EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 January 2019
EMA/180402/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tecentriq

International non-proprietary name: atezolizumab

Procedure No. EMEA/H/C/004143/II/0007/G

Note

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

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List of abbreviations

Abbreviation	Definition
1L	first-line
2L	second-li ne
ADA	anti-drug antibody (same as anti-therapeutic antibody [ATA])
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
AST	aspartate aminotransferase
AUC	area under the curve
CCOD	clinical cut-off date
Cmax	maximum serum or plasma concentration
Cmin	maximum serum or plasma concentration
CSR	clinical study report
CTL	cytotoxic T lymphocytes
DFS	disease-free survival
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance score
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EU	European Union
HRQoL	Health-Related Quality of Life
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IgG1	immunoglobulin G1
IHC	immunohistochemistry
IND	Investigational New Drug
ITT	intent to treat
ITT-WT	intent-to-treat population with the exclusion of patients with a sensitizing epidermal growth factor mutation or anaplastic lymphoma kinase location
IV	intravenous
IWRES	Individual weighted residuals
MAA	Marketing Authorization Application
mAB	monoclonal antibody
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
pcVPC	prediction-corrected visual predictive checks
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PT	preferred term
q3w	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumours
RMP	Risk Mitigation Plan
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
Teff	T-effector
Teff-high WT	Teff-high population with the exclusion of patients who have a sensitizing epidermal growth factor receptor mutation or anaplastic lymphoma kinase translocation
tGE	tumour gene expression
TKI	tyrosine kinase inhibitor
TSH	thyroid stimulating hormone
UC	urothelial carcinoma
VEGF	vascular endothelial growth

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 12 February 2018 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
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 Tecentriq in combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC), based on the interim results of study GO29436 (IMpower 150). As a consequence sections 4.1, 4.2, 4.8, 5.1, 6.2 and 6.6 of the SmPC are updated. In addition update of section 4.8 of the SmPC in order to update the monotherapy safety data and reflect the largest pooled monotherapy population available (now including also data from study IMvigor211 and PCD4989g studies). The Package Leaflet and the RMP (version 4.0) are updated in accordance. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to make small corrections and formatting changes throughout the SmPC.

The requested group of variations 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 but it was withdrawn during the procedure.

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	12 February 2018
Start of procedure:	3 March 2018
CHMP Co-Rapporteur Assessment Report	27 April 2018
CHMP Rapporteur Assessment Report	27 April 2018
PRAC Rapporteur Assessment Report	3 May 2018
PRAC Outcome	17 May 2018
CHMP members comments	22 May 2018
Updated CHMP Rapporteurs Joint Assessment Report	26 May 2018
Request for supplementary information (RSI)	31 May 2018
Submission of responses	19 July 2018
Procedure re-start	23 July 2018
CHMP Rapporteurs Joint Assessment Report	29 August 2018
PRAC Rapporteur Assessment Report	29 August 2018
PRAC Outcome	6 September 2018
CHMP members comments	10 September 2018
Updated CHMP Rapporteurs Joint Assessment Report	13 September 2018
Request for supplementary information (RSI)	20 September 2018
Submission of responses	30 November 2018
Procedure re-start	3 December 2018
CHMP Rapporteurs Joint Assessment Report	21 December 2018
CHMP members comments	21 January 2019
Updated CHMP Rapporteurs Joint Assessment Report	24 January 2019
Opinion	31 January 2019

2. Scientific discussion

2.1. Introduction

Lung cancer remains the leading cause of cancer death worldwide, estimated to be responsible for nearly one in five cancer deaths globally (1.59 million deaths, 19.4% of the total; Globocan 2012). There were estimated to be 1.8 million new cases in 2012 (12.9% of the total), 58% of which occurred in less developed regions. This disease is the most common cancer in men worldwide (1.4 million, 15% of the total cancers in men) and accounts for the highest absolute number of cancer deaths globally (1.2 million deaths, 24% of cancer deaths in men). Non-small cell lung cancer (NSCLC) is the predominant subtype, accounting for approximately 85% of all cases. NSCLC can be divided into two major histologic types: non-squamous and squamous cell carcinoma. Non-squamous histology accounts for more than half of all NSCLC, whereas squamous histology accounts for approximately 30% (Brambilla et al, 2014 and Schrump DS et al. NSCLC; Principles and Practice of Oncology. 9th Edition. 2011).

For patients who have metastatic NSCLC without an oncogenic driver mutation (such as EGFR mutations or ALK translocation), the standard of care is platinum-based chemotherapy, partnered with agents such as taxanes (paclitaxel, docetaxel), vinorelbine, gemcitabine, and pemetrexed, with or without bevacizumab.

The most common oncogenic driver mutations in NSCLC are EGFR mutations, seen in 10-15% of Western patients and 30-50% of East Asian patients. To date, the tyrosine kinase inhibitors (TKIs) erlotinib, gefitinib, afatinib, and, more recently, osimertinib, represent the standard treatments for EGFR-mutated NSCLC and have dramatically improved the prognosis of NSCLC patients who harbour these mutations. A smaller subset of NSCLC patients (2-6%) harbours the anaplastic lymphoma kinase (ALK) translocation, which is also an oncogenic driver in NSCLC. The first generation ALK inhibitor crizotinib and, more recently, alectinib, a second generation ALK inhibitor are now approved for the 1L treatment of ALK+ NSCLC. For both EGFR mutant tumours and tumours with ALK translocation, the standard of care after failure of TKIs is platinum-based chemotherapy.

Over the past 4 years, immune checkpoint inhibitors, such as PD-1/PD-L1 blocking antibodies, have emerged as effective alternatives to chemotherapy for many tumor types. In 2L+ NSCLC, PD-1 inhibitors (nivolumab, pembrolizumab) and PD-L1 inhibitors (atezolizumab) demonstrated superiority over docetaxel as monotherapy. Subsequently, it was also shown that pembrolizumab monotherapy is effective in the first line setting for patients who express high levels of PD-L1. Pembrolizumab is currently approved for 1L treatment of NSCLC patients whose tumors express high levels of PD-L1 (≥ 50% tumor proportion score).

Tecentriq (atezolizumab) is an Fc-engineered humanized IgG1 monoclonal antibody (MAb) that binds to programmed death−ligand 1 (PD-L1) and blocks interaction of programmed death-1 (PD-1) and PD-L1 (B7-H1) ligands.

In the European Union (EU), atezolizumab has been granted Marketing Authorization for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior platinum containing chemotherapy (provided that patients with EGFR activating mutations or ALK positive tumour mutations should also have received targeted therapy before receiving Tecentriq), and for the treatment of adult patients with locally advanced or metastatic UC after treatment with platinum containing chemotherapy or who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%.

The current submission supports the extension of the licensed indication to the use of atezolizumab in combination with bevacizumab, carboplatin, and paclitaxel for the treatment of chemotherapy-naïve patients with metastatic, non-squamous NSCLC. The evidence comes from IMpower150 (GO29436), a

Phase III trial comparing the efficacy and safety of atezolizumab in combination with carboplatin + paclitaxel with (Atezo + Bev + CP) or without (Atezo + CP) bevacizumab, versus carboplatin + paclitaxel + bevacizumab (Bev + CP), in metastatic non-squamous NSCLC in the first-line (1L) setting.

The following indication was adopted by the CHMP:

"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"

During the induction phase, the recommended dose of Tecentriq is 1,200 mg administered by intravenous infusion, followed by bevacizumab, paclitaxel, and then carboplatin every three weeks for four or six cycles.

The induction phase is followed by a maintenance phase without chemotherapy in which 1,200 mg Tecentriq followed by bevacizumab, is administered by intravenous infusion every three weeks (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 a protein, which 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 an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

2.2.2. Discussion and conclusion on non-clinical aspects

The applicant did not submit studies for the ERA. According to the 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 (Data cutoff date) [a]
Pivotal Study						
GO29436 (IMpower150)	Phase III, open-label, randomized 1:1:1 to Bev + CP vs. Atezo + Bev + CP vs. Atezo + CP	1L chemotherapy-naive non-squamous patients, stratified by sex (male vs. female), presence of liver metastases at baseline (yes vs. no), and PD-L1 tumor expression by IHC (TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1).	Total: n = 1202 n=400 Bev + CP n=400 Atezo + Bev + CP n=402 Atezo + CP	Atezo fixed dose of 1200 mg IV q3w until loss of clinical benefit Bevacizumab 15 mg/kg IV until disease progression Carboplatin AUC of 6 mg/mL/min and Paclitaxel 200 mg/m^2 IV until disease progression	Overall survival and investigator-assessed PFS per RECIST v1.1	After 517 PFS events had been observed in the ITT–WT population in the combined Bev + CP and Atezo + Bev + CP arms (15 September 2017)

2.3.2. Pharmacokinetics

The PK objectives for the IMpower150 study were the following:

- To characterize the PK of atezolizumab when given in combination with carboplatin and paclitaxel with and without bevacizumab (Arms A and B)
- To characterize the PK of carboplatin when given in combination with paclitaxel with and without atezolizumab and/or bevacizumab (Arms A, B, and C)
- To characterize the PK of paclitaxel when given in combination with carboplatin with and without atezolizumab and/ or bevacizumab (Arms A, B, and C)
- To characterize the PK of bevacizumab when given in combination with carboplatin and paclitaxel with and without atezolizumab (Arms B and C)

Analytical methods

Plasma concentrations of paclitaxel were determined by a validated liquid chromatography tandem mass spectrometry (LC-MSMS) method with Paclitaxel-d5 as an internal standard and ranged from 2-2500 ng/mL. Covance, Madison US.

Carboplatin plasma concentrations were determined by quantitation of platinum using a validated inductively coupled plasma tandem mass spectrometry (ICP-MS) method with Iridium as an internal standard. The method ranged from 100-10,000 ng/mL Archinova, UK.

A validated indirect sandwich ELISA was used to quantify atezolizumab in human serum.

The method for the quantification of bevacizumab concentrations was an enzyme-linked immunosorbent assay.

Anti-drug antibody (ADA) testing

All ADA samples were screened in validated bridging enzyme-linked immunosorbent assays (ELISA). Atezolizumab ADA testing was conducted at ICON Laboratory Services, Inc. (ICON). Bevacizumab ADA testing was conducted at QPS, Netherlands B.V.

Any sample that was deemed positive by the screening ADA assay was assessed for ADA specificity to the specific molecule (atezolizumab or bevacizumab) using a confirmatory competitive bridging ELISA. Samples that were confirmed positive were then serially diluted to obtain a titer value.

Using a surrogate positive control antibody, the relative sensitivity of the atezolizumab ADA screening assay was determined to be 20.4 ng/mL in the absence of atezolizumab. The ADA screening assays were

able to detect 500 ng/mL of the surrogate positive control in the presence of 200 µg/mL atezolizumab to enable the detection of ADAs in the presence of high trough levels of atezolizumab.

Using a surrogate positive control antibody, the relative sensitivity of the bevacizumab ADA screening assay was determined to be 7.72 ng/mL in the absence of bevacizumab. The ADA screening assays were able to detect 500 ng/mL of the surrogate positive control in the presence of 100 µg/mL bevacizumab to enable the detection of ADAs in the presence of high trough levels of bevacizumab.Pharmacokinetic data

The descriptive statistics of the available Cmax (30 minutes following the end of the infusion in Cycle 1 or Cycle 3) and Cmin (pre-dose) concentrations of atezolizumab in serum for the Atezo+CP arm and Atezo +Bev +CP arm following 1200 mg q3w IV administration are summarized in Table 1. Steady state based on trough concentration (Cmin) was reached by approximately Cycle 3.

Table 1: Summary statistics for atezolizumab Cmax and Cmin following multiple IV doses of atezolizumab 1200 mg given every 3 weeks in combination with carboplatin and paclitaxel with or without bevacizumab

Treatment	Visit[1]	Nominal Time From First Dose (day)	N[2]	AM (µg/mL)	AM SD (µg/mL)	GM (µg/mL)	GM %CV	Min (µg/mL)	Median (µg/mL)	Max (µg/mL)
Atezo+Bev+CP	C1D1	0	369	NA	NA	NA	NA	NA	0.00	332
	C1D1	0.0625	364	414	127	345	194	0.0300	407	937
	C1D21	21	345	80.8	41.4	70.1	75.4	0.100	79.5	478
	C2D21	42	319	130	57.1	114	82.8	0.0300	124	451
	C3D1	42.04	302	540	198	507	38.5	55.5	514	2530
	C3D21	63	307	160	102	139	65.5	4.25	146	1420
	C7D21	147	249	220	99.0	196	58.1	9.28	214	913
Atezo+CP	C1D1	0	389	NA	NA	NA	NA	NA	0.00	440
	C1D1	0.0625	378	410	157	357	134.5	0.0300	392	1950
	C1D21	21	354	76.4	37.7	62.2	120.4	0.0300	75.7	428
	C2D21	42	322	119	55.7	95.8	125.6	0.0300	119	336
	C3D1	42.04	310	498	160	460	67.3	0.0642	485	1360
	C3D21	63	312	146	58.9	129	72.0	0.226	142	341
	C7D21	147	230	219	89.6	195	82.6	0.0300	206	672

[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 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.

[2] N = number used to calculate statistics; AM = Arithmetic Mean; SD = standard deviation; CV = coefficient of variation; GM = Geometric Mean; NA = Not Available

Data source: t_pkct01_RO554_PKEV in the IMpower150 CSR.

The mean serum atezolizumab concentrations over time by arm, are shown in Figure 1. The mean concentration time profiles of atezolizumab in the Atezo+ CP arm and Atezo +Bev +CP arm were similar.

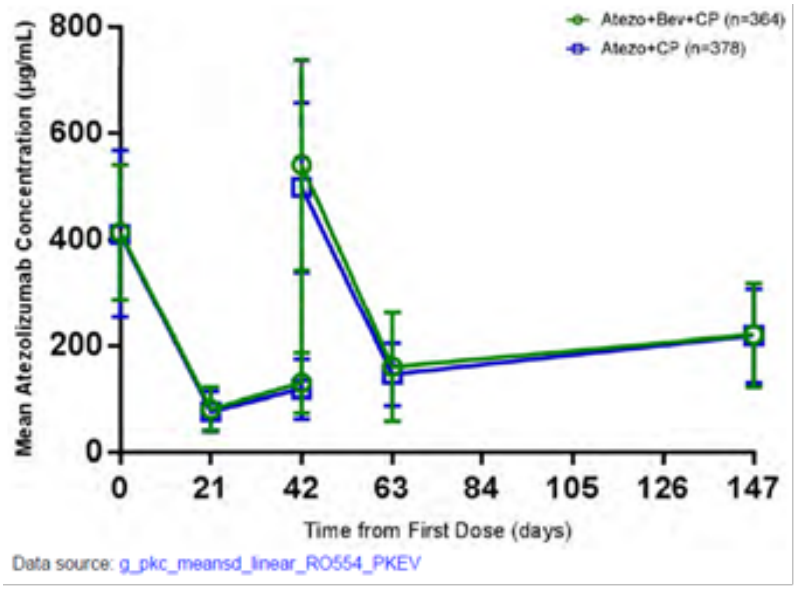


Figure 1: Mean (±SD) plot of atezolizumab concentrations versus time following multiple IV doses of atezolizumab 1200 mg given every 3 weeks in combination with carboplatin and paclitaxel with or without bevacizumab

ADA results from IMpower150

The baseline prevalence of atezolizumab ADAs was 2.9% in the Atezo +Bev +CP arm and 4.6% in the Atezo +CP arm for atezolizumab-treated patients with a baseline ADA sample. The post-baseline treatment-emergent ADA incidences were comparable in both arms where patients received atezolizumab, with ADA-positive incidences of 36.4% in the Atezo +Bev +CP arm and 38.5% in the Atezo +CP arm. Average atezolizumab Cmin for both ADA-positive and ADA-negative patients appeared to approach a plateau (or steady-state) between 4–8 cycles of dosing. There was a consistent trend for lower exposure in ADA-positive patients, but Cmin for both groups was in excess of the target serum concentration of 6 µg/mL.

Of 787 ADA evaluable patients in the safety evaluable population, one patient had a positive, treatment induced bevacizumab ADA and the baseline prevalence was <2%.

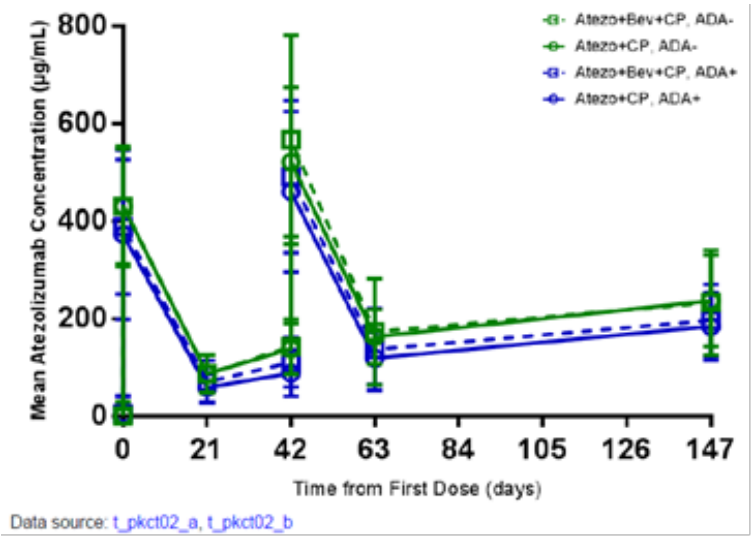


Figure 2: Mean (±SD) plot of atezolizumab concentrations versus time following multiple IV doses of atezolizumab 1200 mg given every 3 weeks in combination with carboplatin and paclitaxel with or without bevacizumab by ADA status

The individual atezolizumab minimum plasma concentration (Cmin) for treatment-emergent anti-drug antibody (ADA)–positive subjects (at Week 4 landmark) in the low exposure group (Cmin <median) for each arm: n=51 in the Atezo+Bev+CP arm (Cycle 1 Cmin [C1Cmin] ranged from 28–75.3 μg/mL); n=59 in the Atezo+CP arm (C1Cmin ranged from 6.05–68.9 μg/mL.

