 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 'AE of Special Interest Medical Concept' 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. All treatment emergent AEs are included. Adverse events with missing grade are not included. Sort order is by decreasing frequency in Atezo+CE treatment arm.
Atezo=Atezolizumab, PBO=Placebo, CE=Carboplatin+Etoposide. Atezo+Chemo Combo: GO29537 (IMPOWER130) Arm A + GO29437 (IMPOWER131) Arm A+B + GO29436 (IMPOWER150) Arm A+B + GO29438 (IMPOWER132) Arm A + GO30081 (IMPOWER133) Arm A. Atezo Mono: GO28915 (OAK) + GO28753 (POPLAR) + GO28754 (BIRCH) + GO28625 (FIR) + GO27831 (PCD4989g – All Cohorts) + GO29293 (IMVIGOR210) + GO29294 (IMVIGOR211) + WO29074 (IMMOTION150 Arm B). Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO29293:04JUL2016, GO28915:07JUL2016, GO29294:13MAR2017, GO29436:22JAN2018, GO29437:20APR2018, GO29438:22MAY2018, GO29537:15MAR2018, GO30081:24APR2018, WO29074:17OCT2016.

Laboratory findings

Table 62: Summary of clinically relevant laboratory shifts from baseline

	PBO+CE	Atezo+CE
Hematology		
Hemoglobin (high)	3/194 (1.5%)	3/193 (1.6%)
Hemoglobin (low)	36/194 (18.6%)	32/193 (16.6%)
Lymphocytes Abs (high)	0	1/193 (0.5%)
Lymphocytes Abs (low)	16/195 (8.2%)	26/193 (13.5%)
Neutrophils, Total, Abs (low)	92/196 (46.9%)	87/192 (45.3%)
Platelet (low)	32/195 (16.4%)	39/193 (20.2%)
International normalized ratio (high)	0	1/95 (1.1%)
White Blood Cell Count (high)	0	1/193 (0.5%)
White Blood Cell Count (low)	39/195 (20.0%)	45/193 (23.3%)
Chemistry		
Albumin (low)	0	2/187 (1.1%)
Alkaline phosphatase (high)	4/193 (2.1%)	2/193 (1.0%)
ALT (high)	2/194 (1.0%)	6/193 (3.1%)
AST (high)	3/193 (1.6%)	2/192 (1.0%)
Calcium (high)	2/195 (1.0%)	3/192 (1.6%)
Calcium (low)	8/195 (4.1%)	5/192 (2.6%)
Creatinine (high)	1/195 (0.5%)	8/193 (4.1%)
Glucose (low)	4/195 (2.1%)	1/192 (0.5%)
Magnesium (high)	5/191 (2.6%)	5/185 (2.7%)
Magnesium (low)	7/191 (3.7%)	2/185 (1.0%)
Phosphorus (low)	4/191 (2.1%)	3/183 (1.5%)
Potassium (high)	1/195 (0.5%)	2/193 (1.0%)
Potassium (low)	7/195 (3.6%)	6/193 (3.1%)
Sodium (high)	0	1/193 (0.5%)
Sodium (low)	15/195 (7.7%)	18/193 (9.3%)
Bilirubin (high)	2/195 (1.0%)	3/193 (1.6%)

Note: A clinically relevant shift is defined as a shift from Grade 0, 1, or 2 at baseline to Grade 3 or 4 post-baseline.

Table 63: Thyroid stimulating hormone, safety evaluable patients

Treatment:	Post-Baseline Status	Status at Baseline: Normal	Status at Baseline: High	Status at Baseline: Low
PBO + CE (Actual) (N=196)	Normal	127/167 (76.0%)	7/23 (30.4%)	2/6 (33.3%)
	High	7/167 (4.2%)	11/23 (47.8%)	0/6 (0.0%)
	Low	20/167 (12.0%)	2/23 (8.7%)	4/6 (66.7%)
	Total	154/167 (92.2%)	20/23 (87.0%)	6/6 (100.0%)
Atezo + CE (Actual) (N=198)	Normal	99/170 (58.2%)	6/15 (40.0%)	3/12 (25.0%)
	High	28/170 (16.5%)	7/15 (46.7%)	1/12 (8.3%)
	Low	41/170 (24.1%)	1/15 (6.7%)	7/12 (58.3%)
	Total	168/170 (98.8%)	14/15 (93.3%)	11/12 (91.7%)

Hy's law: Hy's law cases were defined in the study protocol as elevated ALT or AST (> 3 x baseline value) in combination with either an elevated total bilirubin (> 2 x ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia. One patient in the Atezo + CE arm had laboratory abnormalities suggestive of a Hy's law case. This patient developed changes in liver function tests after 1 cycle of Atezo + CE, which was confounded by his liver metastasis at enrollment. Atezolizumab was permanently discontinued and chemotherapy was interrupted, and the patient received treatment with

systemic corticosteroids, after which his liver function tests followed a downward trend. No further atezolizumab re-challenge was conducted. The positive dechallenge and the laboratory improvement after steroid treatment were indicative of an immune-related etiology and not drug induced liver injury. This patient had AESI of transaminases increased.