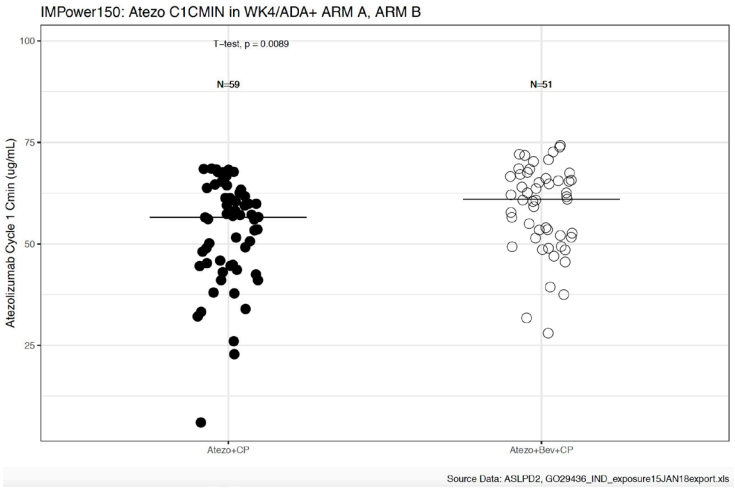


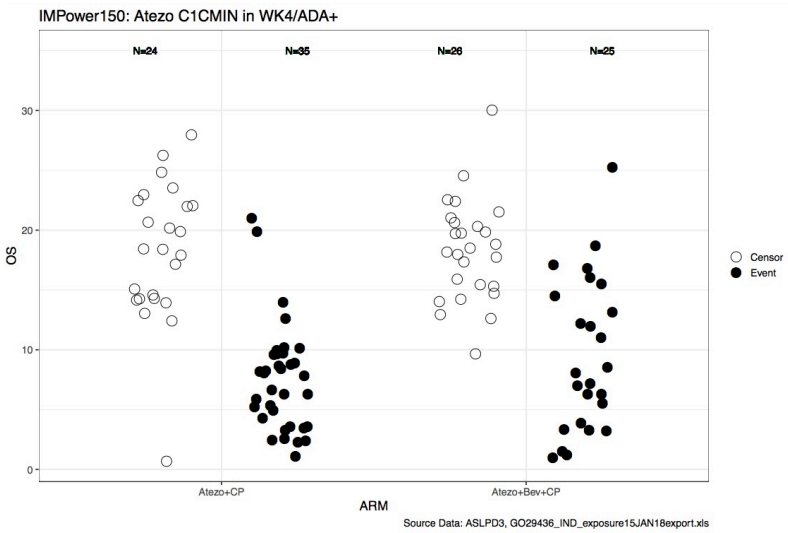
Figure 3: Model-Predicted Individual Cycle 1 C_{min} in ADA+ Patients, Low-Exposure Group (C_{min} <median) for Arm A (Atezo+CP) and Arm B (Atezo+Bev+CP)

The best overall response (BOR) and the distribution of overall survival in ADA+ low-exposure group for Arm B (Atezo+Bev+CP) and Arm A (Atezo+CP) were submitted (see below).

Table 2: **Summary of Best Overall Response in ADA+ Patients, Low-Exposure Group (C_{min} <Median) for Arm A (Atezo+CP) and Arm B (Atezo+Bev+CP)**

IMpower150 Study	Atezo+Bev+CP Arm B (N=51)	Atezo+CP Arm A (N=59)
CR	3 (5.9%)	0
PR	26 (51%)	22 (37.3%)
SD	14 (27.5%)	19 (32.2%)
PD	3 (5.9%)	15 (25.4%)

ADA=anti-drug antibody; Atezo=atezolizumab; Bev=bevacizumab; CP=carboplatin and paclitaxel; CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.
Note: In Arm A, 2 patients were not evaluable and 1 patient was missing overall response; in Arm B, 2 patients were not evaluable and 3 patients were missing overall response.



ADA=anti-drug antibody; Atezo=atezolizumab; Bev=bevacizumab; CP=carboplatin and paclitaxel; OS=overall survival.
Figure 4: Individual Plot of Overall Survival in ADA-Positive, Low Exposure Group by Treatment (Arm A: Atezo+CP and Arm B: Atezo+Bev+CP)

2.3.3. PK/PD modelling

Overview of population Pharmacokinetics

The popPK of atezolizumab was first assessed based on Phase I data from two clinical studies PCD4989g and JO28944 (n = 472 patients, 4563 PK samples). This "Phase I popPK Model" was subsequently subjected to an external evaluation with the use of atezolizumab PK data collected in Study IMpower150.

The objectives of this analysis were to:

- Assess the PK of atezolizumab in chemotherapy naive patients with non-squamous NSCLC in Study IMpower150 through external evaluation of the Phase 1 popPK Model
- Derive exposure metrics of atezolizumab in chemotherapy naive non-squamous NSCLC patients in the IMpower150 study
- Explore the potential impact of chemotherapy with or without bevacizumab coadministration on atezolizumab PK

The IMpower150 population PK dataset included 4386 evaluable atezolizumab serum concentrations from 778 patients with NSCLC receiving 1200 mg of atezolizumab q3w by IV infusion. In the Atezo+CP Arm, there were 395 patients receiving both atezolizumab and chemotherapy (carboplatin+paclitaxel) and 383 patients in the Atezo+Bev+CP Arm who received Atezolizumab+chemotherapy+bevacizumab.

Population PK analysis was performed using a non-linear mixed-effects modelling approach with NONMEM, Version 7.3 (ICON Development Solutions, USA). Perl-Speaks-NONMEM (PsN) (Version 3.7.6 Uppsala University, Uppsala, Sweden) was used to evaluate/validate the population PK model using predictive checks. Data exploration and visualization as well as descriptive statistics were performed using R+ V3.3.1 in addition to Comprehensive R Archive Network (CRAN) packages.

A population PK model of atezolizumab developed previously using Phase 1 data was used to predict IMpower150 data and to derive the individual Bayesian post-hoc PK parameter estimates based on the observed time-concentration profiles in IMpower150 data. The atezolizumab Phase 1 popPK model was a two-compartment disposition model with first-order elimination including covariate effects. The model used was the final model including covariate effects.

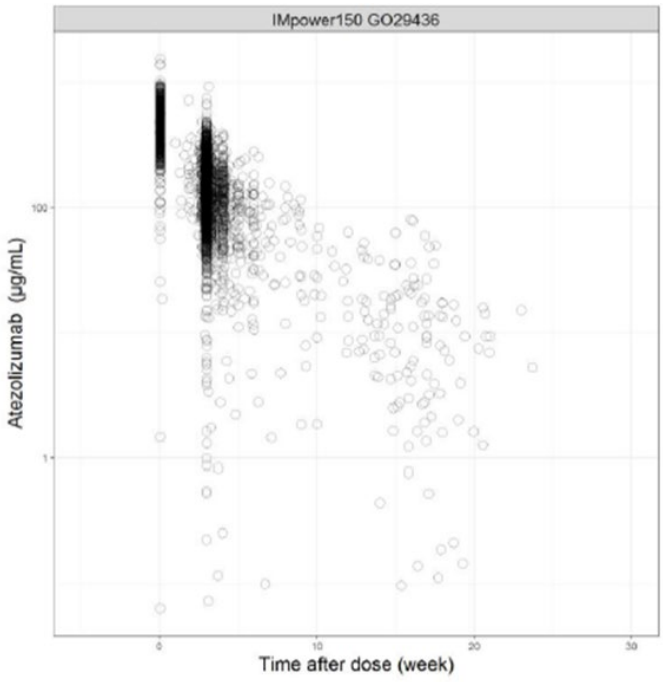


Figure 5: Graphical data exploration of atezolizumab concentration data in the study IMpower150

The number of evaluable PK concentrations (with concentrations above the assay LOQ), excluded samples, samples below the limit of quantification (BLQ) as well as the total number of patients included in the analysis are presented in Table 4. Serum atezolizumab concentrations versus time were explored graphically for identification of outliers. Of the 778 patients included in the population PK dataset, the ratio of males to females was 468:310 (60.2% male). Median age was 63 years (range: 31-89 years) and body weight ranged from 37 to 196 kg. Approximately 81.5% of the patients were white.

Table 3: Number of PK samples and patients included or excluded in the atezolizumab analysis

	Number of patients in the dataset			Number of PK samples in the dataset			
Study / Arm	Total	No Eval PK	Eval	Total	Excl	Eval	BLQ
IMpower150	788♯	10	778 (99%)	5303**	103 (2%)	4386 (83%)	814 (15%)
Atezo+CP Arm	398	3	395 (99%)	2685	50 (2%)	2217 (83%)	418 (16%)
Atezo+Bev+CP Arm	390	7	383 (98%)	2618	53 (2%)	2169 (83%)	396 (15%)

Eval = patient or sample evaluable; Excl = sample excluded (DV greater than 0); No Eval PK = Patients without any evaluable PK sample; BLQ = number of BLQ concentrations, not used for the analysis.
** sum of Exclusion + evaluable + BLQ
♯ Number of patients in "p29436k_poppk_20180112.csv" file
Atezo + CP Arm = Atezolizumab + carboplatin + paclitaxel
Atezo + Bev + CP Arm = Atezolizumab + bevacizumab + carboplatin + paclitaxel

Covariates

Missing covariates values, when missing in less than 15% of the total number of patients, were imputed to median values by gender for continuous covariates or to the most frequent category for categorical covariates. No unexpected covariate effect was identified in the IMpower150 study. Exploratory analyses of the relationships between individual CL, V1 and V2 patient-level random effects and covariates (continuous, categorical, and including body weight, albumin, tumor burden, gender, and ATAG) indicated that covariate effects in IMpower150 data were generally consistent with those identified in the Phase 1 popPK Model. For any observed trends, no effect reached $p < 0.001$.

Model diagnostics

The ability of the Phase 1 popPK Model to describe atezolizumab PK in NSCLC patients was evaluated by external prediction-corrected visual predictive checks (pcVPC) based on atezolizumab concentrations from 778 patients out of 802 ITT patients (97%). The pcVPC was performed using Cmax and Cmin atezolizumab data by grouping peak or trough samples for the entire period of treatment. Only the IMpower150 PK visits with at least 40 samples were displayed on the plots. Using time-after-dose, peaks were defined for samples occurring between 0.01 and 1-day post-dose while troughs were defined for samples occurring between 10 and 30 days post-dose. PK samples from the visit 120 days after the last dose were not used for the evaluation. For each peak/trough grouping, 95% prediction intervals (PIs) of the 5th, 50th and 95th percentiles of simulated concentrations were computed across 1000 replicates and compared to the 5th, 50th and 95th percentiles of observed concentrations.

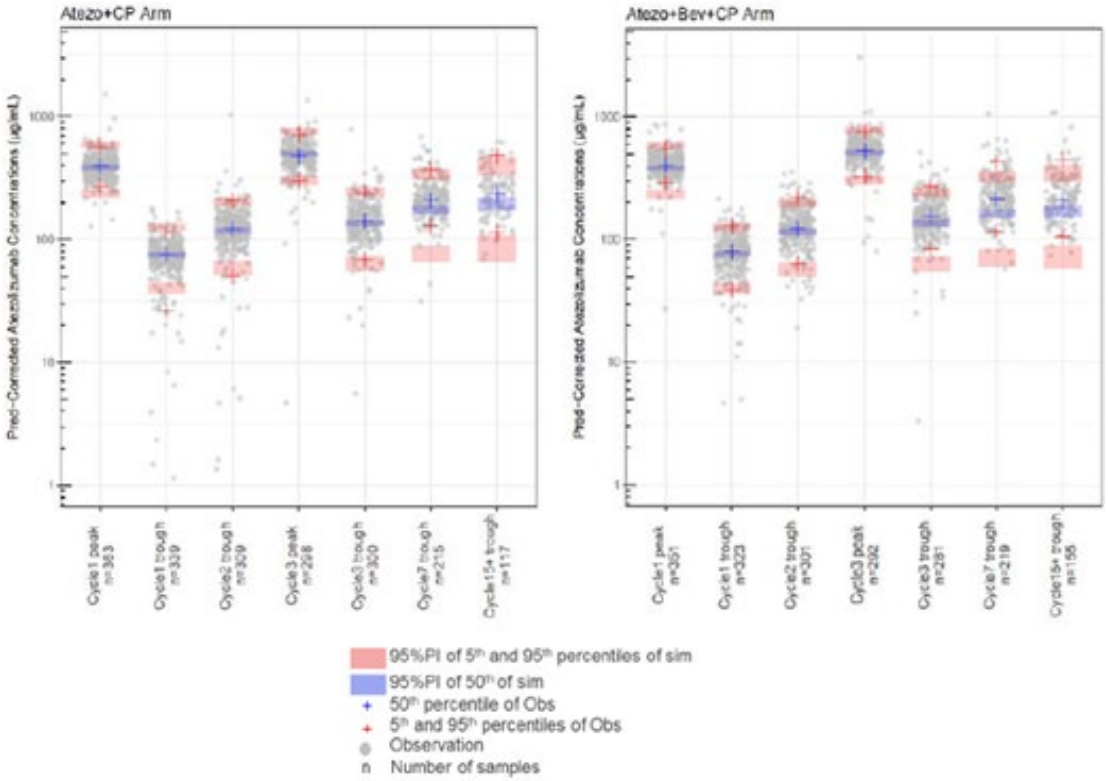


Figure 6: Prediction-corrected VPC of peaks and troughs of atezolizumab stratified y arm (semi-log scale)

The pcVPC as external evaluation revealed an adequate performance of the model for the peak and the troughs of Cycle 1 to 3. A trend to under-prediction of the exposure was observed after long-term treatment.

The 90% PIs of the concentration-time profiles over 50 weeks and concentration versus time-after-dose (cycle 5 and later) profiles, were simulated across 100 replicates and compared to observed concentrations. The atezolizumab concentrations from the visit, "120 days after the last dose" were included.

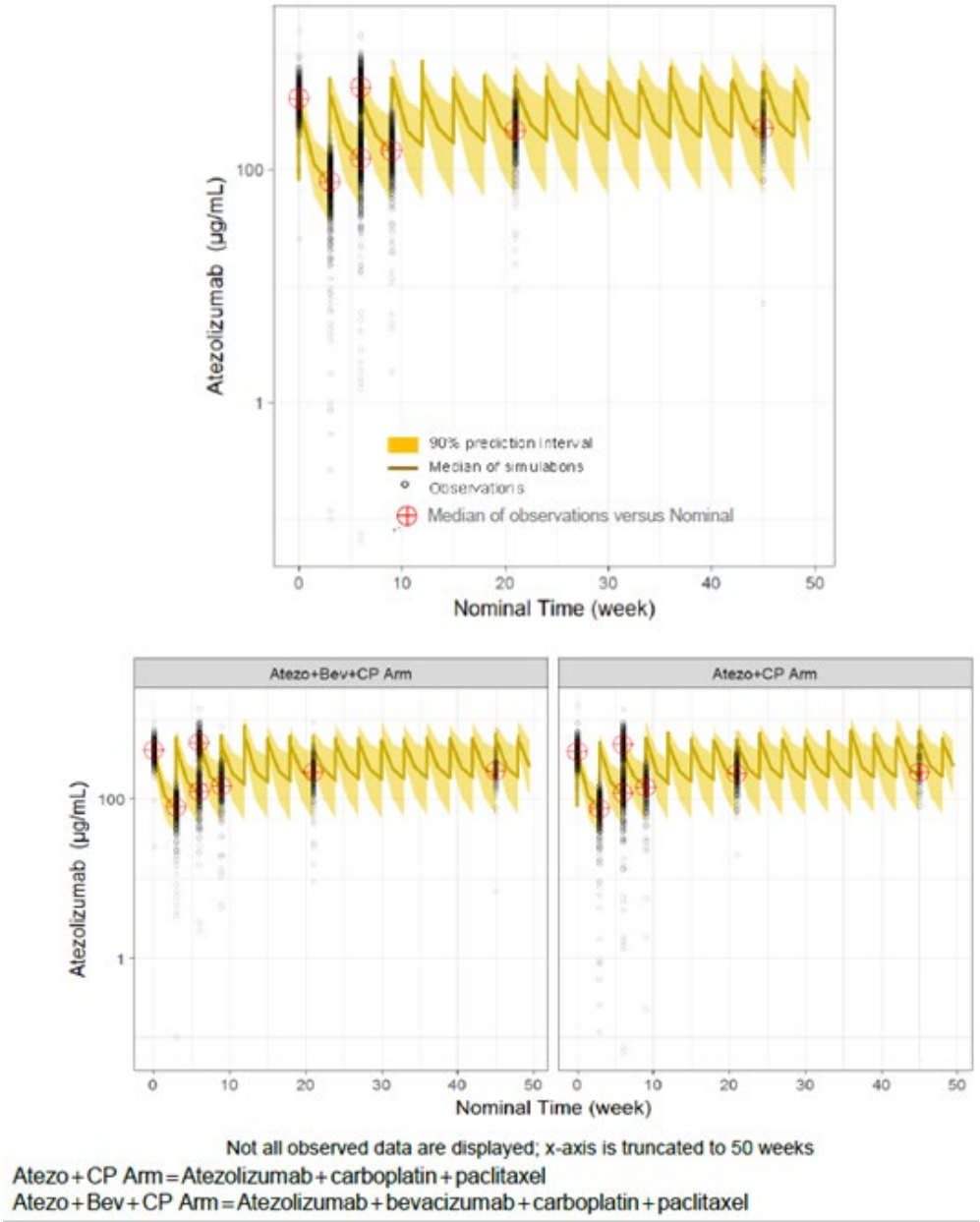
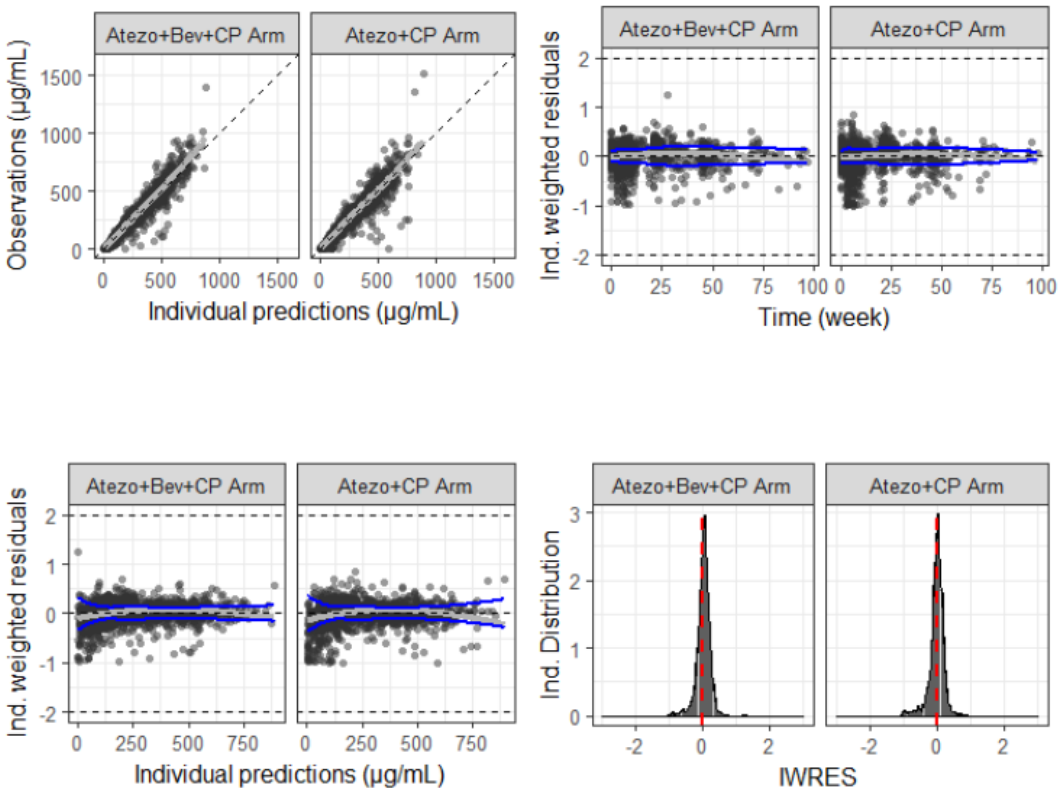


Figure 7: 90% prediction interval of the PK profile using the Phase I PopPK model with IMpower150 observed concentrations

The goodness-of fit plots suggested that the model was able to describe the PK profiles well without re-estimating the Phase 1 popPK Model population parameters. No trends were observed in goodness-of fit plots at the individual level after post-hoc Bayesian estimation, indicating that the Phase 1 popPK Model allowed reliable estimates of individual parameters in Phase 3 patients.