Safety in special populations

Safety in special groups and populations was pooled for the Atezo + Chemo Combo (the "lung-pool") trials:

Safety by age:

Table 64: Overview of safety by age (safety evaluable population)

	Atezo+Chemo Combo (N=2421)				
	<65 (N=1251)	>=65 (N=1170)	65 - 74 (N=927)	75 - 84 (N=234)	>=85 (N=9)
Total number of patients with at least one AE	1237 (98.9%)	1151 (98.4%)	909 (98.1%)	233 (99.6%)	9 (100%)
Total number of Events	17852	17236	13144	3977	115
Total number of patients with at least one					
Treatment-related AE	1169 (93.4%)	1110 (94.9%)	875 (94.4%)	226 (96.6%)	9 (100%)
Atezo-related AE	899 (71.9%)	840 (71.8%)	650 (70.1%)	184 (78.6%)	6 (66.7%)
Grade 3-4 AE	802 (64.1%)	798 (68.2%)	617 (66.6%)	174 (74.4%)	7 (77.8%)
Treatment-related Grade 3-4 AE	673 (53.8%)	707 (60.4%)	542 (58.5%)	159 (67.9%)	6 (66.7%)
Atezo-related Grade 3-4 AE	330 (26.4%)	328 (28.0%)	255 (27.5%)	70 (29.9%)	3 (33.3%)
Grade 5 AE	61 (4.9%)	83 (7.1%)	67 (7.2%)	14 (6.0%)	2 (22.2%)
Treatment-related Grade 5 AE	23 (1.8%)	27 (2.3%)	23 (2.5%)	3 (1.3%)	1 (11.1%)
Atezo-related Grade 5 AE	16 (1.3%)	15 (1.3%)	12 (1.3%)	3 (1.3%)	0
Serious AE	507 (40.5%)	566 (48.4%)	439 (47.4%)	122 (52.1%)	5 (55.6%)
Treatment-related serious AE	281 (22.5%)	298 (25.5%)	238 (25.7%)	57 (24.4%)	3 (33.3%)
Atezo-related serious AE	184 (14.7%)	176 (15.0%)	141 (15.2%)	34 (14.5%)	1 (11.1%)
AE leading to Treatment withdrawal	264 (21.1%)	324 (27.7%)	254 (27.4%)	67 (28.6%)	3 (33.3%)
AE leading to Atezo withdrawal	144 (11.5%)	175 (15.0%)	139 (15.0%)	33 (14.1%)	3 (33.3%)
AE leading to Treatment modification/interruption	806 (64.4%)	802 (68.5%)	623 (67.2%)	173 (73.9%)	6 (66.7%)

Safety by gender:

Table 65: Overview of safety by gender (safety evaluable population)

	Atezo+Chemo Combo (N=2421)	
	Female (N=812)	Male (N=1609)
Total number of patients with at least one AE	802 (98.8%)	1586 (98.6%)
Total number of Events	13605	21483
Total number of patients with at least one		
Treatment-related AE	779 (95.9%)	1500 (93.2%)
Atezo-related AE	603 (74.3%)	1136 (70.6%)
Grade 3-4 AE	573 (70.6%)	1027 (63.8%)
Treatment-related Grade 3-4 AE	508 (62.6%)	872 (54.2%)
Atezo-related Grade 3-4 AE	249 (30.7%)	409 (25.4%)
Grade 5 AE	33 (4.1%)	111 (6.9%)
Treatment-related Grade 5 AE	15 (1.8%)	35 (2.2%)
Atezo-related Grade 5 AE	10 (1.2%)	21 (1.3%)
Serious AE	378 (46.6%)	695 (43.2%)
Treatment-related serious AE	208 (25.6%)	371 (23.1%)
Atezo-related serious AE	128 (15.8%)	232 (14.4%)
AE leading to Treatment withdrawal	186 (22.9%)	402 (25.0%)
AE leading to Atezo withdrawal	90 (11.1%)	229 (14.2%)
AE leading to Treatment modification/interruption	582 (71.7%)	1026 (63.8%)

Safety by race:

Table44: Overview of safety by race (safety evaluable population)

	Atezo+Chemo Combo (N=2421)			
	White (N=1986)	Black (N=39)	Asian (N=293)	Other (N=103)
Total number of patients with at least one AE	1956 (98.5%)	39 (100%)	291 (99.3%)	102 (99.0%)
Total number of Events	28044	817	4694	1533
Total number of patients with at least one				
Treatment-related AE	1863 (93.8%)	37 (94.9%)	284 (96.9%)	95 (92.2%)
Atezo-related AE	1385 (69.7%)	30 (76.9%)	248 (84.6%)	76 (73.8%)
Grade 3-4 AE	1271 (64.0%)	26 (66.7%)	232 (79.2%)	71 (68.9%)
Treatment-related Grade 3-4 AE	1081 (54.4%)	23 (59.0%)	218 (74.4%)	58 (56.3%)
Atezo-related Grade 3-4 AE	493 (24.8%)	11 (28.2%)	126 (43.0%)	28 (27.2%)
Grade 5 AE	126 (6.3%)	3 (7.7%)	10 (3.4%)	5 (4.9%)
Treatment-related Grade 5 AE	40 (2.0%)	1 (2.6%)	8 (2.7%)	1 (1.0%)
Atezo-related Grade 5 AE	23 (1.2%)	1 (2.6%)	6 (2.0%)	1 (1.0%)
Serious AE	873 (44.0%)	20 (51.3%)	136 (46.4%)	44 (42.7%)
Treatment-related serious AE	455 (22.9%)	10 (25.6%)	89 (30.4%)	25 (24.3%)
Atezo-related serious AE	266 (13.4%)	7 (17.9%)	70 (23.9%)	17 (16.5%)
AE leading to Treatment withdrawal	474 (23.9%)	8 (20.5%)	81 (27.6%)	25 (24.3%)
AE leading to Atezo withdrawal	253 (12.7%)	5 (12.8%)	49 (16.7%)	12 (11.7%)
AE leading to Treatment modification/interruption	1302 (65.6%)	28 (71.8%)	211 (72.0%)	67 (65.0%)

Safety by region:

Table 67: Overview of safety by region (safety evaluable population)

	Atezo+Chemo Combo (N=2421)				
	Asia-Pacific (N=264)	Australia (N=102)	Central and South America (N=118)	Europe and Middle East (N=1315)	North America (N=622)
Total number of patients with at least one AE	263 (99.6%)	101 (99.0%)	117 (99.2%)	1288 (97.9%)	619 (99.5%)
Total number of Events	4087	1574	1588	16290	11589
Total number of patients with at least one					
Treatment-related AE	258 (97.7%)	98 (96.1%)	110 (93.2%)	1213 (92.2%)	600 (96.5%)
Atezo related AE	227 (86.0%)	69 (67.6%)	70 (59.3%)	887 (67.5%)	486 (78.1%)
Grade 3 4 AE	209 (79.2%)	67 (65.7%)	65 (55.1%)	808 (61.4%)	451 (72.5%)
Treatment-related Grade 3-4 AE	199 (75.4%)	55 (53.9%)	53 (44.9%)	685 (52.1%)	388 (62.4%)
Atezo-related Grade 3-4 AE	116 (43.9%)	21 (20.6%)	17 (14.4%)	336 (25.6%)	168 (27.0%)
Grade 5 AE	11 (4.2%)	5 (4.9%)	17 (14.4%)	73 (5.6%)	38 (6.1%)
Treatment-related Grade 5 AE	8 (3.0%)	0	6 (5.1%)	29 (2.2%)	7 (1.1%)
Atezo-related Grade 5 AE	6 (2.3%)	0	4 (3.4%)	17 (1.3%)	4 (0.6%)
Serious AE	116 (43.9%)	60 (58.8%)	44 (37.3%)	552 (42.0%)	301 (48.4%)
Treatment related serious AE	81 (30.7%)	31 (30.4%)	21 (17.8%)	331 (25.2%)	115 (18.5%)
Atezo-related serious AE	66 (25.0%)	19 (18.6%)	10 (8.5%)	205 (15.6%)	60 (9.6%)
AE leading to Treatment withdrawal	73 (27.7%)	24 (23.5%)	24 (20.3%)	312 (23.7%)	155 (24.9%)
AE leading to Atezo withdrawal	45 (17.0%)	13 (12.7%)	16 (13.6%)	167 (12.7%)	78 (12.5%)
AE leading to Treatment modification/interruption	190 (72.0%)	69 (67.6%)	70 (59.3%)	825 (62.7%)	454 (73.0%)

Safety by ADA status:

Table 68: Safety summary profile by atezolizumab ADA status (ADA-evaluable atezolizumab patients in safety evaluable population)

	ADA- (N=153)	ADA+ (N=35)
Total number of patients with at least one adverse event	153 (100.0%)	35 (100.0%)
Total number of events	1768	339
Total number of patients with at least one		
Treatment-related AE	147 (96.1%)	33 (94.3%)
Any Treatment	147 (96.1%)	33 (94.3%)
Atezolizumab/Placebo	102 (66.7%)	21 (60.0%)
Grade 3-4 AE	107 (69.9%)	22 (62.9%)
Treatment-related Grade 3-4 AE	89 (58.2%)	20 (57.1%)
Grade 5 AE	1 (0.7%)	0
Treatment-related Grade 5 AE	0	0
Serious AE	54 (35.3%)	14 (40.0%)
AE leading to withdrawal from treatment	13 (8.5%)	7 (20.0%)
Any Treatment	13 (8.5%)	7 (20.0%)
Atezolizumab/Placebo	12 (7.8%)	7 (20.0%)
Carboplatin	4 (2.6%)	0
Etoposide	5 (3.3%)	2 (5.7%)
AE leading to any dose modification/interruption	107 (69.9%)	26 (74.3%)
Any Treatment	107 (69.9%)	26 (74.3%)
Atezolizumab/Placebo	90 (58.8%)	23 (65.7%)
Carboplatin	86 (56.2%)	21 (60.0%)
Etoposide	90 (58.8%)	19 (54.3%)

Safety related to drug-drug interactions and other interactions

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

Discontinuation due to adverse events

Table 69: AEs leading to treatment withdrawal (safety evaluable population)