Grey lines are LOESS (locally weighted scatterplot smoothing);
Blue lines are LOESS in positive or negative residuals
One IWRES>20 is not displayed
Atezo+CP Arm = Atezolizumab + carboplatin + paclitaxel
Atezo+Bev+CP Arm = Atezolizumab + bevacizumab + carboplatin + paclitaxel

Figure 8: Goodness-of-fit for the Phase I PopPK model from IMpower150 at individual level stratified by arm

Estimation of atezolizumab exposure

Individual CL, V1 and V2 patient-level random effects estimated with the Phase 1 popPK Model were used to predict atezolizumab concentration profiles and calculate exposure metrics both at Cycle 1 and Cycle 10 (steady state). The predicted cycle 1 and steady-state PK profiles for each individual were based on the starting dose (dose on Day 1 given q3w, and the actual duration of infusion for cycle 1, then 30 min of infusion for all the subsequent doses and time points: 0, every 0.01 day for the first 3 days, every 0.5 days until 20.99 days post-dose at cycle 1 and at steady-state.

Table 4: Summary statistics (geometric mean [geometric mean CV%]) of atezolizumab exposure metrics at cycle 1 predicted using PopPK model

Study (N)/Arm (N)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC (µg.day/mL)	t1/2 beta (day)*
IMpower150 (N = 778)	393 [20.7]	77.1 [32.6]	2981 [21.6]	22.9 [8.23]
IMpower150, Atezo+CP Arm (N = 395)	388 [21.2]	75.0 [35.7]	2932 [22.7]	22.3 [7.74]
IMpower150, Atezo+Bev+CP Arm (N = 383)	398 [20.2]	79.4 [29.0]	3032 [20.3]	23.5 [8.69]

N = Number of patients; C_{max} = C_{max} at cycle 1; C_{min} = C_{min} at cycle 1; AUC = $AUC_{(0\text{-}21)}$ at cycle 1;
CV% = coefficient of variation; *t1/2 beta is the terminal half-life based on post-hoc parameter estimates; for this parameter harmonic mean and standard deviation are reported;
Atezo + CP Arm = Atezolizumab + carboplatin + paclitaxel;
Atezo + Bev + CP Arm = Atezolizumab + bevacizumab + carboplatin + paclitaxel

Table 5: Summary statistics (geometric mean [geometric mean CV%]) of atezolizumab exposure metrics at steady state predicted using PopPK model

Study (N)/Arm (N)	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)	$AUC_{,ss}$ (µg.day/mL)	Accumulation ratio
IMpower150 (N=778)	578 [24.7]	176 [50.1]	5864 [34.8]	1.97 [18.7]
IMpower150, Atezo+CP Arm (N=395)	567 [25.9]	169 [54.9]	5696 [37.0]	1.94 [19.1]
IMpower150, Atezo+Bev+CP Arm (N=383)	590 [23.3]	184 [44.4]	6042 [32.0]	1.99 [18.2]

N=Number of patients; $C_{max,ss}=C_{max}$ at steady-state; $C_{min,ss}=C_{min}$ at steady-state; $AUC_{,ss}$=AUC at steady-state; Accumulation ratio is derived as the ratio between AUC at cycle 1 and $AUC_{,ss}$;
CV%=coefficient of variation;
Atezo + CP Arm=Atezolizumab + carboplatin + paclitaxel
Atezo + Bev + CP Arm=Atezolizumab + bevacizumab + carboplatin + paclitaxel

2.3.4. Discussion and conclusion on clinical pharmacology

The covariate effects in IMpower150 data were consistent with those identified in the Phase I popPK Model. Atezolizumab ADA-positive patients (about one third of all patients) experienced lower atezolizumab exposure expressed as Cmin (about 20%) than ADA-negative but all in excess of the target serum concentration (6 µg/mL).

Due to the low sample size in the ADA-positive population (n=101 in the Atezo+Bev+CP arm and n=96 in the Atezo+CP arm), the Applicant provided the exposure-response (ER) OS analyses in two exposure groups divided by median first cycle Cmin (High: Cmin ≥ median; Low: Cmin <median). (data not shown)

The Applicant presented, upon request, an overview of post baseline incidence of ADA across 8 clinical studies (data not shown). The frequency of % ADA positive seems independent of indication and treatment ranging from 30.4% to 54.5%.

There is a trend towards lower efficacy in the Cmin <median subgroup (without Adjustment of Baseline Imbalanced Prognostic Factors). This is more pronounced in the ADA+ population of the Atezo+CP Arm; the HR (95% PI) for low and high exposure (Cmin) groups were 1.0 (0.74, 1.3) and 0.8 (0.58, 1.1), respectively, in ADA-positive patients who received Atezo + CP after adjustment of prognostic factors (TGI-OS model simulations).

In the data submitted during the procedure, the exposure of ADA+ patients in the low-exposure group (Atezo+CP arm; arm A) was slightly lower compared to that of the Atezo+Bev+CP arm (arm B). It is however agreed that there was a large overlap in exposure range between the two arms; the HR (95% PI) for low and high exposure (Cmin) groups were 0.66 (0.43, 0.93) and 0.71 (0.50, 1.0), respectively, in ADA-positive patients who received Atezo+Bev+CP after adjustment of prognostic factors (TGI-OS model simulations).

Summary of best overall Response in ADA+Patients, Low Exposure Group (Cmin <Median) for Arm A (Atezo+CP) and Arm B (Atezo+Bev+CP) indicated a higher percentage of patients in IMpower150 Study in Arm B showing complete response, partial response and lower percentage regarding progressive disease. Individual plots of overall survival in ADA+ patients indicated comparable results regarding both arms.

Samples collected for ADA evaluation in the IMpower150 study were not evaluated for neutralising ADA's. Although it is considered acceptable that nADA data are not submitted within the present procedure, the Applicant should provide this data post-approval. Furthermore, the MAH is recommended to conduct an assessment of the effect of atezolizumab ADAs on PK and efficacy endpoints including OS, PFS, and ORR in NSCLC Studies POPLAR, OAK, IMpower150, IMpower130, IMpower131, and IMpower132. The MAH has presented an acceptable proposal/plan.

The goodness-of-fit plots for population and individual predictions appeared adequate. Individual weighted residuals (IWRES) were evenly distributed around 0, suggesting no bias in the predictions of high and low concentrations of atezolizumab. The pcVPC revealed the mean atezolizumab concentrations were under-predicted after long term use (after Cycle 3). This effect, not captured by the model, was suggested to be caused by a decrease in clearance and considered as being of no clinical relevance. The Phase 1 popPK Model is suitable to describe the individual PK data from the IMpower150 Study and seems suitable for determination of atezolizumab exposure metrics (Cycle 1 and steady-state) for comparison of the exposure between two treatment arms, with and without bevacizumab, in patients from Study IMpower150.

The mean atezolizumab exposure, expressed as AUC (after a single dose and at steady-state) and achieved after simulation using individual predicted Cl and V1/V2 parameters, were slightly higher in the arm with bevacizumab. The exposure difference between the arms was highest at steady-state but not considered clinically relevant.

The exposure during Cycle 1 and after long-term therapy seems to be similar in both arms: in presence or absence of bevacizumab, indicating no impact of co-administration of bevacizumab on atezolizumab PK. Both cycle 1 and steady-state exposure metrics were similar to those estimated in other NSCLC studies using atezolizumab in monotherapy, which suggested that the atezolizumab exposure is not impacted by the co-administration of the chemotherapy (carboplatin+paclitaxel).

It is agreed that atezolizumab PK is not affected by the presence or absence of bevacizumab.

In order to address the uncertainties in relation to ADA, the MAH is recommended:

-To submit and discuss the neutralising ADA data for both atezolizumab monotherapy and when co-administered with Carboplatin-paclitaxel with or without bevacizumab in IMpower150.

- To submit an assessment of the effect of atezolizumab ADAs on PK and efficacy endpoints including OS, PFS, and ORR in NSCLC Studies POPLAR, OAK, IMpower150, IMpower130, IMpower131, and IMpower132.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No additional dose-response study was performed, and data are limited to those submitted at the time of the initial Marketing Authorisation Application. The 1200 mg Q3W dose was used in the OAK study and therefore approved in 2L-NSCLC.

2.4.2. Main study

IMpower150 (GO29436): A Phase III, open-label, randomized study of atezolizumab (anti-PD-L1 antibody) in combination with carboplatin + paclitaxel with or without bevacizumab compared with carboplatin + paclitaxel + bevacizumab in chemotherapy-naïve patients with stage IV non-squamous non-small cell lung cancer

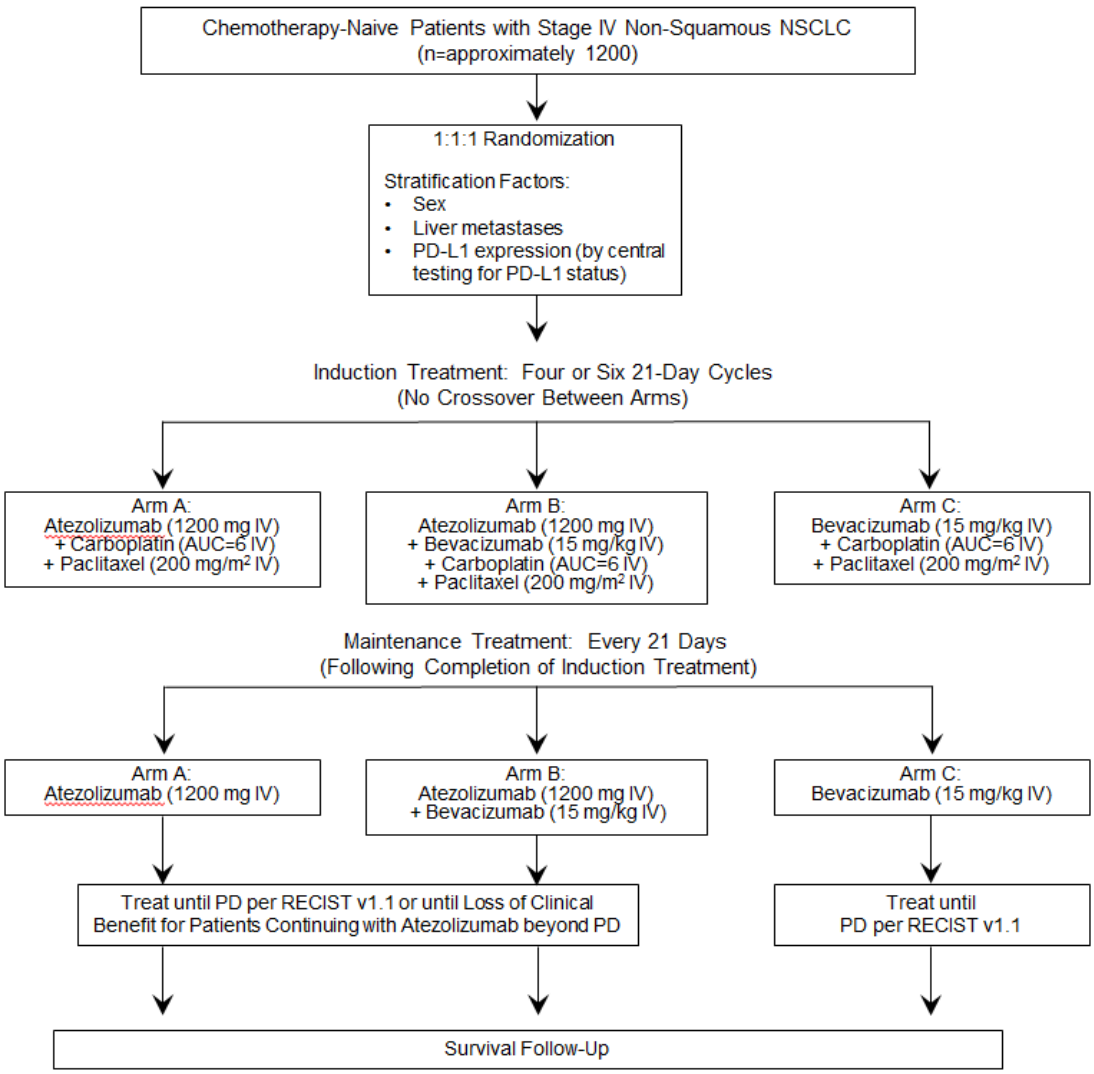
Methods

The study enrolled an "all-comer" patient population, meaning that patients were eligible for the study regardless of their PD-L1 expression level in tumour tissue, and included those with epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase ALK)-positive tumours (EGFR mutant/ALK +). No prior treatment for metastatic non-squamous NSCLC was allowed except for EGFR

mutant/ALK+ patients who had experienced progressive disease (PD) (during or after treatment) or intolerance to treatment with one or more EGFR or ALK tyrosine kinase inhibitors (TKIs), respectively.

Patients were randomized in a 1:1:1 ratio to one of the following treatment regimens:

- Arm A treatment: atezolizumab +carboplatin + paclitaxel (Atezo + CP) (induction: four or six 21-day cycles); atezolizumab (maintenance: 21-day cycles)
- Arm B treatment: atezolizumab + bevacizumab + carboplatin+ paclitaxel (Atezo + Bev + CP) (induction: four or six 21-day cycles); atezolizumab + bevacizumab (maintenance: 21-day cycles)
- Arm C treatment: bevacizumab + carboplatin+ paclitaxel (Bev + CP) (induction: four or six 21-day cycles); bevacizumab (maintenance: 21-day cycles)



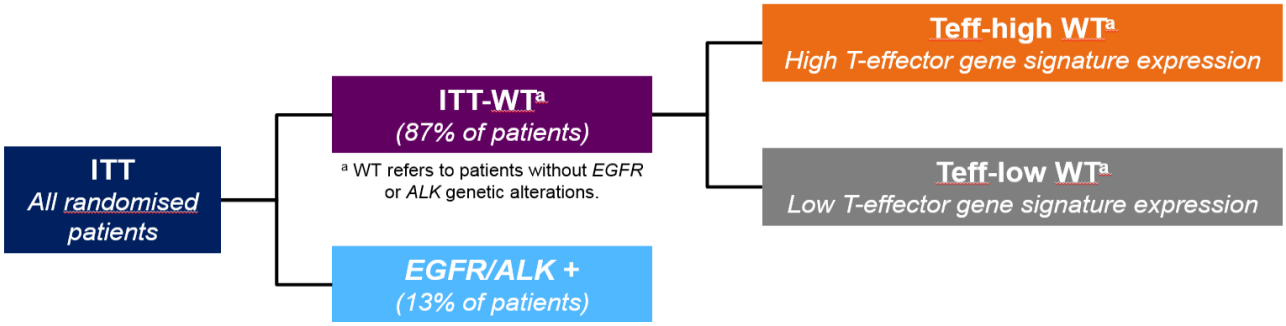
The ITT population is defined as all randomized patients, regardless of receipt of the assigned treatment.

The ITT–WT population is defined as the ITT population excluding patients with an activating EGFR mutation or ALK translocation. As stated in the SAP, sensitizing EGFR mutations include all activating EGFR in exons 18 through 21.

The Teff gene signature population is defined using expression of a T-effector gene signature in tumor tissue, as analyzed using a centrally performed (Targos), quantitative, real-time, polymerase chain

reaction based clinical trial assay developed by Roche Molecular Systems. This signature is defined by the average mRNA expression of 3 genes—PD-L1 (CD274), CXCL9, and IFN-γ, normalized to a reference gene. It is a surrogate for both PD-L1 expression and a pre-existing immunity within the tumour microenvironment (Kowanetz et al, 2017). The Teff-high population is defined as patients in the ITT population with Teff signature expression ≥ – 1.91. On the converse, the Teff-low population is defined as ITT patients with Teff signature expression <–1.91.

The Teff-high WT population is defined as the Teff-high population excluding patients with an activating EGFR mutation or ALK translocation.



The PD-L1 population is defined as one of the following: TC2/3 or IC2/3 population, defined as ITT patients with PD-L1 TC2/3 or IC2/3 expression in baseline tumor tissue; PD-L1 TC1/2/3 or IC1/2/3 population is defined as ITT patients with PD-L1 TC1/2/3 or IC1/2/3 expression in baseline tumor tissue.

The PD-L1 WT populations are defined as the PD-L1 populations (TC2/3 or IC2/3 population or TC1/2/3 or IC1/2/3 population) excluding patients with an activating EGFR mutation (see above) or ALK translocation.