AEs leading to withdrawal from:	Any treatment		Atezolizumab/Placebo*		Carboplatin or Etoposide**		All treatment	
MedDRA System Organ Class MedDRA Preferred Term	PBO+CE N=196	Atezo+CE N=198	PBO+CE N=196	Atezo+CE N=198	PBO+CE N=196	Atezo+CE N=198	PBO+CE N=196	Atezo+CE N=198
Total number of patients with at least one AE	6 (3.1%)	22 (11.1%)	5 (2.6%)	21 (10.6%)	2 (1.0%)	8 (4.0%)	1 (0.5%)	4 (2.0%)
GASTROINTESTINAL DISORDERS	2 (1.0%)	4 (2.0%)	1 (0.5%)	4 (2.0%)	0	0	0	1 (0.5%)
Abdominal distension	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0
Abdominal pain	1 (0.5%)	0	0	0	1 (0.5%)	0	0	0
Anal haemorrhage	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0
Diarrhoea	1 (0.5%)	0	0	0	1 (0.5%)	0	0	0
Gastritis	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0
Ileus	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.5%)
Nausea	1 (0.5%)	0	0	0	1 (0.5%)	0	0	0
Pancreatitis	1 (0.5%)	0	1 (0.5%)	0	0	0	0	0
Vomiting	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	5 (2.5%)	0	5 (2.5%)	0	0	0	1 (0.5%)
Infusion related reaction	0	5 (2.5%)	0	5 (2.5%)	0	2 (1.0%)	0	1 (0.5%)
INFECTIONS AND INFESTATIONS	1 (0.5%)	3 (1.5%)	1 (0.5%)	2 (1.0%)	0	0	0	2 (1.0%)
Pneumonia	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0	1 (0.5%)	0	1 (0.5%)
Lower respiratory tract infection	0	1 (0.5%)	0	0	0	1 (0.5%)	0	0
Urinary tract infection	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.5%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.5%)	2 (1.0%)	1 (0.5%)	2 (1.0%)	0	0	0	0
Asthenia	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0	0	0	0
General physical health deterioration	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	2 (1.0%)	0	0	0	1 (0.5%)	0	0
Leukopenia	0	1 (0.5%)	0	0	0	1 (0.5%)	0	0
Neutropenia	0	1 (0.5%)	0	0	0	1 (0.5%)	0	0
Thrombocytopenia	0	1 (0.5%)	0	0	0	1 (0.5%)	0	0

CARDIAC DISORDERS	2 (1.0%)	0	2 (1.0%)	0	0	0	1 (0.5%)	0
Atrial fibrillation	1 (0.5%)	0	1 (0.5%)	0	0	0	0	0
Pericardial effusion	1 (0.5%)	0	1 (0.5%)	0	1 (0.5%)	0	1 (0.5%)	0
VASCULAR DISORDERS	0	2 (1.0%)	0	2 (1.0%)	0	0	0	0
Hypotension	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0
Superior vena cava syndrome	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0
HEPATOBILIARY DISORDERS	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0
Jaundice	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0
IMMUNE SYSTEM DISORDERS	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0
Anaphylactic reaction	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0
INVESTIGATIONS	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0
Transaminases increased	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0
NERVOUS SYSTEM DISORDERS	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0
Trigeminal neuralgia	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0
RENAL AND URINARY DISORDERS	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0
Tubulointerstitial nephritis	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.5%)	0	1 (0.5%)	0	0	0	0	0
Pneumonitis	1 (0.5%)	0	1 (0.5%)	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0
Erythema	0	1 (0.5%)	0	1 (0.5%)	0	0	0	0

*: Atezolizumab/placebo withdrawal irrespective of chemotherapy

**: Carboplatin or etoposide withdrawal irrespective of other study treatment

Table 70: AEs leading to dose modification/interruption reported in ≥2% of patients in either treatment arm (safety evaluable population)

	Any treatment		Atezolizumab/Placebo		Carboplatin		Etoposide	
MedDRA System Organ Class MedDRA Preferred Term	PBO + CE N=196	Atezo + CE N=198	PBO + CE N=196	Atezo + CE N=198	PBO + CE N=196	Atezo + CE N=198	PBO + CE N=196	Atezo + CE N=198
Total number of patients with at least one adverse event	119 (60.7%)	138 (69.7%)	102 (52.0%)	117 (59.1%)	96 (49.0%)	111 (56.1%)	95 (48.5%)	113 (57.1%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	64 (32.7%)	72 (36.4%)	49 (25.0%)	61 (30.8%)	58 (29.6%)	68 (34.3%)	55 (28.1%)	66 (33.3%)
Neutropenia	46 (23.5%)	53 (26.8%)	35 (17.9%)	43 (21.7%)	43 (21.9%)	53 (26.8%)	41 (20.9%)	50 (25.3%)
Anaemia	12 (6.1%)	19 (9.6%)	11 (5.6%)	17 (8.6%)	10 (5.1%)	15 (7.6%)	9 (4.6%)	16 (8.1%)
Thrombocytopenia	15 (7.7%)	13 (6.6%)	10 (5.1%)	10 (5.1%)	12 (6.1%)	11 (5.6%)	12 (6.1%)	10 (5.1%)
Leukopenia	5 (2.6%)	13 (6.6%)	3 (1.5%)	13 (6.6%)	5 (2.6%)	9 (4.5%)	5 (2.6%)	9 (4.5%)
Febrile neutropenia	5 (2.6%)	3 (1.5%)	2 (1.0%)	3 (1.5%)	5 (2.6%)	1 (0.5%)	4 (2.0%)	1 (0.5%)
INVESTIGATIONS	42 (21.4%)	38 (19.2%)	37 (18.9%)	27 (13.6%)	37 (18.9%)	32 (16.2%)	38 (19.4%)	32 (16.2%)
Neutrophil count decreased	33 (16.8%)	25 (12.6%)	30 (15.3%)	21 (10.6%)	30 (15.3%)	24 (12.1%)	31 (15.8%)	22 (11.1%)
Platelet count decreased	10 (5.1%)	6 (3.0%)	8 (4.1%)	3 (1.5%)	7 (3.6%)	6 (3.0%)	7 (3.6%)	4 (2.0%)
White blood cell count decreased	10 (5.1%)	4 (2.0%)	8 (4.1%)	3 (1.5%)	8 (4.1%)	4 (2.0%)	8 (4.1%)	3 (1.5%)
Alanine aminotransferase increased	0	4 (2.0%)	0	3 (1.5%)	0	1 (0.5%)	0	2 (1.0%)
INFECTIONS AND INFESTATIONS	18 (9.2%)	12 (6.1%)	17 (8.7%)	11 (5.6%)	7 (3.6%)	10 (5.1%)	8 (4.1%)	11 (5.6%)
Pneumonia	4 (2.0%)	4 (2.0%)	3 (1.5%)	4 (2.0%)	1 (0.5%)	4 (2.0%)	2 (1.0%)	4 (2.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	7 (3.6%)	16 (8.1%)	5 (2.6%)	10 (5.1%)	4 (2.0%)	4 (2.0%)	4 (2.0%)	6 (3.0%)
Fatigue	0	10 (5.1%)	0	8 (4.0%)	0	3 (1.5%)	0	3 (1.5%)
Pyrexia	0	4 (2.0%)	0	2 (1.0%)	0	0	0	2 (1.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	8 (4.1%)	8 (4.0%)	6 (3.1%)	8 (4.0%)	0	0	2 (1.0%)	2 (1.0%)
Infusion related reaction	6 (3.1%)	7 (3.5%)	5 (2.6%)	7 (3.5%)	0	0	1 (0.5%)	1 (0.5%)

Post marketing experience

Since the International Birth Date (18 May 2016) through 17 May 2018, an estimated cumulative total of 20,783 patients have received atezolizumab from marketing experience (United States n=18,470; European Union n=987; Japan n=181; Rest of the World n=1,145). No new or unexpected safety findings were identified in the post marketing setting for atezolizumab used as a monotherapy. The combination regimen of atezolizumab with carboplatin and etoposide administrated in study IMpower133 is not approved yet.

2.5.1. Discussion on clinical safety

Likely reflecting worse prognosis of SCLC as compared to NSCLC, exposure to ATZ in IMpower133 (median 7 doses) was lower than the other first-line NSCLC studies (median 10 doses). Importantly,

exposure to ATZ/PBO and chemotherapy between both arms of the trial was similar, with data that reflect completed induction (4 cycles) and started maintenance phase for 81% of the safety population.

AEs were observed in almost all treated subjects from the trial. The proportion of patients with G3-4 AEs was high, although comparable between both arms of treatment (67% ATZ+CE, 64% PBO+CE), as was the rate of serious AEs (37% and 35%, respectively). G5 AEs, however, were more common in the PBO+CE arm (6% vs. 2%). On the other hand, most patients with AEs that prompted permanent treatment withdrawal were in the ATZ+CE arm (22 out of 28).

The most common AEs of any grade that occurred in the trial were anaemia (39%), neutropenia (36%), alopecia (36%), nausea (35%), constipation (28%) and fatigue (26%), corresponding to what is expected from carboplatin + etoposide, the backbone of both arms.

AEs with a considerably higher frequency in the ATZ+CE arm were hypothyroidism (10% vs. 0.5%), decreased appetite (27% vs. 18%), anaemia (43% vs. 35%) and nausea (38% vs. 33%). Conversely, hypokalaemia occurred more often in the PBO+CE arm (9% vs. 4%).

Excluding neutropenia, most AEs from the ATZ+CE arm occurred in a similar proportion of patients from the lung-pool studies (37% vs. 27%).

G3-4 events that occurred in the trial were in general related to myelotoxicity and hence most likely associated to carboplatin + etoposide. G3-4 gastrointestinal disorders –such as diarrhoea, vomiting and nausea– occurred more in ATZ+CE (9% vs. 6% in PBO+CE). The incidence of G3-4 neutropenia was comparable in both arms (23% ATZ+CE, 25% PBO+CE), albeit considerably higher than in the lung-pool (17%).

Based on the review of the pooled safety data set for atezolizumab in combination with chemotherapy, the following ADRs have been added to the section 4.8 of the SmPC: lymphocyte count decreased, headache, vomiting, AST/ALT increased and asthenia.

The majority of serious AEs were also related to myelotoxicity and were observed in a similar proportion of patients from both arms. The proportion of patients with febrile neutropenia was higher in the PBO+CE arm (4.6% vs. 2.5%).

The proportion of patients with AESIs in the ATZ+CE arm was noticeably higher than in the PBO+CE arm (40 vs. 25%). Most AESIs were immune-related but only about a quarter of the patients from each arm required systemic corticosteroids. Of these, the most frequent was rash, followed by thyroid disorders and hepatitis. As compared to the lung-pool, the incidence and severity of AESIs in the ATZ+CE arm was slightly lower.