*PD-L1 populations: To asses PD-L1 status, sections from tumour specimens from eligible patients were prospectively stained and evaluated by an external central laboratory using the VENTANA PD-L1 (SP142) IHC assay, according to scoring algorithm measuring PD-L1 on tumor cells (TC) and tumor-infiltrating immune cells (IC) (see the following Table). Patients were subsequently stratified at TC3 or IC2 cut-off at enrollment. TC1/2/3 or IC1/2/3, as well as TC2/3 or IC2/3 scores used for the secondary endpoint analyses were determined from re-reads to corresponding cut-offs prior to database lock for the primary PFS analysis, using the same previously PD-L1 stained tumor sections from the enrollment. TC3 or IC3 scores were derived from raw percentage scores also prior to the database lock.

Table 6: Criteria for PD-L1 expression assessment

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

Study participants

Inclusion Criteria:

- Male or female, 18 years of age or older
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Histologically or cytologically confirmed, Stage IV non–squamous NSCLC
- No prior treatment for Stage IV non–squamous NSCLC
    - Patients with a sensitizing mutation in the EGFR gene had to have experienced PD (during or after treatment) or intolerance to treatment with one or more EGFR TKIs.
    - Patients with an ALK fusion oncogene had to have experienced PD (during or after treatment) or intolerance to treatment with one or more ALK inhibitors.
- Patients who had received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease had to have experienced a treatment-free interval of at least 6 months from randomization since the last chemotherapy, radiotherapy, or chemoradiotherapy.
- Patients with a history of treated asymptomatic CNS metastases were eligible, provided they met all of the following criteria:
    - Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)
    - No ongoing requirement for corticosteroids as therapy for CNS disease

- No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomization
- No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
- Patients with new asymptomatic CNS metastases detected at the screening scan had to have received radiation therapy and/or surgery for CNS metastases.

• Known PD-L1 tumour status as determined by an IHC assay performed by a central laboratory on previously obtained archival tumour tissue or tissue obtained from a biopsy at screening.

• Measurable disease, as defined by RECIST v1.1

- Previously irradiated lesions could only be considered as measurable disease if PD 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, defined by the following laboratory results obtained within 14 days prior to randomization:

- ANC $\geq$ 1500 cells/μL without granulocyte colony-stimulating factor support
- Lymphocyte count $\geq$ 500/μL
- Platelet count $\geq$ 100,000/μL without transfusion
- Hemoglobin $\geq$ 9.0 g/dL
- INR or aPTT $\leq$ 1.5 $\times$ upper limit of normal (ULN)
- $\leq$ 2.5 $\times$ ULN, with the following exceptions:
  - Patients with documented liver metastases: AST and/or ALT $\leq$ 5 $\times$ ULN
  - Patients with documented liver or bone metastases: alkaline phosphatase $\leq$ 5 $\times$ ULN.
- Serum bilirubin $\leq$ 1.25 $\times$ ULN
- Patients with known Gilbert disease who had serum bilirubin level $\leq$ 3 $\times$ ULN could be enrolled.
- Serum creatinine $\leq$ 1.5 $\times$ ULN

• For female patients of childbearing potential and male patients with female partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception

<u>Exclusion criteria:</u>

• Active or untreated CNS metastases as determined by 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 $>$ 2 weeks prior to randomization

• Leptomeningeal disease

• Uncontrolled tumour-related pain

• Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

- Uncontrolled or symptomatic hypercalcemia > 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected serum calcium > ULN)
- Patients who were receiving denosumab prior to randomization had to be willing and eligible to receive a bisphosphonate instead while in the study.
- Malignancies other than NSCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative intent.
- Known tumour PD-L1 expression status as determined by an IHC assay from other clinical studies
- Women who were pregnant, lactating, or intending to become pregnant during the study
- 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 autoimmune disease.
- 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 for HIV
- Patients with active hepatitis B or hepatitis C
- Active tuberculosis
- Severe infections within 4 weeks prior to randomization
- Received therapeutic oral or IV antibiotics within 2 weeks prior to randomization
- Significant cardiovascular disease
- 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
- Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation that such a live attenuated vaccine would be require during the study
- 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 rendered the patient at high risk from treatment complications
- Patients with illnesses or conditions that interfered with their capacity to understand, follow and/or comply with study procedures
- Treatment with any approved anti-cancer therapy, including hormonal therapy, within 3 weeks prior to initiation of study treatment; the following exceptions were allowed:
    - TKIs approved for treatment of NSCLC discontinued > 7 days prior to randomization; the baseline scan had to be obtained after discontinuation of prior TKIs.

- Treatment with any other investigational agent with therapeutic intent within 28 days prior to randomization
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti–PD-1, and anti–PD-L1 therapeutic antibodies
    - Patients who had prior anti–CTLA-4 treatment could be enrolled
- Treatment with systemic immunostimulatory agents (including but not limited to interferons, interleukin-2) within 4 weeks or five half-lives of the drug, whichever was longer, prior to randomization. Prior treatment with cancer vaccines was allowed.
- Treatment with systemic immunosuppressive medications within 2 weeks prior to randomization.
- Inadequately controlled hypertension.
- Prior history of hypertensive crisis or hypertensive encephalopathy
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to randomization
- History of hemoptysis ($\geq$ one-half teaspoon of bright red blood per episode) within 1 month prior to randomization.
- Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (within 10 days of randomization) use of aspirin ($>$ 325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, and cilostazol
- Current use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes that had not been stable for $>$ 2 weeks prior to randomization
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to the first dose of bevacizumab
- History of abdominal or tracheosphageal fistula or gastrointestinal perforation within 6 months prior to randomization
- Clinical signs of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding
- Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
- Serious, non-healing wound, active ulcer, or untreated bone fracture
- Proteinuria, as demonstrated by urine dipstick or $>$ 1.0 g of protein in a 24-hour urine collection
- Known sensitivity to any component of the combination regimen
- Clear tumour infiltration into the thoracic great vessels was seen on imaging
- Clear cavitation of pulmonary lesions was seen on imaging
- Grade $\geq$ 2 peripheral neuropathy as defined by NCI CTCAE v4.0 (paclitaxel)

Treatments

The induction phase of the study consisted of four or six cycles of a combination regimen, each cycle being 21 days in duration. On Day 1 of each cycle, all eligible patients received drug infusions in the following order:

- Arm A: Atezolizumab → paclitaxel → carboplatin
- Arm B: Atezolizumab → bevacizumab → paclitaxel → carboplatin
- Arm C: Bevacizumab → paclitaxel → carboplatin

After the fourth or sixth-cycle induction phase, patients began maintenance therapy (atezolizumab and/or bevacizumab).

Agent		Atezolizumab	Bevacizumab	Paclitaxel	Carboplatin
Dose and administration route		1200 mg IV	15 mg/kg IV	200 mg/m^2 IV [a]	AUC 6 IV [b]
Infusion rate		Over 60 (±15) min (for the first infusion); 30 (±10) min for subsequent infusions if tolerated	Over 90 (±15) min (for the first infusion); shortening to 60 (±10) then 30 (±10) min for subsequent infusions if tolerated	Over 3 hours [c]	Over approximately 15–30 min
Frequency		Day 1 of every 21 days			
Induction Phase (Four or Six Cycles)	Arm A	x		x	x
	Arm B	x	x	x	x
	Arm C		x	x	x
Maintenance Phase	Arm A	x			
	Arm B	x	x		
	Arm C		x		

No dose reductions were permitted in the study for atezolizumab or bevacizumab. If AEs occurred that necessitated withholding atezolizumab or bevacizumab, the dose remained unchanged once treatment resumed. Dose reductions, interruptions, and discontinuation of carboplatin and paclitaxel were allowed.

No crossover was permitted from the control arm (Arm C) to either of the experimental arms (Arm A and B). Following the induction phase, patients continued treatment with maintenance therapy. Patients received study treatment until disease progression or unacceptable toxicity (bevacizumab, carboplatin, and paclitaxel), or loss of clinical benefit (atezolizumab), or study termination by the Sponsor.

Objectives

*Of note: Arm C (Bev + CP) is considered a SOC. Unless otherwise specified, efficacy objectives were analysed comparing arms B vs. C or arms A vs. C.

Co-Primary Efficacy Objectives

- To evaluate the efficacy of atezolizumab as measured by investigator-assessed PFS according to RECIST v1.1 in the Teff-high WT population and the ITT–WT population
- To evaluate the efficacy of atezolizumab as measured by OS in the ITT–WT population

Secondary Efficacy Objectives

- To evaluate the efficacy of atezolizumab as measured by OS in the Teff-high WT population

- To evaluate the efficacy of atezolizumab as measured by investigator-assessed PFS according to RECIST v1.1 and OS in the PD-L1 TC2/3 or IC2/3 WT population and the PD-L1 TC1/2/3 or IC1/2/3 WT population

- To evaluate the efficacy of atezolizumab as measured by investigator-assessed PFS according to RECIST v1.1 and OS in the Teff population and the ITT population

- To evaluate the efficacy of atezolizumab as measured by investigator-assessed objective response rate (ORR) according to RECIST v1.1 in the Teff-high WT population and the ITT−WT population

- To evaluate the efficacy of atezolizumab as measured by investigator-assessed duration of response (DOR) according to RECIST v1.1 in the Teff-high WT population and the ITT−WT population

- To evaluate the efficacy of atezolizumab as measured by an Independent Review Facility (IRF)-assessed PFS according to RECIST v1.1 in the Teff-high WT population and the ITT−WT population

- To evaluate the OS rate at 1 and 2 years in each treatment arm for the Teff-high WT population and the ITT−WT population

- To compare the efficacy of the two atezolizumab-containing arms, Atezo + CP arm versus Atezo + Bev + CP arm, as measured by investigator-assessed PFS according to RECIST v1.1 and by OS in the Teff-high WT population and the ITT−WT 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, or arm/shoulder pain, using the European Organisation for the Research and Treatment of Cancer (EORTC) Quality-of-Life

Questionnaire Core (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13) in the Teff-high WT population and the ITT−WT population

- To determine the impact of atezolizumab as measured by change from baseline (i.e., improvement or deterioration based upon presenting symptomatology) in patient-reported lung cancer symptom (chest pain, dyspnea, and cough) score using the Symptoms in Lung Cancer (SILC) scale symptom severity score for the Teff-high WT population and the ITT−WT population

<u>Safety objectives</u>

- To evaluate the safety and tolerability of atezolizumab in each of the two treatment comparisons (i.e. experimental arm vs. control arm)

- To evaluate the incidence and titers of anti-drug antibodies (ADAs), also known as anti-therapeutic antibodies (ATAs), against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics (PK), safety, and efficacy

<u>Pharmacokinetic objectives</u>

- To characterize the PK of atezolizumab when given in combination with carboplatin and paclitaxel with and without bevacizumab

- To characterize the PK of carboplatin when given in combination with paclitaxel with and without atezolizumab and/or bevacizumab

- To characterize the PK of paclitaxel when given in combination with carboplatin with and without atezolizumab and/ or bevacizumab

- To characterize the PK of bevacizumab when given in combination with carboplatin and paclitaxel with and without atezolizumab

Exploratory objectives

- To evaluate the efficacy of atezolizumab as measured by investigator-assessed time to response (TTR) and time-in-response (TIR) according to RECIST v1.1
- To evaluate ORR and DOR according to RECIST v1.1 as assessed by the IRF
- To evaluate investigator-assessed ORR, PFS, and DOR, according to modified RECIST for the atezolizumab-containing treatment arms
- To evaluate PFS at 6 months and at 1 year in each treatment arm
- To evaluate the OS rate at 3 years in each treatment arm
- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status, mechanisms of resistance, and/or response to study treatment
- To evaluate the utility of biopsy at the time of apparent PD to distinguish apparent increases in tumor volume related to the immunomodulatory activity of atezolizumab (i.e., pseudoprogression/tumor-immune infiltration) from true PD
- To evaluate and compare patient's health status as assessed by the EuroQoL 5 Dimensions 3-Level (EQ-5D-3L) questionnaire to generate utility scores for use in economic models for reimbursement
- To determine the impact of atezolizumab as measured by change from baseline in patient-reported outcomes (PROs) of health-related quality of life (HRQoL), lung cancer−related symptoms, and functioning as assessed by the EORTC QLQ-C30 and QLQ-LC13

Outcomes/endpoints

The co-primary efficacy endpoints were PFS as assessed by the investigator according to RECIST v1.1 in the Teff-high WT and the ITT-WT populations, and OS in the ITT-WT populations. Secondary endpoints are PFS and OS in other populations, PFS as assessed by IRF, ORR and DOR.

If the difference in OS between Atezo+CP (Arm A) and Bev+CP (Arm C) in the ITT-WT population is statistically significant, a comparison of Atezo+Bev+CP (Arm B) versus Bev+CP (Arm C) and a comparison of Atezo+CP (Arm A) versus Bev+CP (Arm C) will be conducted in the Teff-high population and the ITT population, with a comparison of Atezo+Bev+CP (Arm B) versus Bev+CP (Arm C) prioritized.

Tumor assessments occurred every 6 weeks (± 7 days) for 48 weeks following Cycle 1, Day 1 and then every 9 weeks (± 7 days) after the completion of the Week 48 tumor assessment, regardless of treatment delays, until radiographic PD per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who had continued treatment after radiographic PD according to RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurred first.

Summary of analysis methods for efficacy parameters

Endpoint / SAP Section	Definition	Censoring	Methodology
Co-Primary Endpoints			
PFS per RECIST v1.1 by investigator in Teff-high WT and ITT–WT populations Section 4.4.1	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 included: sex [male vs. female], presence of liver metastases at baseline [yes vs. no], and PD-L1 tumor expression by IHC ([TC3 and any IC, TC0/1/2 and IC2/3 combined] vs. TC0/1/2 and IC0/1), as recorded in the IxRS (Note: PD-L1 tumor expression by IHC was not included as stratification factor for the analysis in Teff-high WT population.) • For each comparison, a hierarchical analysis and an α-spending algorithm to control for the type I error rate and account for an interim OS analysis were used.
OS in ITT–WT population Section 4.4.1	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 in the ITT-WT population
Secondary Endpoints			
OS in Teff-high WT population	Same as above	Same as above	Similar methods as for co-primary endpoints (Note: PD-L1 tumor expression by IHC was not included as stratification factor for the analysis in Teff-high WT population.)
PFS and OS in PD-L1 TC2/3 or IC2/3 WT and TC1/2/3 or IC1/2/3 WT populations	Same as above	Same as above	Similar methods as for co-primary endpoints (Note: PD-L1 tumor expression by IHC was not included as stratification factor for the analyses.)
PFS and OS in Teff-high and ITT populations	Same as above	Same as above	Similar methods as for co-primary endpoints (Note: PD-L1 tumor expression by IHC was not included as stratification factor for the analysis in Teff-high population.)
ORR (confirmation not required) per RECIST v1.1 by investigator in Teff-high WT and ITT–WT populations[a] Section 4.4.2.4	Proportion of patients with an objective response, either CR or PR	N/A	Clopper-Pearson method for 95% CI of response rates and stratified Cohran-Mantel-Haenszel test for difference in rates (Note: PD-L1 tumor expression by IHC was not included as stratification factor for the analysis in Teff-high WT population.)
DOR (confirmation not required) per RECIST v1.1 by investigator Section 4.4.2.5	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.	Kaplan-Meier methodology Comparisons between treatment arms using stratified and unstratified log-rank test are for descriptive purposes only
PFS per RECIST v1.1 by IRF in Teff-high WT and ITT–WT populations	Time from randomization to the first documented PD as determined by IRF or death from any cause, whichever occurred first	Same as for PFS as assessed by investigator	Same methods as for investigator-assessed PFS (Note: PD-L1 tumor expression by IHC was not included as stratification factor for the analysis in Teff-high WT population.)
OS at 1– and 2–year landmark timepoints in Teff-high WT and ITT–WT populations Section 4.4.2.7	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, with standard errors computed using the Greenwood methods

Sample size

The sample size of this study was based on the number of events required to demonstrate efficacy with regard to both PFS and OS (co-primary endpoints) for the comparison of the Atezo+Bev+CP arm versus Bev+CP arm.

The estimate of the number of events required to demonstrate efficacy with regard to PFS in the comparison of Atezo+Bev+CP arm versus Bev+CP arm was based on the following assumptions:

- One-sided significance level of 0.003 for the comparison of the Atezo + Bev + CP arm versus Bev + CP arm in the Teff-high WT population
- One-sided significance level of 0.003 for the comparison of the Atezo + Bev + CP arm versus Bev + CP arm in the ITT−WT population
- 98% power to detect an HR of 0.55, corresponding to an improvement in median PFS from 6 months to 10.9 months in the Teff-high WT population
- 98% power to detect an HR of 0.65, corresponding to an improvement in median PFS from 6 months to 9.2 months in the ITT−WT population
- No interim analysis for PFS
- Dropout rate of 5% per 12 months

The estimate of the number of events required to demonstrate efficacy with regard to OS in the comparison of the Atezo+Bev+CP arm versus Bev +CP arm was based on the following assumptions:

- One-sided significance level of 0.019 for the comparison of the Atezo + Bev + CP arm versus Bev + CP arm in the ITT−WT population
- 87% power to detect an HR of 0.75, corresponding to an improvement in median OS from 12 months to 16 months in the ITT-WT population
- One interim OS analysis performed at the time of the final PFS analysis, at which time approximately 73% of the total number of OS events required for the final analysis are expected to have occurred as determined through use of the Lan-DeMets approximation to the O'Brien-Fleming boundary
- Dropout rate of 5% per 24 months

The estimate of the number of events required to demonstrate efficacy with regard to PFS and OS in the comparison of the Atezo+CP arm versus Bev+CP arm was based on assumptions similar to those outlined above.

With these assumptions, approximately 1200 patients in total were enrolled into this study, with approximately 720 patients in each comparison in the ITT-WT population. The ITT-WT population included approximately 1080 patients, assuming 10% prevalence for sensitizing *EGFR* mutations or ALK-positive disease. The Teff-high WT population included approximately 540 patients, assuming 50% prevalence with the chosen Teff cutoff.

Randomisation

Randomization to one of the three treatment arms occurred in a 1:1:1 ratio. Permuted block randomization was applied to ensure a balanced assignment to each treatment arm. Randomization was stratified by the following criteria:

- Sex (male vs. female)

- Presence of liver metastases at baseline (yes vs. no)
- PD-L1 expression by IHC (TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1)

Patients received their first dose of study drug on the day of randomization if possible.