As expected from chemotherapy-related myelotoxicity, the majority of clinically relevant shifts occurred in haematology (CBC) parameters.

The safety profile from the pooled lung-studies suggests particular sensitivity of elderly and Asian patients to treatment with ATZ+chemotherapy.

As compared to PBO+CE (3%), 11% of patients from the ATZ+CE arm required treatment withdrawal due to AEs. The main reasons for permanently discontinuing ATZ in 21 patients from the ATZ+CE arm were infusion-related reactions and gastrointestinal disorders. Similarly, the proportion of patients who required dose modification/interruption of ATZ/PBO in the ATZ+CE arm was higher than in the PBO+CE arm (59% vs. 52%). This difference seems mainly driven by the incidence of leukopenia (6.6% vs. 1.5%).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics. No changes to the RMP are needed as a result of the new safety data

submitted as part of the application.

2.5.2. Conclusions on clinical safety

Overall, the safety profile from carboplatin + etoposide (CE) in both arms of IMpower133 corresponded to the known safety profile of the individual study drugs in clinical practice. Adding ATZ to CE slightly increases the incidence of G3-4 and serious AEs and led to higher proportions of patients that require dose modification/interruption or permanent treatment withdrawal. Nonetheless, the majority of ADRs from ATZ were manageable and resolved with treatment. The safety profile of ATZ+CE in the IMpower133 study was generally consistent with the safety profile of atezolizumab in combination with platinum-based chemotherapy in the Atezo + Chemo Combo population (lung-pool studies). No new safety concerns arise from the use of ATZ+CE in ES-SCLC patients.

The current RMP is adequate to manage the risks associated with Tecentriq is this new indication.

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

The PRAC considered that the risk management plan version 9.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 9.1 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	Concomitant use with other immuno-modulatory drugs Long term use Concomitant or sequential use of atezolizumab with intra-vesical Bacillus Calmette-Guérin vaccine for the treatment of urothelial carcinoma

No changes to the list of safety concerns were made as a result of this extension of indication.

Pharmacovigilance plan

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
There are no Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
There are no Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Category 3 - Required additional pharmacovigilance activities				
GO28915 (OAK) A Phase III, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab (Anti-PD-L1 Antibody) Compared with Docetaxel in Patients with Non−Small Cell Lung Cancer After Failure with Platinum-Containing Chemotherapy Ongoing	To determine if atezolizumab treatment results in an improved OS compared with docetaxel To evaluate safety and tolerability of atezolizumab compared with docetaxel To evaluate incidence of ADAs against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy	Anti-drug antibodies	Final CSR	December 2019
GO29322: A Phase IB Study of the Safety and Pharmacology of atezolizumab Administered with Ipilimumab or Interferon-Alpha in Patients with Locally Advanced or Metastatic Solid Tumors Ongoing	To evaluate the safety and tolerability of atezolizumab and ipilimumab in combination in patients with advanced or metastatic NSCLC or melanoma. To evaluate the safety and tolerability of atezolizumab and interferon alfa-2b in combination in patients with advanced or metastatic RCC or melanoma	Concomitant use with other immunomodulatory drugs	Final CSR	March 2020
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: 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
WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of	The overall objective is to evaluate the effectiveness of the HCP brochure designed to mitigate important immune-related risks in patients receiving atezolizumab	Immune-related hepatitis Immune-related pneumonitis Immune-related colitis Immune-related pancreatitis Immune-related	Protocol submission Interim report	February 2018 December 2020

the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions Ongoing	in the European Union. Data from HCP surveys and reporting rates for the important identified immune related risks will be collected and analyzed to evaluate effectiveness of the HCP brochure	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	Final Report	December 2022

No new studies were added to the pharmacovigilance plan as a result of this extension of indication.

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:** • Educational materials for HCPs • Patient alert cards	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.
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:** • Educational materials for HCPs • Patient alert cards	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.
Immune-Related Colitis	**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**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP

Safety concern	Risk minimization measures	Pharmacovigilance activities
	measures: • Educational materials for HCPs • Patient alert cards	educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.
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:** • Educational materials for HCPs • Patient alert cards	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.
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:** • Educational materials for HCPs • Patient alert cards	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis and infusion-related reactions.
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:** • Educational materials for HCPs • Patient alert cards	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.

Safety concern	Risk minimization measures	Pharmacovigilance activities
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:** • Educational materials for HCPs • Patient alert cards	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis and infusion-related reactions.
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 **Additional risk minimization measures:** • Educational materials for HCPs • Patient alert cards	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.
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:** • Educational materials for HCPs • Patient alert cards	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition of and intervention in the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.
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:** • Educational materials for HCPs Patient alert cards	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition of and intervention in the following important immune-related risks: Pneumonitis, hepatitis, colitis,

Safety concern	Risk minimization measures	Pharmacovigilance activities
		pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.
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:** • Educational materials for HCPs • 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:** Study GO28915 (OAK)
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

Safety concern	Risk minimization measures	Pharmacovigilance activities
Concomitant use with other immuno-modulatory agents	**Routine risk minimization measures:** This safety concern considered as missing information is mentioned as one of the exclusion criteria within the Warnings and Precautions and description of studies included in the E.U. SmPC. **No Additional risk minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study GO29322
Long-term use	**Routine risk minimization measures:** Proposed text in E.U. SmPC: None **No Additional risk minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Studies: • MO29983 • 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

The risk minimisations measures remain unchanged as a result of this extension of indication.