Blinding (masking)

This was an open-label study. The Sponsor was blinded to treatment arm allocation and patient-level data on PD-L1 expression and Teff gene signature until the database had been locked for analysis.

Statistical methods

Treatment comparisons were conducted by first comparing Arm B versus Arm C and then comparing Arm A versus Arm C based on a stratified log-rank test in the biomarker-selected Teff-high-WT and ITT-WT populations for the PFS endpoint and in the ITT-WT population for the OS endpoint. ITT population is tested after ITT-WT population. For each comparison, analyses were conducted according to α-spending algorithm to control for the one-sided type I error rate (0.025) and to account for an interim OS analysis.

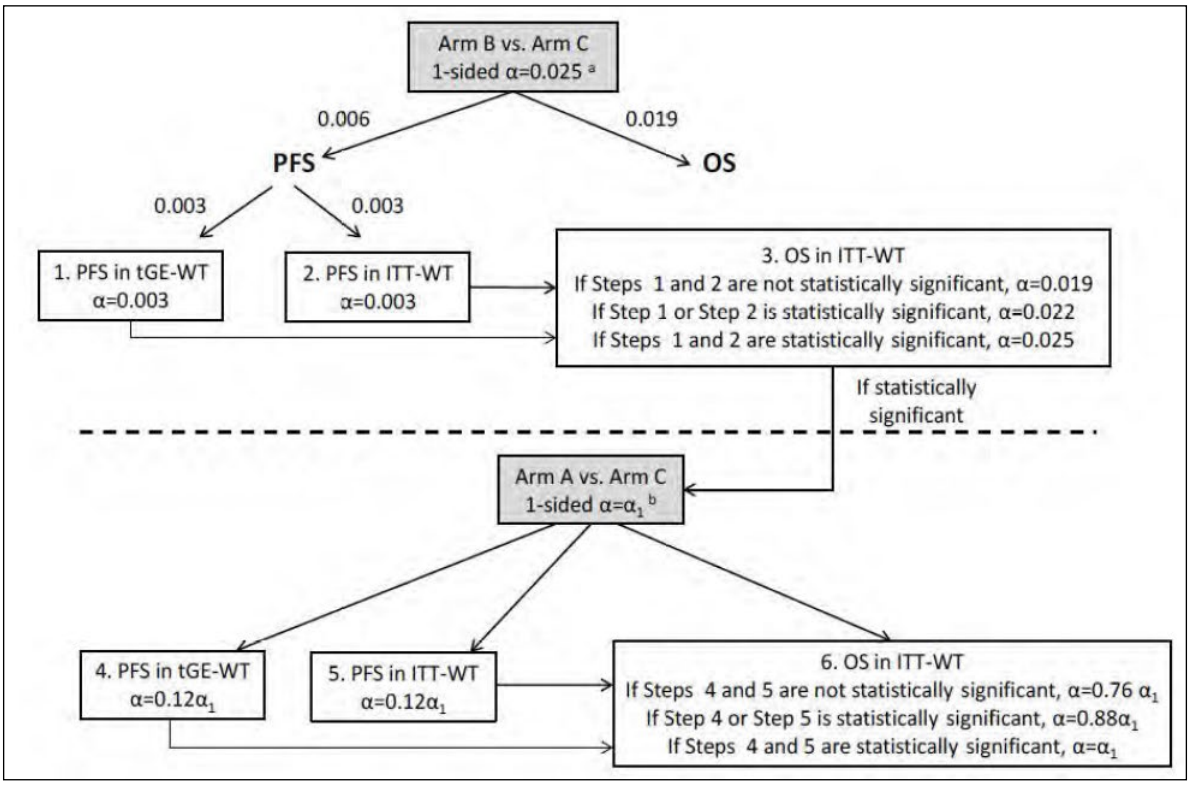


Figure 9: **α-spending algorithm for PFS and OS analysis hierarchy, alpha allocation and alpha recycling**

Kaplan-Meier methodology was used to estimate the median PFS and the median OS for each treatment arm, and a Kaplan-Meier curve was constructed to provide a visual description of the difference between treatment arms. The Brookmeyer-Crowley methodology was used to construct the 95% CI for the median PFS and the median OS for each treatment arm.

Definition, censoring and methodology for primary and secondary endpoints has been previously detailed in the *Summary of analysis methods for efficacy parameters* (Outcomes/endpoints section).

Hypotheses

The null and alternative hypotheses regarding PFS and OS in each population (Teff-high WT, ITT-WT) can be phrased in terms of the survival functions SA(t) or SB(t) for the atezolizumab-containing arms and SC(t) for the control arm:

$$H0: SA(t) = SC(t) \text{ versus } H1: SA(t) > SC(t)$$
$$\text{or } H0: SB(t) = SC(t) \text{ versus } H1: SB(t) > SC(t)$$

The HRs, λA/λC and λB/λC (where λA, λB, and C represent the hazard of having a PFS or death in the Atezo+CP, Atezo+Bev+CP and Bev+CP arms, respectively), comparing the treatment effect between the two treatment arms, was estimated using a stratified Cox regression model with the same stratification variables used for the stratified log-rank test, and the 95% CI was provided.

Discussion on modification of endpoints along study design:

Initially, the co-primary endpoints for this study were investigator-assessed PFS in the ITT population and PD-L1 population (protocol version 1). However, efficacy data with atezolizumab and other check-point inhibitors in 2L+ NSCLC show that OS is in fact the most sensitive endpoint for cancer immunotherapy in the monotherapy setting. For example, in the randomized Phase III Study GO28915 (OAK) in previously treated patients with advanced NSCLC, an OS benefit with atezolizumab monotherapy compared with docetaxel was observed in the ITT population, with a stratified HR of 0.73 (95% CI: 0.62, 0.87). PFS in the ITT population was similar between both treatment arms: HR of 0.95 (95% CI: 0.82, 1.10). These data, together with the fact that OS is the most objective measure of clinical benefit for patients with advanced/unresectable or metastatic lung cancer, led to the inclusion of OS as a co-primary endpoint, along with the PFS primary endpoints (protocol version 5). Since an OS analysis might be confounded by the fact that many of patients in IMpower150 would likely receive subsequent immunotherapy after progression, crossover from the control arm to either of the experimental arms after PD was not permitted. In addition to changes to the primary efficacy objectives during the IMpower150 study conduct, the primary analysis populations were also modified to exclude patients with known activating *EGFR* mutations or ALK-positive tumors. These populations are defined as "wild-type" patients (ITT-WT and Teff-high WT populations; protocol version 6). This change was based on the observations from monotherapy studies in 2L+ NSCLC where the survival benefit of immunotherapy was similar to chemotherapy in the EGFRmutant/ALK+ patients, whereas OS was clinically and numerically improved in patients that did not have driver mutations such as EGFR mutation or ALK translocation.

Furthermore, the primary biomarker analysis population was also changed from PD-L1 expression by IHC to expression of a Teff gene signature, defined as the Teff-high WT population. The Teff gene signature had been identified based on analyses in the POPLAR (Phase II Study GO28753) and OAK studies in patients with locally advanced or metastatic NSCLC. These analyses had shown that the Teff signature may have a stronger association with efficacy of atezolizumab monotherapy than PD-L1 expression on TCs and/or ICs as determined by IHC. More detail on the Teff gene signature is provided in Section 3.8.2. Efficacy in Teff-high and ITT populations (including EGFR mutant/ALK+ patients) were pre-specified as secondary objectives.

Interim analyses

No interim analyses were planned for the co-primary endpoint of PFS in this study.

The final PFS analysis was conducted when both of the following criteria had been met: approximately 516 PFS events had occurred in the Atezo+Bev+CP and Bev+CP arms combined in the ITT-WT population and the last patient had enrolled in the study. The final PFS analysis was expected to occur approximately 29 months after the first patient was enrolled. At the time of the final PFS analysis, it was expected that approximately 249 events would have occurred in the Teff-high WT population. These numbers of events

would allow for a minimum detectable difference corresponding to an HR of approximately 0.70 in the Teff-high WT population and 0.78 in the ITT-WT population.

The OS interim analysis for the primary comparison of Arm B versus Arm C will be conducted by the Sponsor at the time of the final PFS analysis for the primary comparisons. It is expected that there will be approximately 370 OS events in the ITT-WT population in the combined Arm B and Arm C at this timepoint, in which case an interim OS analysis will be conducted with the stopping boundaries for the OS interim and final analyses computed using the Lan-DeMets approximation to the O'Brien-Fleming boundary. If there are significantly fewer than 370 OS events at the PFS final analysis, a nominal α of 0.01% (negligible impact on overall type I error rate) could be spent on the OS analysis at the time of the PFS final analysis. The next interim will be conducted after approximately 370 OS events are observed, with the stopping boundaries for the OS interim and final analyses calculated the same way as above.

The final OS analysis for the primary comparison of Atezo+Bev+CP arm versus Bev+CP arm will be conducted when there are approximately 507 OS events in the ITT-WT population in the combined Atezo +Bev+CP and Bev+CP arms. This number of events corresponds to a minimum detectable difference in HR of approximately 0.83 in the ITT-WT population. The OS final analysis is expected to occur approximately 40 months after the first patient was randomized.

Subgroup analyses

The consistency of PFS and OS results in subgroups will be examined in the populations where PFS and/or OS benefit had been demonstrated. The subgroups were defined by the following:

- Demographics (age, sex, race/ethnicity)
- Baseline disease characteristics (e.g., ECOG performance status; presence of liver metastases at baseline; smoking status; metastatic sites such as brain, bone, etc.; *EGFR* mutation status; Kirsten rat sarcoma [*KRAS*] mutation status; EML4-ALK rearrangement status, intended number of cycles of induction treatment, etc.)
- PD-L1 IHC status (e.g., TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3, and their corresponding complementary groups)
- Complementary biomarker population defined by Teff cutoff value - 1.91 and additional biomarker populations defined by the Teff cutoff values of - 2.38 and - 2.93

Summaries of PFS and OS, including the unstratified HR estimated from a Cox proportional hazards model and KM estimates of median PFS and OS, were produced separately for each level of the subgroup for the comparisons between two treatment arms and displayed in a forest plot. KM plots of PFS and/or OS were also produced for selected subgroups. Summaries of ORR by subgroup are also provided.

Sensitivity analyses

Sensitivity analyses 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. The following two imputation rules will be considered:

• If a patient missed two or more scheduled tumor assessments immediately prior to the date of the PFS event according to RECIST v1.1, the patient will be censored at the last tumor assessment prior to the first of these missed visits.

• If a patient missed two or more tumor assessments scheduled immediately prior to the date of the PFS event according to RECIST v1.1, the patient will be counted as having progressed on the date of the first of these missing assessments.

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

If > 5% of patients received non-protocol therapy before a PFS event in any treatment arm, a sensitivity analysis will be performed for the comparisons between two treatment arms (i.e., Arm A vs. Arm C, Arm B vs. Arm C and, if applicable, Arm A vs. Arm B) in which patients who receive non-protocol therapy before a PFS event will be censored at the last tumor assessment date before receipt of non-protocol therapy.

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 (i.e., Arm A vs. Arm C, Arm B vs. Arm C, and, if applicable, Arm A vs. Arm B) 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.

Results

Participant flow

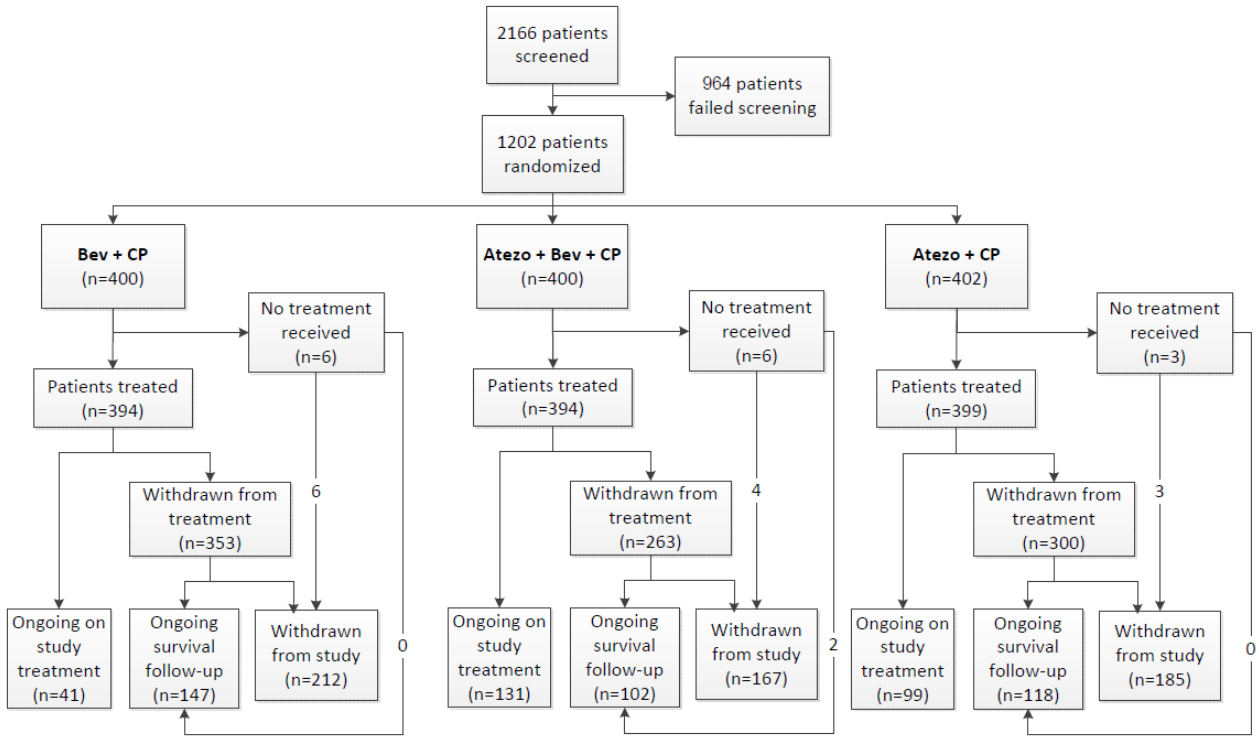


Figure 10: Patient disposition

Table 7: Patient disposition from Study GO29436 (ITT population) – Data cut: 15 September 2017

	Bev+CP (Randomized) (N=400)	Atezo+Bev+CP (Randomized) (N=400)	Atezo+CP (Randomized) (N=402)	All Patients (N=1202)
Received Treatment	394 (98.5%)	394 (98.5%)	399 (99.3%)	1187 (98.8%)
On-study Status	188 (47.0%)	233 (58.3%)	217 (54.0%)	638 (53.1%)
Alive: On Treatment	41 (10.3%)	131 (32.8%)	99 (24.6%)	271 (22.5%)
Alive: In Follow-Up	147 (36.8%)	102 (25.5%)	118 (29.4%)	367 (30.5%)
Discontinued Study	212 (53.0%)	167 (41.8%)	185 (46.0%)	564 (46.9%)
Death	195 (48.8%)	151 (37.8%)	165 (41.0%)	511 (42.5%)
Lost To Follow-Up	1 (0.3%)	2 (0.5%)	1 (0.2%)	4 (0.3%)
Other	2 (0.5%)	2 (0.5%)	1 (0.2%)	5 (0.4%)
Physician Decision	1 (0.3%)	1 (0.3%)	1 (0.2%)	3 (0.2%)
Protocol Violation	0	0	2 (0.5%)	2 (0.2%)
Withdrawal By Subject	13 (3.3%)	11 (2.8%)	15 (3.7%)	39 (3.2%)

Atezo=Atezolizumab, Bev=Bevacizumab, CP=Carboplatin+Paclitaxel.
Data Cut-off: 15 Sep 2017; RAVE Data Extracted: 10 Nov 2017.

Recruitment

In the ITT population, a total of 2166 patients were screened; of these, 1202 patients from 240 centers in 26 countries were randomized.

The first patient was randomized on 31 March 2015. The last patient was randomized on 30 December 2016. Data Cut-off was on 15 September 2017.

The number of patients randomized per country, followed by the number of centers (in parentheses), is summarized below:

United States 266 (61), Spain 138 (20), Germany 94 (17), Japan 93 (15), Australia 88 (16), Ukraine 74 (13), France 72 (12), Italy 50 (11), Chile 44 (3), Netherlands 39 (12), Russia 37 (5), Taiwan 34 (10), Brazil 27 (9), Portugal 23 (6), Latvia 17 (2), Belgium 16 (2), Switzerland 14 (3), Austria 12 (2), Argentina 10 (7), Bulgaria 10 (2), Mexico 9 (3), Peru 9 (3), Singapore 9 (1), Slovakia 8 (3), Canada 6 (1), Lithuania 3 (1).

Failed screening: A total of 964 patients failed screening based on information collected on the IxRS. The most common reasons for screen failure were lack of known PD-L1 tumor status by IHC (137 patients), prior treatment for Stage IV non-squamous NSCLC (127 patients), and a history of treated asymptomatic CNS metastases that failed specific protocol eligibility criteria (94 patients).

Allocation: A total of 1202 patients were randomized: 400 patients to the Bev+CP arm, 400 patients to the Atezo+Bev+CP arm and 402 patients to the Atezo+CP arm. Overall, 15 patients did not receive any study treatment (6 patients each in the Bev+CP and Atezo+Bev+CP arms and 3 patients in the Atezo+CP arm).

Discontinuation from Study: In the ITT population, a higher proportion of patients discontinued from the study in the Bev+CP arm (53.0%) compared with the Atezo+Bev+CP (41.8%) and Atezo+CP (46.0%) arms. The most common reason for study discontinuation was death (42.5% of all patients).

Follow up: The median duration of survival follow-up among ITT patients was consistent across the arms: 15.4 months in the Bev+CP arm (range 0.0-28.6), 15.1 months in the Atezo+Bev+CP arm (range 0.0-26.3), and 15.4 months in the Atezo+CP arm (range 0.0-25.1). As of the clinical cutoff date of 15 September 2017, two untreated patients remained on study; 13 untreated patients had discontinued the

study due to withdrawal by subject (3 patients), death (3), other (3), protocol violation (2), and physician decision (2).

Conduct of the study

The first version of the protocol was issued on 21 November 2014 and was amended five times. The key changes to the protocol are summarized below.

- Protocol Amendment 1 (Version 2) – 29 March 2015

Protocol GO29436 was amended to clarify the inclusion criterion on contraception and extend the requirement for its use to 6 months after last dose of study drug for all patients randomized to a bevacizumab-containing treatment arm. In addition, reporting for SAEs and AESIs was extended to 90 days after last dose of study treatment or until initiation of a new anticancer therapy, whichever occurred first.

- Protocol Amendment 2 (Version 3) – 14 August 2015

Major changes to Protocol GO29436, Version 3 are as follows:

The evaluations of PFS at 6 months and at 1 year and OS at 3 years were added as exploratory objectives.

The contraception requirements in the inclusion and exclusion criteria and the pregnancy-reporting information were revised to comply with prescribing information for bevacizumab.

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

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

The study exclusion criterion regarding treatment with systemic immunostimulatory agents within 6 weeks or 5 half-lives of the drug (whichever was shorter) prior to randomization was modified to 4 weeks prior to randomization.

The exclusion criterion specifying that patients with a history of allergic reaction to intravenous contrast that required steroid pretreatment should have baseline and subsequent tumor assessments performed via magnetic resonance imaging (MRI) was removed. Patients with contraindications to contrast could have assessments done with non-contrast computed tomography or MRI.

Bevacizumab was changed to an investigational medicinal product (IMP). Text was added to clarify that bevacizumab would be supplied to all sites by the Sponsor.

The guideline to administer paclitaxel 60 minutes after the completion of bevacizumab was removed. Paclitaxel could be administered immediately following the completion of bevacizumab.

Additional requirements were added for hepatitis B and hepatitis C testing to ensure that patients did not have active disease at screening.

Additional detail was added to ensure that PRO assessments were collected as intended for patients who discontinued treatment for any reason other than PD or loss of clinical benefit (for atezolizumab-treated patients who continued treatment beyond RECIST v1.1 PD and who continued atezolizumab).

Collection of mandatory tumour specimens, if clinically feasible, was now required for all patients.

- Protocol Amendment 3 (Version 4) – 11 November 2015

Protocol GO29436, Version 4 was amended to clarify that a wash-out period of at least 4 weeks or five half-lives, whichever was longer, of any systemic immunomodulatory agent was required prior to enrollment.

- Protocol Amendment 4 (Version 5) – 31 May 2016

Protocol GO29436, Version 5 was amended to add a co-primary endpoint of OS to the PFS primary endpoint due to recent data suggesting that OS may be a more sensitive endpoint for cancer immunotherapy. Changes were made to the statistical testing procedure, accordingly. In addition, this amendment includes the following key changes:

A secondary efficacy objective and outcome measure was added to evaluate the efficacy of atezolizumab as measured by investigator-assessed TTR according to RECIST v1.1 for the ITT population, the TC1/2/3 or IC1/2/3 population, and the TC2/3 or IC2/3 population.

The exploratory objectives and outcome measures to evaluate IRF assessment of PFS, overall response rate, disease control rate, duration of response, and TIR according to modified RECIST for the atezolizumab-containing treatment arms were removed.

The inclusion criteria were modified to specify that patients who had received prior radiotherapy with curative intent had to be treatment-free for at least a 6-month interval prior to randomization.

Based on the half-life of atezolizumab of 27 days, the length of female patient contraception and follow-up of pregnancy reporting was revised from 90 days to 5 months. The contraception requirements for male patients and pregnancy-reporting requirements for female partners of male patients who received atezolizumab were updated on the basis of the safety information for atezolizumab.

General medical exclusion criteria were revised to include cerebrovascular accident as a significant cardiovascular disease and to exclude patients with illnesses or conditions that interfered with their capacity to understand, follow, and/or comply with the study procedures.

Two exclusion criteria were added related to bevacizumab in response to fatal adverse events of pulmonary hemorrhage that occurred in the study and to be consistent with other clinical studies that use bevacizumab: clear tumour infiltration into the thoracic great vessels is seen on imaging and clear cavitation of pulmonary lesions is seen on imaging. These additional exclusion criteria were endorsed by the iDMC.

Permitted therapy was modified by removing hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer because they are considered anti-cancer therapies.

Traditional herbal medicines were removed from prohibited therapies, and language was added to state that concomitant use of herbal therapies was not recommended. Use of herbal therapies for patients in the study was allowed only at the discretion of the investigator, provided that there were no known interactions with any study treatment.

The screening assessments were revised, specifying that either a computed tomography or magnetic resonance imaging scan of the pelvis was required at screening.

The timepoint for the whole blood sample collection at Cycle 1, Day 1 was moved to screening to enable the sample to be taken prior to any Cycle 1, Day 1 pretreatment with steroids.

For patients who discontinued study treatment for any reason other than PD or loss of clinical benefit, the schedule of subsequent electronic PRO (ePRO) assessments had changed to align with the tumor assessment schedule.

For patients whose native language was not available on the ePRO device, an exemption from all ePRO assessments was provided.

The length of time that atezolizumab could be withheld was clarified to be a maximum of 105 days beyond the last dose of atezolizumab; exceptions required Medical Monitor approval.

The requirement for a tumor response assessment at the treatment discontinuation visit was removed.

- Protocol Amendment 5 (Version 6) – 01 March 2017

Protocol GO29436 was amended to reflect changes in the analysis populations and in statistical methodology described in the SAP. Key changes to the protocol are summarized below:

The primary analysis populations for the co-primary endpoints of PFS and OS had changed. PFS was analyzed in the ITT–WT population and Teff-high WT population (Teff gene signature as determined by an RNA-based assay); OS was analyzed in the ITT–WT population. Both populations excluded patients with sensitizing EGFR mutations or ALK–positive tumors. The analyses of PFS and OS in patients defined by their PD-L1 expression status on TCs and ICs as determined by IHC would be performed as secondary analyses. The analyses of PFS and OS in all randomized patients would be conducted as secondary analyses.

The testing hierarchy and α-spending algorithm were adjusted and the comparison between the Atezo + Bev + CP and Bev + CP arms would be conducted prior to the comparison between the Atezo + CP and Bev + CP arms.

On the basis of updated U.S. FDA guidance, the additional censoring rule for the primary endpoint of PFS for U.S. registration purposes was removed (FDA 2015). The impact of the missing visits would be assessed as a sensitivity analysis.

The statistical testing procedures were amended to reflect the change in analysis populations.

To focus the efficacy analyses on more meaningful endpoints, the secondary objectives and outcome measures regarding investigator-assessed time-to response (TTR) and investigator-assessed time-in-response (TIR) per RECIST v1.1, had been changed to exploratory objectives and outcome measures. The exploratory objectives and outcome measures of disease control rate, TTR, and TIR by IRF assessment per RECIST v1.1 and by investigator assessment per modified RECIST were removed.

In patients of Asian race/ethnicity, the paclitaxel starting dose was lowered from 200 mg/m2 to 175 mg/m2. This change was recommended by the iDMC after a review of the safety data that noted a higher overall level of hematologic toxicities in patients from Asian countries compared with those from non-Asian countries.

Based on the half-life of atezolizumab of 27 days, the use of live, attenuated vaccines was extended to 5 months after the last dose of atezolizumab.

Language was added to clarify that tumour tissue collected at screening would be evaluated for the expression of PD-L1 and the T-effector gene signature. Exploratory biomarkers would be identified by IHC, quantitative reverse transcriptase-polymerase chain reaction, next-generation sequencing, and/or other methods.

Statistical methods for exploratory PRO measures were added.

<u>Protocol deviations:</u>

Major protocol deviations were reported in relation to the following four categories: procedural, medication, inclusion criteria, and exclusion criteria. All patients with protocol deviations were included in the efficacy analyses.

33.9% of ITT patients had at least one major protocol deviation; the majority of patients had procedural deviations (24.0%), 7.6% had medication deviations, 5.2% had inclusion criteria deviations, and 3.6% had exclusion criteria deviations. Overall, the frequency and types of deviations were similar between treatment arms.

Table 8: Summary of major protocol deviations and violations – ITT patients (Data cut: 15 September 2017)

Protocol Deviation Category Protocol Deviation Description	Bev+CP (Randomized) (N=400)	Atezo+Bev+CP (Randomized) (N=400)	Atezo+CP (Randomized) (N=402)	All Patients (N=1202)
Total number of patients with at least one deviation	141 (35.3%)	137 (34.3%)	129 (32.1%)	407 (33.9%)
Overall total number of deviations	204	238	184	626
PROCEDURAL				
Total number of patients with at least one deviation	104 (26.0%)	99 (24.8%)	86 (21.4%)	289 (24.0%)
Total number of events	141	148	111	400
ICF - OTHER (E.G. PROCEDURAL ISSUES)	43 (10.8%)	38 (9.5%)	47 (11.7%)	128 (10.6%)
OMISSION OF LAB TEST REQ. BY PROTOCOL	32 (8.0%)	38 (9.5%)	21 (5.2%)	91 (7.6%)
ELIGIBILITY PROCEDURAL ISSUE (E.G. OUT OF WINDOW)	22 (5.5%)	26 (6.5%)	16 (4.0%)	64 (5.3%)
FAILURE TO REPORT SAES OR PREGNANCY PER PROTOCOL	7 (1.8%)	4 (1.0%)	8 (2.0%)	19 (1.6%)
OMISSION OF TUMOR ASSESSMENT	6 (1.5%)	8 (2.0%)	4 (1.0%)	18 (1.5%)
ON STUDY ASSESSMENT NOT DONE/OUTSIDE OF WINDOW	2 (0.5%)	7 (1.8%)	0	9 (0.7%)
ERROR WITH STRATIFICATION	2 (0.5%)	2 (0.5%)	0	4 (0.3%)
ON STUDY DISEASE ASSESSMENT OUTSIDE OF WINDOW	3 (0.8%)	1 (0.3%)	0	4 (0.3%)
BIOPSY AT PD NOT PERFORMED	0	1 (0.3%)	1 (0.2%)	2 (0.2%)
ERROR WITH RANDOMIZATION	1 (0.3%)	0	0	1 (<0.1%)
MEDICATION				
Total number of patients with at least one deviation	27 (6.8%)	36 (9.0%)	28 (7.0%)	91 (7.6%)
Total number of events	31	53	30	114
SIGNIFICANT CHANGE FROM PLANNED CHEMOTHERAPY DOSE	16 (4.0%)	22 (5.5%)	17 (4.2%)	55 (4.6%)
CONTINUATION OF STUDY TX IN CONFLICT WITH PROTOCOL	7 (1.8%)	9 (2.3%)	3 (0.7%)	19 (1.6%)
RECEIVED EXPIRED STUDY TREATMENT	2 (0.5%)	5 (1.3%)	3 (0.7%)	10 (0.8%)
RECEIVED PROHIBITED CONCOMITANT THERAPY/MEDICATION	2 (0.5%)	1 (0.3%)	3 (0.7%)	6 (0.5%)
DOSE MISSED OR SIGNIFICANT OUT OF WINDOW	0	0	2 (0.5%)	2 (0.2%)
RECEIVED INCORRECT STUDY MEDICATION	0	1 (0.3%)	0	1 (<0.1%)
SIGNIFICANT DEVIATION FROM PLANNED MPDL3280A DOSE	0	1 (0.3%)	0	1 (<0.1%)
INCLUSION CRITERIA				
Total number of patients with at least one deviation	19 (4.8%)	22 (5.5%)	21 (5.2%)	62 (5.2%)
Total number of events	19	23	24	66
INCLUSION-RELATED TEST NOT DONE	7 (1.8%)	6 (1.5%)	6 (1.5%)	19 (1.6%)
DOES NOT MEET PRIOR NSCLC THERAPY REQUIREMENTS	7 (1.8%)	5 (1.3%)	5 (1.2%)	17 (1.4%)
INCLUSION LAB VALUES OUTSIDE ALLOWED LIMITS	1 (0.3%)	4 (1.0%)	3 (0.7%)	8 (0.7%)
INELIGIBLE HISTOLOGY OR CURRENT NSCLC STAGE	1 (0.3%)	2 (0.5%)	3 (0.7%)	6 (0.5%)
OTHER INCLUSION CRITERIA	0	2 (0.5%)	2 (0.5%)	4 (0.3%)
ICF - ENROLLED OR SCREENED PRIOR TO CONSENT	0	2 (0.5%)	1 (0.2%)	3 (0.2%)
NO MEASURABLE DISEASE PER RECIST 1.1	2 (0.5%)	0	1 (0.2%)	3 (0.2%)
TREATMENT OF CURATIVE INTENT WITHIN 6M OF RAND	0	1 (0.3%)	1 (0.2%)	2 (0.2%)
ICF - OTHER (E.G. PROCEDURAL ISSUES)	1 (0.3%)	0	0	1 (<0.1%)
EXCLUSION CRITERIA				
Total number of patients with at least one deviation	13 (3.3%)	13 (3.3%)	17 (4.2%)	43 (3.6%)
Total number of events	13	14	19	46
EXCLUSION RELATED TEST NOT DONE	3 (0.8%)	9 (2.3%)	7 (1.7%)	19 (1.6%)
RECEIVED PRIOR PROHIBITED MEDICATION OR THERAPY	4 (1.0%)	1 (0.3%)	6 (1.5%)	11 (0.9%)
EXCLUDED POSITIVE VIRAL TEST (HIV, HBV, HCV, TB)	2 (0.5%)	1 (0.3%)	1 (0.2%)	4 (0.3%)
OTHER EXCLUSION CRITERIA	2 (0.5%)	0	2 (0.5%)	4 (0.3%)
KNOWN EXCLUDED AUTOIMMUNE DISEASE	1 (0.3%)	1 (0.3%)	1 (0.2%)	3 (0.2%)
ACTIVE OR UNTREATED CNS METS	0	0	1 (0.2%)	1 (<0.1%)
EXCLUSIONS RELATED TO BEVACIZUMAB OR CHEMOTHERAPY	0	1 (0.3%)	0	1 (<0.1%)
UNCONTROLLED CONCURRENT CONDITION	1 (0.3%)	0	0	1 (<0.1%)

Baseline data

Table 9: Demographic and baseline disease characteristics, ITT population (Data cut: 15 September 2017)

	Bev+CP (Randomized) (N=400)	Atezo+Bev+CP (Randomized) (N=400)	Atezo+CP (Randomized) (N=402)	All Patients (N=1202)
Sex				
n	400	400	402	1202
Male	239 (59.8%)	240 (60.0%)	241 (60.0%)	720 (59.9%)
Female	161 (40.3%)	160 (40.0%)	161 (40.0%)	482 (40.1%)
Liver Metastasis at Enrollment				
n	400	400	402	1202
Yes	57 (14.3%)	53 (13.3%)	53 (13.2%)	163 (13.6%)
No	343 (85.8%)	347 (86.8%)	349 (86.8%)	1039 (86.4%)
Liver Metastasis at Enrollment from IxRS				
n	400	400	402	1202
Present	69 (17.3%)	67 (16.8%)	68 (16.9%)	204 (17.0%)
Not Present	331 (82.8%)	333 (83.3%)	334 (83.1%)	998 (83.0%)
PD-L1 IHC Strat Factor from IxRS				
n	400	400	402	1202
TC0/1/2_IC0/1	301 (75.3%)	299 (74.8%)	304 (75.6%)	904 (75.2%)
TC0/1/2_IC2/3	50 (12.5%)	53 (13.3%)	51 (12.7%)	154 (12.8%)
TC3_ANY IC	49 (12.3%)	48 (12.0%)	47 (11.7%)	144 (12.0%)
Age (years)				
n	400	400	402	1202
Mean (SD)	63.1 (9.3)	63.0 (9.5)	62.3 (9.2)	62.8 (9.3)
Median	63.0	63.0	63.0	63.0
Min - Max	31 - 90	31 - 89	32 - 85	31 - 90
Age Group 4 Categories (years)				
n	400	400	402	1202
<65	226 (56.5%)	215 (53.8%)	223 (55.5%)	664 (55.2%)
65 to 74	132 (33.0%)	149 (37.3%)	152 (37.8%)	433 (36.0%)
75 to 84	39 (9.8%)	33 (8.3%)	26 (6.5%)	98 (8.2%)
>=85	3 (0.8%)	3 (0.8%)	1 (0.2%)	7 (0.6%)
Weight (kg) at baseline				
n	394	394	399	1187
Mean (SD)	71.39 (15.80)	72.40 (18.01)	73.34 (17.24)	72.38 (17.05
Median	71.00	70.75	71.50	71.00
Min - Max	39.4 - 140.6	37.0 - 196.0	40.0 - 155.0	37.0 - 196.0
Ethnicity				
n	400	400	402	1202
Hispanic or Latino	43 (10.8%)	40 (10.0%)	32 (8.0%)	115 (9.6%)
Not Hispanic or Latino	341 (85.3%)	338 (84.5%)	345 (85.8%)	1024 (85.2%)
Not reported	12 (3.0%)	18 (4.5%)	20 (5.0%)	50 (4.2%)
Unknown	4 (1.0%)	4 (1.0%)	5 (1.2%)	13 (1.1%)
Race				
n	400	400	402	1202
American Indian or Alaska Native	1 (0.3%)	3 (0.8%)	0	4 (0.3%)
Asian	46 (11.5%)	56 (14.0%)	48 (11.9%)	150 (12.5%)
Black or African American	12 (3.0%)	3 (0.8%)	9 (2.2%)	24 (2.0%)
White	335 (83.8%)	322 (80.5%)	331 (82.3%)	988 (82.2%)
Multiple	0	3 (0.8%)	4 (1.0%)	7 (0.6%)
Unknown	6 (1.5%)	13 (3.3%)	10 (2.5%)	29 (2.4%)
Tobacco Use History				
n	400	400	402	1202
Never	77 (19.3%)	82 (20.5%)	77 (19.2%)	236 (19.6%)
Current	92 (23.0%)	90 (22.5%)	98 (24.4%)	280 (23.3%)
Previous	231 (57.8%)	228 (57.0%)	227 (56.5%)	686 (57.1%)