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. The Package Leaflet has been updated accordingly.

The new indication has only been reflected in the SmPC for the 1,200 mg strength, however the safety sections have been aligned between the 840 mg and 1,200 mg strengths.

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. The new additions follow the same structure and use similar descriptions and terminology as used in the approved package leaflet.

• The target group of users will be similar between the approved indication (locally advanced or metastatic NSCLC previously treated with chemotherapy) and the applied indication (first-line treatment of adult patients with extensive-stage SCLC), with no significant age difference.

• Moreover, the posology proposed in this application is the same as for the currently approved indication.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed new therapeutic indication in this procedure is in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

SCLC is a deadly tumour accounting for approximately 13-15% of lung cancers and is pathologically, molecularly, biologically and clinically very different from other lung cancers (Gazdar et al, Nat Rev 2017;17:725-37). Most SCLC patients have a history of tobacco use.

3.1.2. Available therapies and unmet medical need

SCLC is usually widely metastatic at diagnosis and initially responds to cytotoxic therapy and radiotherapy, but it nearly always rapidly relapses with resistance to further therapies. Despite numerous clinical trials, including at least 40 phase 3 trials since the 1970s, systemic treatment for patients with SCLC (commonly carboplatin or cisplatin + etoposide) has not changed significantly in the past several decades (Früh et al, Ann Onc 2013;24:Supp6). Consequently, the 5-year survival rate remains low (<7% overall), and most patients survive for only 1 year or less after diagnosis. Unlike non-small cell lung cancer (NSCLC), in which major advances have been made using targeted agents and immunotherapy, there are still no approved targeted drugs or immunotherapy for SCLC (Byers and Rudin, Cancer 2015;121:665-72). However, over the past 5 years, there has been a worldwide resurgence of studies on SCLC, including comprehensive molecular analyses, the development of relevant genetically engineered mouse models and the establishment of patient-derived xenografts. These studies have led to the discovery of new potential therapeutic vulnerabilities for SCLC and therefore to new clinical trials. (Gazdar et al, Nat Rev 2017;17:725-37).

3.1.3. Main clinical studies

One pivotal, double-blind, placebo-controlled, randomized phase I/III study was submitted by the MAH to support the first-line indication in patients with extensive-stage small cell lung cancer (ES-SCLC). IMpower133 investigated the efficacy and safety of 4 cycles of carboplatin plus etoposide with or without atezolizumab (n=403). Following the induction phase, patients continued maintenance therapy with either atezolizumab or placebo (no re-randomization). The co-primary efficacy endpoints of the trial were INV-assessed PFS and OS in the ITT population.

3.2. Favourable effects

The study has met its two co-primary efficacy endpoints. At the primary analysis (data cut-off 24-APR-2018), 59% of OS events had occurred and median follow-up was 13.9 months for all patients. First interim OS analysis showed significant statistical benefit from atezolizumab+CE (mOS 12.3 months) over PBO+CE (mOS 10.3 months), with a stratified HR of 0.701 (95% CI 0.54-0.91, p=0.0069), for a net gain of 2 months of median OS for the ITT.

Final exploratory OS analysis for the ITT (data cut-off 24-JAN-2019, 302 OS events = 75%) seems overall consistent with the first interim OS analysis. Median OS in both arms is unchanged (12.3 months in the atezolizumab+CE arm and 10.3 months in the PBO+CE arm), although HR has decreased [HR 0.76 (95%CI 0.61, 0.96] and the p-value is now 0.0154.

For the final PFS analysis, 89% INV-declared PFS events are accounted for. PFS from atezolizumab+CE is also superior to PBO+CE, but with a meagre difference: median PFS 5.2 vs. 4.3 months and stratified HR of 0.772 (95% CI 0.62-0.96, p=0.0170). The net gain of median PFS is 0.9 months.

Forest plots on PFS and OS (updated) suggest the treatment effect from atezolizumab+CE was consistent across the majority of subgroups evaluated. The practiced sensitivity analyses do not alter the statistical benefit indicated from the primary endpoints.

3.3. Uncertainties and limitations about favourable effects

It is not clear whether the treatment effect is related to the use of atezolizumab during the induction or the maintenance phase.

The benefit of treatment with atezolizumab beyond progressive disease is not established and is therefore left at the discretion of the physician (see section 4.2 of the SmPC).

Patients with brain metastases are underrepresented in the pivotal trial (9%, n=35); only subjects with pre-treated and asymptomatic brain metastases were allowed for enrolment; data are too limited to draw conclusions on this population and this has been reflected in section 5.1 of the SmPC.

Updated analyses of OS by treatment-emergent ADA status based on the 24 January 2019 cutoff analyses reported a large difference for the median OS values between both ADA subgroups (mOS 14.1 months in ADA- subgroup and 10.9 months in the ADA+ subgroup), but the data are limited due to the small sample size of the ADA+ (n=35) subgroup. However, complete ADA analyses across several indications (including SCLC) will be performed by the MAH.

3.4. Unfavourable effects

Overall, atezolizumab in combination with CE is well tolerated. Similar rates of AEs were observed in both arms of the trial. The most common AEs of any grade that occurred in the trial were anaemia, neutropenia, alopecia, nausea, constipation and fatigue, likely corresponding to the chemotherapy backbone.

AEs with a considerably higher frequency in the atezolizumab+CE arm were hypothyroidism (10% vs. 0.5%), decreased apetite (27% vs. 18%), anemia (43% vs. 35%) and nausea (38% vs. 33%).

The proportion of patients with G3-4 AEs was high, although comparable between both arms of treatment (67% atezolizumab+CE, 64% PBO+CE), as was the rate of serious AEs (37% and 35%, respectively). The majority of G3-4 and serious AEs were related to myelotoxicity from chemotherapy. G5 AEs were rare: 11 (5.6%) patients from the PBO+CE arm and 4 (2.0%) from the atezolizumab+CE arm.

As expected, AESIs occurred more in the atezolizumab+CE arm than in the PBO+CE arm (40% vs. 25%). The majority of AESIs were immune-related and the most frequent were rash, thyroid disorders and hepatitis. Overall, AESIs were manageable and resolved with treatment.

The main safety concern from adding atezolizumab to CE derives from the high proportion of patients who permanently withdrew from treatment due AEs: 22 (11%) vs. 6 (3%) in the PBO+CE arm.

3.5. Uncertainties and limitations about unfavourable effects

There are no uncertainties about the unfavourable effects.

3.6. Effects Table

Table 71: Effects Table for ATZ+CE vs. PBO+CE in the first line treatment of patients with extensive-stage small cell lung cancer, data cut-off 24 January 2019 for OS (exploratory final analysis) and 24 April 2018 for PFS (primary analysis)

Effect	Unit	ATZ+CE (experimental)	PBO+CE (control)	Uncertainties / Strength of evidence
Favourable Effects				
*OS ITT (n=403)	Months	12.3	10.3	Stratified HR 0.76 (0.60, 0.95) p = 0.0154
*INV-assessed PFS ITT (n=403)	Months	5.2	4.3	Stratified HR 0.77 (0.62, 0.96) p = 0.0170
¤Unfavourable Effects				
AESIs	%	39.9	24.5	
Grade 3-4 AEs	%	67	64	
AEs leading to treatment discontinuation	%	11.1	3.1	

*Co-primary efficacy endpoints
¤Safety population n=394 (ATZ+CE n=198, PBO+CE n=196)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The need for improving outcomes in ES-SCLC is imperative, but a clinically compelling benefit must be proven against potential risks of add-on treatments. In NSCLC, three different immune checkpoint inhibitors (nivolumab, pembrolizumab and atezolizumab) were approved as monotherapy in the second-line setting before escalating to first-line in combination with backbone chemotherapy (pembrolizumab + carboplatin + paclitaxel was approved by CHMP in July 2018). This is not the case with SCLC, since immunotherapy in any setting has not demonstrated an advantage that supersedes its hazards.

Although IMpower133 has met both its co-primary endpoints (superior OS and PFS from atezolizumab+CE vs. PBO+CE in ITT), with a modest net gain of 0.9 months in median PFS (HR=0.77) and 2 months in median OS (HR=0.76). Furthermore, this benefit is not firmly supported by surrogate endpoints such as ORR and DoR. However, given the high unmet medical need in this population and the lack of any survival improvements in the last years, even a small OS advantage could be accepted as clinically meaningful in this patient population.

A retrospective and limited (42% of the ITT) analysis on PD-L1 IHC status and efficacy does not allow for reliable conclusions regarding this as a predictive biomarker for response to immunotherapy in ES-SCLC.

In regards to safety, adding atezolizumab to standard of care platinum + etoposide did not seem to make it less tolerable or significantly increase its risks, but there are two issues that cannot be overlooked from the atezolizumab+CE arm: a high rate of immune-related adverse events and a considerable proportion of patients who withdrew from treatment due AEs. However no new safety signals have been identified and given the overall tolerability of the combination therapy, the added toxicity would not outweigh a clinical relevant improvement in survival.

3.7.2. Balance of benefits and risks

Based on the provided data, the B/R balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

PD-L1 IHC (Ventana SP263) results are available for 168 patients (42% from ITT), 93 in the PBO+CE arm and 75 in the atezolizumab+CE arm. PD-L1 positivity, defined as staining of ≥1% of tumour cells, was 55% in the PBO+CE arm and 56% in the atezolizumab+CE arm. In PD-L1 positive patients (n=93), median OS is 10.6 in atezolizumab+CE and 11.1 in PBO+CE. In PD-L1 negative patients (n=75), median OS is 10.5 in atezolizumab+CE and 8.8 in PBO+CE. No reliable conclusions regarding the relationship between PD-L1 IHC status and efficacy can be drawn.

The actual PFS difference was considerably smaller than the expected one.

3.8. Conclusions

The overall B/R of atezolizumab in combination with carboplatin + etoposide is positive as first line treatment for all-comer patients with extensive-stage small cell lung cancer.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus 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, in combination with carboplatin and etoposide, first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) for tecentriq; 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 in accordance. The RMP version 9.1 has been agreed.

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

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers by consensus that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).

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

Extension of Indication to include, in combination with carboplatin and etoposide, first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) for tecentriq; 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 in accordance. The RMP version 9.1 has been agreed.

Summary

Please refer to the Scientific Discussion Tecentriq-H-C-4143-II-0018.