	Bev+CP (Randomized) (N=400)	Atezo+Bev+CP (Randomized) (N=400)	Atezo+CP (Randomized) (N=402)	All Patients (N=1202)
Non-squamous Histology Detail				
n	400	400	402	1202
Adenocarcinoma	377 (94.3%)	378 (94.5%)	383 (95.3%)	1138 (94.7%)
Adenocarcinoma With Neuroendocrine Features	2 (0.5%)	3 (0.8%)	0	5 (0.4%)
Adenosquamous	3 (0.8%)	1 (0.3%)	2 (0.5%)	6 (0.5%)
Bronchioloalveolar Carcinoma	5 (1.3%)	2 (0.5%)	2 (0.5%)	9 (0.7%)
Large Cell	4 (1.0%)	5 (1.3%)	6 (1.5%)	15 (1.2%)
Sarcomatoid	0	1 (0.3%)	1 (0.2%)	2 (0.2%)
Undifferentiated	3 (0.8%)	7 (1.8%)	4 (1.0%)	14 (1.2%)
NA	1 (0.3%)	1 (0.3%)	1 (0.2%)	3 (0.2%)
Unknown	5 (1.3%)	2 (0.5%)	3 (0.7%)	10 (0.8%)
EGFR Mutation Status				
n	400	400	402	1202
Positive	45 (11.3%)	35 (8.8%)	46 (11.4%)	126 (10.5%)
Negative	345 (86.3%)	352 (88.0%)	347 (86.3%)	1044 (86.9%)
Unknown	10 (2.5%)	13 (3.3%)	9 (2.2%)	32 (2.7%)
EML4-ALK Rearrangement Status				
n	400	400	402	1202
Positive	21 (5.3%)	13 (3.3%)	9 (2.2%)	43 (3.6%)
Negative	375 (93.8%)	383 (95.8%)	388 (96.5%)	1146 (95.3%)
Unknown	4 (1.0%)	4 (1.0%)	5 (1.2%)	13 (1.1%)
KRAS Mutation Status				
n	400	400	402	1202
Positive	38 (9.5%)	47 (11.8%)	36 (9.0%)	121 (10.1%)
Negative	77 (19.3%)	59 (14.8%)	88 (21.9%)	224 (18.6%)
Unknown	285 (71.3%)	294 (73.5%)	278 (69.2%)	857 (71.3%)
Baseline ECOG				
n	397	397	402	1196
0	179 (45.1%)	159 (40.1%)	180 (44.8%)	518 (43.3%)
1	218 (54.9%)	238 (59.9%)	222 (55.2%)	678 (56.7%)
Intended Cycles at Induction Tx Period				
n	400	400	402	1202
4 Cycles	217 (54.3%)	215 (53.8%)	224 (55.7%)	656 (54.6%)
6 Cycles	183 (45.8%)	185 (46.3%)	178 (44.3%)	546 (45.4%)

Atezo=Atezolizumab, Bev=Bevacizumab, CP=Carboplatin+Paclitaxel.
EGFR mutation = Sensitizing EGFR mutations include all EGFR activating mutations in exons 18-21.
ALK positive = ALK translocation.
Data Cut-off: 15 Sep 2017; RAVE Data Extracted: 10 Nov 2017.

Biomarker status, ITT

Table 10: Baseline PD-L1 expression status (ITT population)

	Bev + CP (n=400)	Atezo + Bev + CP (n=400)	Atezo + CP (n=402)	All Patients (n=1202)
TC3 or IC3 vs. TC0/1/2 and IC0/1/2				
TC3 or IC3	73 (18.3%)	75 (18.8%)	68 (16.9%)	216 (18.0%)
TC0/1/2 and IC0/1/2	327 (81.8%)	325 (81.3%)	334 (83.1%)	986 (82.0%)
TC2/3 or IC2/3 vs. TC0/1 and IC0/1				
TC2/3 or IC2/3	133 (33.3%)	140 (35.0%)	137 (34.1%)	410 (34.1%)
TC0/1 and IC0/1	266 (66.5%)	260 (65.0%)	264 (65.7%)	790 (65.7%)
TC1/2/3 or IC1/2/3 vs. TC0 and IC0				
TC1/2/3 or IC1/2/3	195 (48.8%)	209 (52.3%)	213 (53.0%)	617 (51.3%)
TC0 and IC0	205 (51.3%)	191 (47.8%)	188 (46.8%)	584 (48.6%)
TC/IC 4 incremental subgroups				
TC3 or IC3	73 (18.3%)	75 (18.8%)	68 (16.9%)	216 (18.0%)
TC2/3 or IC2/3 exclude TC3 or IC3	60 (15.0%)	65 (16.3%)	69 (17.2%)	194 (16.1%)
TC1/2/3 or IC1/2/3 exclude TC2/3 or IC2/3	67 (16.8%)	70 (17.5%)	79 (19.7%)	216 (18.0%)
TC0 and IC0	200 (50.0%)	190 (47.5%)	185 (46.0%)	575 (47.8%)

Table 11: Summary of baseline Teff gene signature expression status across the study arms (ITT population)

	Bev + CP (n=400)	Atezo + Bev + CP (n=400)	Atezo + CP (n=402)	All Patients (n=1202)
Tumor Gene Expression ≥ –1.91				
Yes	148 (37.0%)	166 (41.5%)	177 (44.0%)	491 (40.8%)
No	231 (57.8%)	217 (54.3%)	210 (52.2%)	658 (54.7%)
Unknown	21 (5.3%)	17 (4.3%)	15 (3.7%)	53 (4.4%)
Tumor Gene Expression ≥ –2.38				
Yes	192 (48.0%)	202(50.5%)	220(54.7%)	614 (51.1%)
No	187 (46.8%)	181 (45.3%)	167 (41.5%)	535 (44.5%)
Unknown	21 (5.3%)	17 (4.3%)	15 (3.7%)	53 (4.4%)
Tumor Gene Expression ≥ –2.93				
Yes	242 (60.5%)	248 (62.0%)	263 (65.4%)	753 (62.6%)
No	137 (34.3%)	135 (33.8%)	124 (30.8%)	396 (32.9%)
Unknown	21 (5.3%)	17 (4.3%)	15 (3.7%)	53 (4.4%)

Numbers analysed

Table 12: Patient populations – All patients (Data cut: 15 September 2017)

	Bev+CP	Atezo+Bev+CP	Atezo+CP	All Patients
Intent-to-Treat Patients	400	400	402	1202
Measurable Disease at Baseline per Investigator in Intent-to-Treat Patients	393	397	401	1191
Safety Evaluable Patients	394	393	400	1187
WT in Intent-to-Treat Patients	336	356	348	1040
WT in Safety Evaluable Patients	331	350	347	1028
ADA Evaluable Atezo Patients	0	364	379	743
tGE in Intent-to-Treat Patients	148	166	177	491
tGE in Safety Evaluable Patients	148	163	177	488
tGE-WT in Intent-to-Treat Patients	129	155	161	445
tGE-WT in Safety Evaluable Patients	129	152	162	443

Atezo=Atezolizumab, Bev=Bevacizumab, CP=Carboplatin+Paclitaxel.
WT are patients with EGFR Wild Type/ALK Negative; tGE are patients with Tumor Gene Expression >= - 1.91; tGE-WT are patients with Tumor Gene Expression >= - 1.91 and EGFR Wild Type/ALK Negative; ADA = anti-drug antibodies.
Safety and ADA are actual treatment received. All other populations are randomized treatment.
Data Cut-off: 15 Sep 2017; RAVE Data Extracted: 10 Nov 2017.

Outcomes and estimation

The primary CSR (cutoff 15 SEP 2017) presented the final PFS analysis and the first interim OS analysis. The updated CSR (cutoff 22 JAN 2018) presents results from the second interim OS analysis as well as updated PFS results (which are presented for descriptive purposes only).

Primary endpoints:

Co-primary endpoint 1:

Investigator-assessed PFS in the Teff-high WT population and the ITT-WT population.

Table 13: Time-to-Event Summary for PFS (ITT–WT Population) - Data Cut: 15 September 2017

	Bev+CP (Randomized) (N=336)	Atezo+Bev+CP (Randomized) (N=356)	Atezo+CP (Randomized) (N=348)
Patients with event (%)	276 (82.1%)	241 (67.7%)	264 (75.9%)
Earliest contributing event			
Death	43	59	37
Disease Progression	233	182	227
Patients without event (%)	60 (17.9%)	115 (32.3%)	84 (24.1%)
Time to Event (Months)			
Median	6.8	8.3	6.3
95% CI	(6.0, 7.1)	(7.7, 9.8)	(5.6, 7.0)
25% and 75%-ile	4.0, 10.4	5.4, 18.4	3.6, 11.9
Range	0.0* to 23.5	0.0* to 26.1^	0.0* to 24.1*
Stratified Analysis			
p-value (log-rank)		<.0001	0.4500
Hazard Ratio		0.617	0.936
95% CI		(0.517, 0.737)	(0.787, 1.112)
Time Point Analysis			
6 Months			
Patients remaining at risk	179	232	172
Event Free Rate (%)	56.12	66.86	50.72
95% CI	(50.71, 61.54)	(61.91, 71.81)	(45.41, 56.03)
Difference in Event Free Rate		10.73	-5.40
95% CI		(3.39, 18.07)	(-12.99, 2.18)
p-value (Z-test)		0.0041	0.1626
1 year			
Patients remaining at risk	39	87	50
Event Free Rate (%)	18.03	36.52	24.89
95% CI	(13.44, 22.63)	(31.17, 41.86)	(20.06, 29.71)
Difference in Event Free Rate		18.49	6.85
95% CI		(11.44, 25.53)	(0.19, 13.51)
p-value (Z-test)		<.0001	0.0437

WT are patients with EGFR Wild Type/ALK Negative.
Atezo=Atezolizumab, Bev=Bevacizumab, CP=Carboplatin+Paclitaxel.
* 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.
Stratified by sex, liver metastasis at baseline from IxRS, and PD-L1 tumour expression by IHC from IxRS (TC3 or IC2/3 vs TC0/1/2 and IC0/1).

Table 14: Time-to-event summary for PFS, ITT-WT population (Data cut: 22 January 2018)

	Bev+CP (Randomized) (N=337)	Atezo+Bev+CP (Randomized) (N=359)	Atezo+CP (Randomized) (N=349)
Patients with event (%)	298 (88.4%)	263 (73.3%)	283 (81.1%)
Earliest contributing event			
Death	49	64	40
Disease Progression	249	199	243
Patients without event (%)	39 (11.6%)	96 (26.7%)	66 (18.9%)
Time to Event (Months)			
Median	6.8	8.3	6.3
95% CI	(6.0, 7.1)	(7.7, 9.8)	(5.6, 7.0)
25% and 75%-ile	4.0, 11.0	5.4, 20.3	4.0, 12.5
Range	0.0* to 25.3*	0.0* to 30.3	0.0* to 28.3*
Unstratified Analysis			
p-value (log-rank)		<.0001	0.0681
Hazard Ratio		0.587	0.858
95% CI		(0.496, 0.695)	(0.728, 1.011
Stratified Analysis			
p-value (log-rank)		<.0001	0.1445
Hazard Ratio		0.592	0.883
95% CI		(0.499, 0.703)	(0.747, 1.044
Time Point Analysis			
6 Months			
Patients remaining at risk	180	234	174
Event Free Rate (%)	55.99	66.48	50.85
95% CI	(50.60, 61.38)	(61.55, 71.41)	(45.56, 56.14
Difference in Event Free Rate		10.49	-5.14
95% CI		(3.18, 17.79)	(-12.69, 2.41
p-value (Z-test)		0.0049	0.1824
1 year			
Patients remaining at risk	61	125	80
Event Free Rate (%)	19.94	37.72	25.85
95% CI	(15.56, 24.33)	(32.62, 42.81)	(21.20, 30.51
Difference in Event Free Rate		17.77	5.91
95% CI		(11.05, 24.50)	(-0.48, 12.31
p-value (Z-test)		<.0001	0.0699
1 1/2 years			
Patients remaining at risk	14	53	29
Event Free Rate (%)	7.83	27.47	17.69
95% CI	(4.59, 11.07)	(22.53, 32.42)	(13.26, 22.12
Difference in Event Free Rate		19.64	9.86
95% CI		(13.73, 25.55)	(4.36, 15.35)
p-value (Z-test)		<.0001	0.0004
2 years			
Patients remaining at risk	1	12	6
Event Free Rate (%)	3.08	18.51	11.81
95% CI	(0.18, 5.97)	(13.03, 23.99)	(7.08, 16.55)
Difference in Event Free Rate		15.43	8.73
95% CI		(9.23, 21.63)	(3.18, 14.29)
p-value (Z-test)		<.0001	0.0020

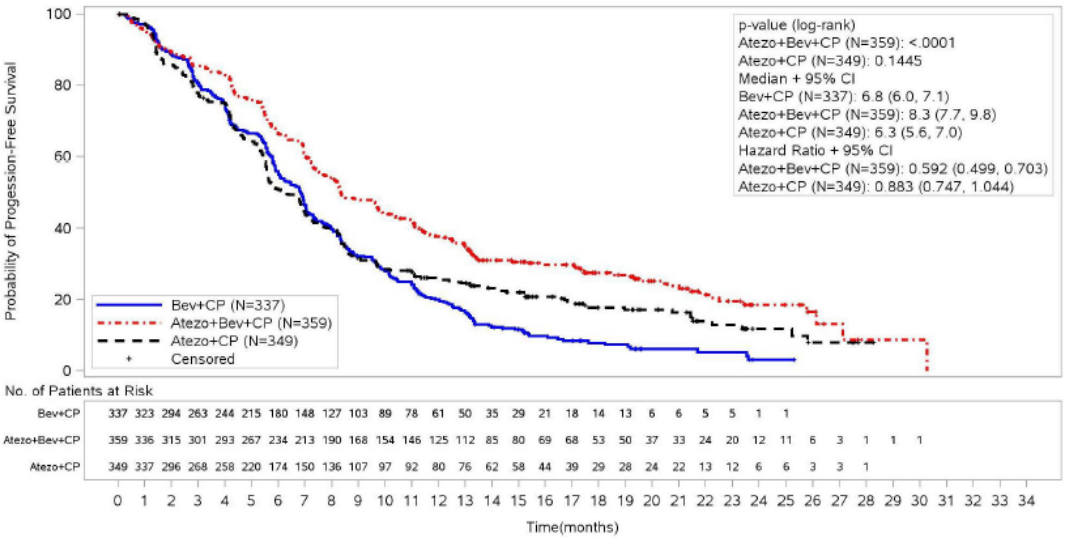


Figure 11: KM plot for PFS with stratified analyses, ITT-WT population (Data cut: 22 January 2018)

Table 15: Time to event summary for progression free survival per investigator Teff high-WT population (Data cut: 22 January 2018)

	Bev+CP (Randomized) (N=129)	Atezo+Bev+CP (Randomized) (N=156)	Atezo+CP (Randomized) (N=162)
Patients with event (%)	111 (86.0%)	103 (66.0%)	129 (79.6%)
Earliest contributing event			
Death	16	33	21
Disease Progression	95	70	108
Patients without event (%)	18 (14.0%)	53 (34.0%)	33 (20.4%)
Time to Event (Months)			
Median	6.8	11.4	6.7
95% CI	(5.9, 7.4)	(9.6, 13.2)	(5.6, 8.2)
25% and 75%-ile	3.6, 10.4	5.5, 25.8	4.2, 14.6
Range	0.3 to 25.3*	0.0* to 30.3	0.4 to 27.5*
Unstratified Analysis			
p-value (log-rank)		<.0001	0.1275
Hazard Ratio		0.487	0.820
95% CI		(0.369, 0.641)	(0.634, 1.059)
Stratified Analysis			
p-value (log-rank)		<.0001	0.1000
Hazard Ratio		0.498	0.803
95% CI		(0.376, 0.660)	(0.617, 1.044)
Time Point Analysis			
6 Months			
Patients remaining at risk	70	109	83
Event Free Rate (%)	57.03	71.24	52.08

Bonferroni-adjusted CI and p-values (unequally weighted Bonferroni method, per EMA/CHMP/44762/2017) are provided for co-primary endpoints that were formally tested by the 22 January 2018 clinical cutoff date (CCOD) based on the alpha spending algorithm. The below table lists the final results for PFS in both ITT-WT and Teff-high WT populations (CCOD: 15 September 2017). The statistical testing conclusions remain the same after the adjustment for all the efficacy analyses listed in the table below. All p-values, confidence intervals, alpha boundaries are two sided.

Table 16: Final PFS in ITT-WT and Teff-High WT Patients

Endpoint	Adjusted CI	Unadjusted Observed P-value vs multiplicity adjusted Alpha Boundary	Adjusted P-value vs Alpha Boundary of 0.05	Comments
Atezo + Bev + CP (Arm B) vs. Bev + CP (Arm C)				
PFS (ITT-WT)	99.4% HR CI [0.466, 0.754]	<0.0001 vs 0.006	0.0001× 0.05/0.006 vs 0.05	Boundary is crossed
PFS (Teff-high WT)	99.4% HR CI [0.336, 0.739]	<0.0001 vs 0.006	0.0001× 0.05/0.006 vs 0.05	Boundary is crossed
Atezo + CP (Arm A) vs. Bev + CP (Arm C)				
PFS (ITT-WT)	99.4% HR CI [0.699, 1.116]	0.1445 vs 0.006	0.1445×0.05/0.006 vs 0.05	Boundary is not crossed
PFS (Teff-high WT)	99.4% HR CI [0.555, 1.160]	0.100 vs 0.006	0.100×0.05/0.006 vs 0.05	Boundary is not crossed

HR=hazard ratio; ITT=intent-to-treat; PFS=progression-free survival; T-eff=T effector; WT=wild type.

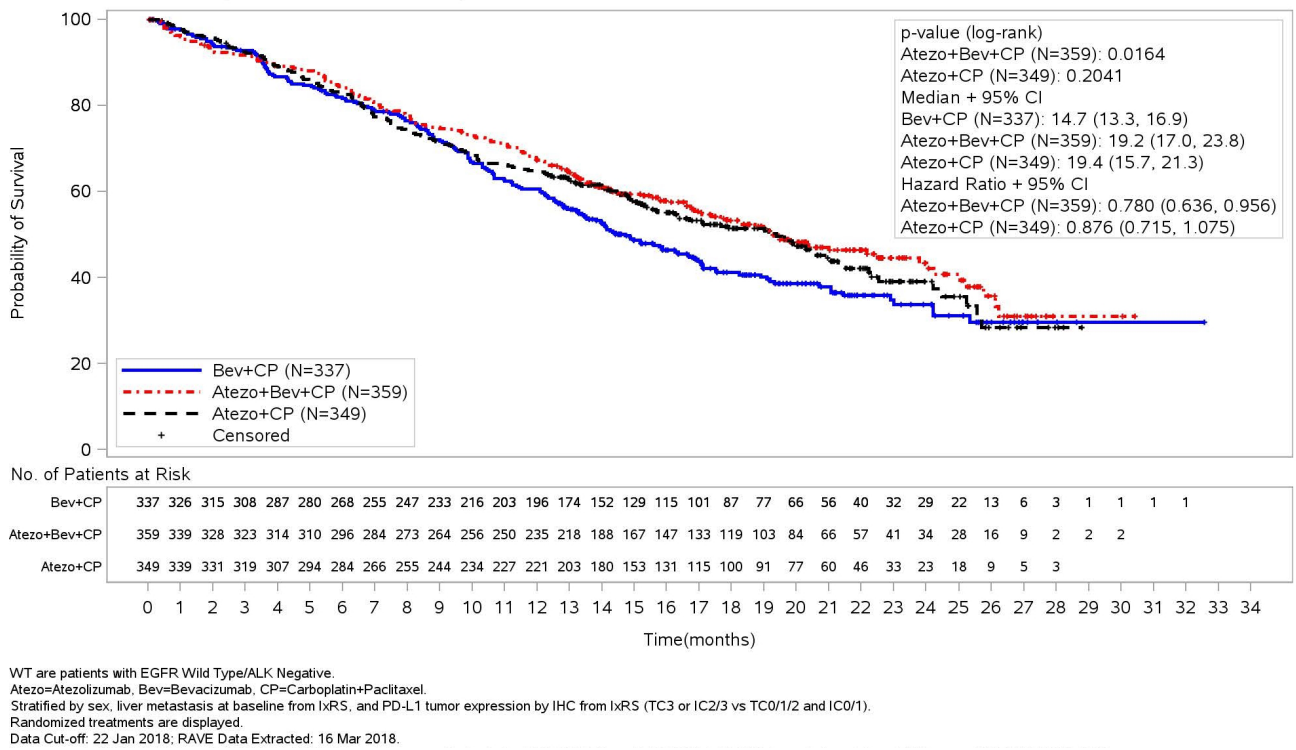
Co-primary endpoint 2:

OS in the ITT-WT population.

At clinical cutoff, 376 death events had been observed among ITT-WT patients in the Bev+CP and Atezo+Bev+CP arms.

Table 17: **Overview of Efficacy (Data cut: 22 January 2018)**

Parameter	Bev + CP	Atezo + Bev + CP	Atezo + CP
Co-Primary Efficacy Objectives (in WT)			
Overall Survival			
ITT–WT Population	n = 337	n = 359	n = 349
Patients with event (%)	197 (58.5%)	179 (49.9%)	179 (51.3%)
Median duration of survival (95% CI) (months)	14.7 (13.3, 16.9)	19.2 (17.0, 23.8)	19.4 (15.7, 21.3)
Stratified Hazard Ratio (95% CI) [a]	---	0.78 (0.64, 0.96)	0.88 (0.72, 1.08)
p-value (log-rank)	---	0.0164	0.2041
Other Key Efficacy Objectives (in ITT)			
Overall Survival			
ITT Population	n = 400	n = 400	n = 402
Patients with event (%)	230 (57.5%)	192 (48.0%)	206 (51.2%)
Median duration of survival (95% CI) (months)	14.9 (13.4, 17.1)	19.8 (17.4, 24.2)	19.5 (16.3, 21.3)
Stratified Hazard Ratio (95% CI) [a]	---	0.76 (0.63, 0.93)	0.85 (0.71, 1.03)
p-value [c, d]		0.0060	0.0983
6-month Overall Survival (%)	81.0	84.8	83.9
12-month Overall Survival (%)	60.6	68.4	66.1
24-month Overall Survival (%)	35.5	45.1	38.3
EGFR mutant/ALK +	n = 63	n = 41	n = 53
Patients with event (%)	33 (52.4%)	13 (31.7%)	27 (50.9%)
Median duration of survival (95% CI) (months)	17.5 (10.4, NE)	NE (17.0, NE)	21.2 (13.6, NE)
Unstratified Hazard Ratio (95% CI) [a]	--	0.542 (0.285, 1.031)	0.823 (0.494, 1.371)



WT are patients with EGFR Wild Type/ALK Negative.
Atezo=Atezolizumab, Bev=Bevacizumab, CP=Carboplatin+Paclitaxel.
Stratified by sex, liver metastasis at baseline from IxRS, and PD-L1 tumor expression by IHC from IxRS (TC3 or IC2/3 vs TC0/1/2 and IC0/1).
Randomized treatments are displayed.
Data Cut-off: 22 Jan 2018; RAVE Data Extracted: 16 Mar 2018.

Figure 12: **Kaplan-Meier Plot for Overall Survival (ITT-WT Population: CCOD 22 January 2018)**

Table 18: **Evolution of Overall Survival Hazard Ratios in Key Efficacy Populations (Between 15 September 2017 and 22 January 2018 Cutoff Dates)**

	Atezo + Bev + CP (Arm B) vs. Bev + CP (Arm C)		**Atezo + CP (Arm A) vs. Bev + CP (Arm C)**	
	First Interim OS 15 September 2017	**Second Interim OS 22 January 2018**	**First Interim OS 15 September 2017**	**Second Interim OS 22 January 2018**
ITT-WT (Stratified HR)	0.78 (0.62, 0.97)	0.78 (0.64, 0.96)	0.92 (0.74, 1.15)	0.88 (0.72, 1.08)
EGFR/ALK+ (Unstratified HR)	0.57 (0.29, 1.11)	0.54 (0.29, 1.03)	0.67 (0.38, 1.17)	0.82 (0.49, 1.37)
ITT (Stratified HR)	0.76 (0.61, 0.93)	0.76 (0.63, 0.93)	0.86 (0.70, 1.06)	0.85 (0.71, 1.03)
Teff Gene Signature Subgroups in the ITT population (Unstratified HR)				
Teff-high [a]	0.78 (0.55, 1.11)	0.80 (0.58, 1.11)	0.92 (0.66, 1.29)	0.93 (0.68, 1.27)
Teff-low [b]	0.78 (0.60, 1.03)	0.78 (0.61, 1.00)	0.84 (0.64, 1.10)	0.81 (0.63, 1.04)
PD-L1 Expression Subgroups in the ITT population (Unstratified HR)				
TC3 or IC3	0.63 (0.37, 1.07)	0.67 (0.42, 1.06)	0.78 (0.47, 1.31)	0.75 (0.47, 1.20)
TC0/1/2 and IC0/1/2	0.79 (0.63, 1.00)	0.80 (0.65, 0.99)	0.86 (0.69, 1.08)	0.86 (0.70, 1.06)
TC2/3 or IC2/3	0.65 (0.45, 0.94)	0.78 (0.56, 1.09)	0.63 (0.43, 0.92)	0.67 (0.47, 0.95)
TC0/1 and IC0/1	0.81 (0.63, 1.05)	0.77 (0.61, 0.97)	0.96 (0.75, 1.23)	0.93 (0.74, 1.16)
TC1/2/3 or IC1/2/3	0.64 (0.47, 0.88)	0.73 (0.55, 0.97)	0.71 (0.53, 0.97)	0.75 (0.57, 1.00)
TC0 and IC0	0.88 (0.66, 1.17)	0.82 (0.63, 1.06)	1.02 (0.77, 1.35)	0.96 (0.74, 1.24)
Key Demographic and Baseline Disease Characteristics Subgroups in the ITT population (Unstratified HR)				
Previous/current tobacco use	0.77 (0.61, 0.97)	0.80 (0.65, 0.98)	0.85 (0.68, 1.06)	0.82 (0.66, 1.01)
Liver metastases (yes)	0.46 (0.27, 0.77)	0.52 (0.33, 0.82)	0.89 (0.57, 1.40)	0.87 (0.57, 1.32)
Liver metastases (no)	0.83 (0.66, 1.04)	0.82 (0.66, 1.01)	0.86 (0.68, 1.08)	0.84 (0.68, 1.04)

Bonferroni-adjusted CI and p-values (unequally weighted Bonferroni method, per EMA/CHMP/44762/2017) are provided for co-primary endpoints that were formally tested by the 22 January 2018 clinical cutoff date (CCOD) based on the alpha spending algorithm. The below table lists the final results for OS in ITT WT population (CCOD: 22 January 2018). The statistical testing conclusions

remain the same after the adjustment for all the efficacy analyses listed in the table below. All p-values, confidence intervals, alpha boundaries are two sided.

Table 19: Final OS in ITT-WT Patients

Endpoint	Adjusted CI	Unadjusted Observed P-value vs multiplicity adjusted Alpha Boundary	Adjusted P-value vs Alpha Boundary of 0.05	Comments
Atezo + Bev + CP (Arm B) vs. Bev + CP (Arm C)				
OS IA2 (ITT-WT)	98.2% HR CI [0.610, 0.997]	0.0164 at interim vs 0.0184	0.0164 × 0.05/0.0184 vs 0.05	Boundary is crossed
Atezo + CP (Arm A) vs. Bev + CP (Arm C)				
OS IA2 (ITT-WT)	98.7% HR CI [0.677, 1.135]	0.204 at interim vs 0.013	0.204×0.05/0.013 vs 0.05	Boundary is not crossed

HR=hazard ratio; IA2=interim analysis 2; ITT=intent-to-treat; OS=overall survival; PFS=progression-free survival; T-eff=T effector; WT=wild type.

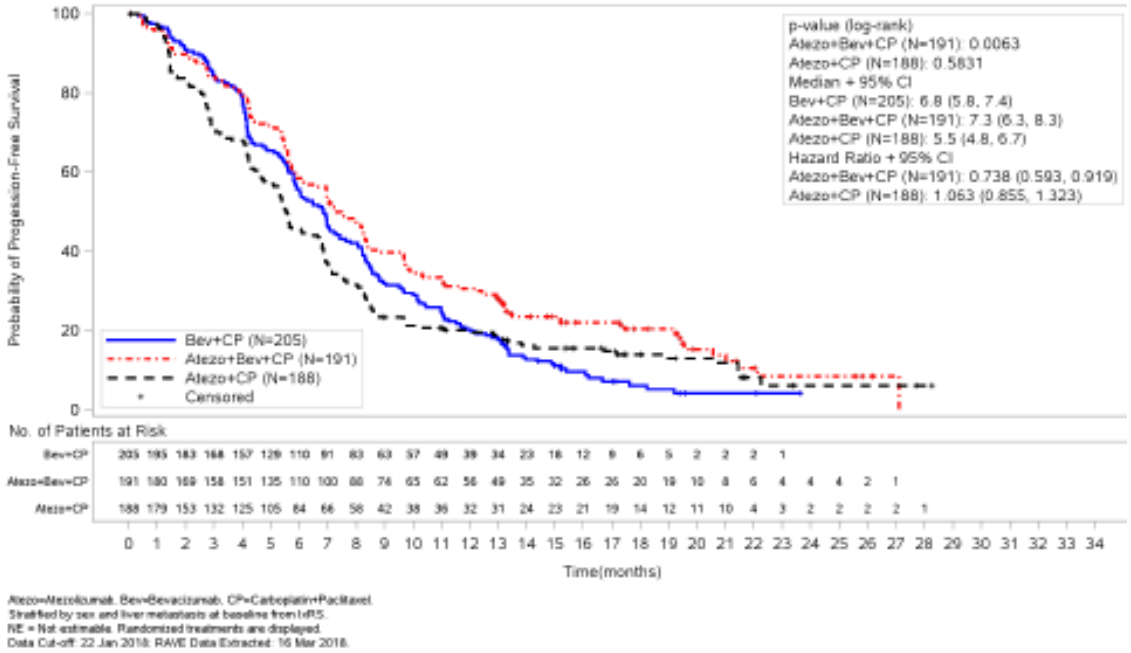
Secondary endpoints

PFS in ITT population

Table 20: Evolution of Progression-Free Survival Hazard Ratios in Key Efficacy Populations (Between 15 September 2017 and 22 January 2018 Cutoff Dates)

	Atezo + Bev + CP (Arm B) vs. Bev + CP (Arm C)		Atezo + CP (Arm A) vs. Bev + CP (Arm C)	
	Final PFS 15 September 2017	Updated PFS 22 January 2018	Final PFS 15 September 2017	Updated PFS 22 January 2018
ITT-WT (Stratified HR)	0.62 (0.52, 0.74)	0.59 (0.50, 0.70)	0.94 (0.79, 1.11)	0.88 (0.75, 1.04)
EGFR/ALK+ (Unstratified HR)	0.59 (0.37, 0.94)	0.55 (0.35, 0.87)	1.13 (0.76, 1.67)	1.13 (0.76, 1.67)
ITT (Stratified HR)	0.61 (0.52, 0.72)	0.59 (0.50, 0.69)	0.96 (0.82, 1.12)	0.91 (0.78, 1.06)
Teff Gene Signature Subgroups in ITT Population (Unstratified HR)				
Teff-high [a]	0.50 (0.38, 0.65)	0.49 (0.37, 0.64)	0.88 (0.69, 1.13)	0.82 (0.63, 1.06)
Teff-low [b]	0.76 (0.61, 0.93)	0.74 (0.59, 0.92)	0.98 (0.80, 1.21)	0.95 (0.76, 1.19)
PD-L1 Expression Subgroups in ITT Population (Unstratified HR)				
TC3 or IC3	0.38 (0.25, 0.58)	0.33 (0.22, 0.51)	0.64 (0.44, 0.94)	0.63 (0.43, 0.92)
TC0/1/2 and IC0/1/2	0.68 (0.57, 0.81)	0.66 (0.56, 0.79)	0.99 (0.84, 1.18)	0.95 (0.81, 1.12)
TC2/3 or IC2/3	0.46 (0.34, 0.62)	0.43 (0.33, 0.58)	0.61 (0.46, 0.81)	0.60 (0.46, 0.79)
TC0/1 and IC0/1	0.71 (0.58, 0.87)	0.69 (0.57, 0.83)	1.15 (0.95, 1.39)	1.10 (0.91, 1.32)
TC1/2/3 or IC1/2/3	0.50 (0.39, 0.63)	0.47 (0.37, 0.59)	0.78 (0.63, 0.98)	0.76 (0.61, 0.94)
TC0 and IC0	0.76 (0.61, 0.96)	0.74 (0.60, 0.92)	1.15 (0.92, 1.44)	1.07 (0.86, 1.32)
Key Demographic and Baseline Disease Characteristics Subgroups in ITT Population (Unstratified HR)				
Previous/current tobacco use	0.59 (0.49, 0.71)	0.57 (0.47, 0.68)	0.84 (0.71, 1.01)	0.81 (0.68, 0.95)
Liver metastases (yes)	0.40 (0.26, 0.62)	0.41 (0.26, 0.62)	0.88 (0.59, 1.32)	0.81 (0.55, 1.21)
Liver metastases (no)	0.64 (0.53, 0.76)	0.61 (0.52, 0.73)	0.94 (0.79, 1.11)	0.90 (0.77, 1.06)

PFS by PD-L1 Subgroups



Atezo=Atezolizumab, Bev=Bevacizumab, CP=Carboplatin+Paclitaxel.
Stratified by sex and liver metastasis at baseline from IxRS.
NE = Not estimable. Randomized treatments are displayed.
Data Cut-off: 22 Jan 2018; RAVE Data Extracted: 16 Mar 2018.

Figure 13: Kaplan-Meier plot of progression free survival per investigator with stratified analysis TC0 and IC0, ITT patients (Fata cut: 22 January 2018)

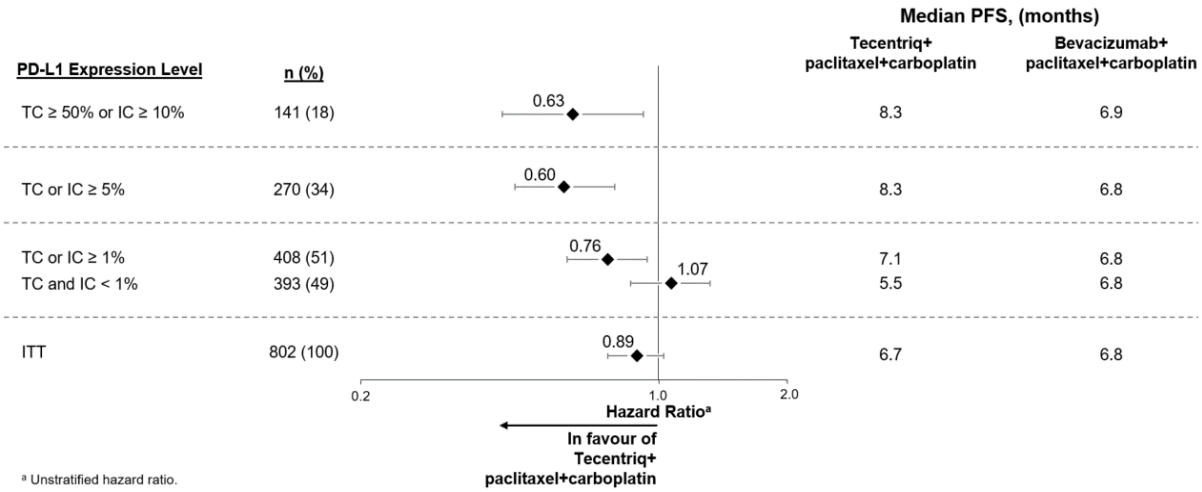


Figure 14: Forest plot of progression free survival by PD-L1 expression in the ITT population, Arm A vs C (IMpower150)

IRF-PFS in ITT-WT and ITT populations

*Data not updated in 22-JAN-2018 cutoff.

Table 21: Time-to-event summary for PFS-INV and PFS-IRF (ITT-WT and ITT populations)

	PFS-INV per RECIST v1.1			PFS-IRF per RECIST v1.1		
	Bev + CP	Atezo + Bev + CP	Atezo + CP	Bev + CP	Atezo + Bev + CP	Atezo + CP
ITT–WT Population	n=336	n=356	n=348	n=336	n=356	n=348
Patients with event (%)	276 (82.1)	241 (67.7)	264 (75.9)	246 (73.2)	245 (68.8)	244 (70.1)
Median duration of PFS (months)	6.8	8.3	6.3	7.0	8.5	6.7
95% CI	(6.0, 7.1)	(7.7, 9.8)	(5.6, 7.0)	(6.3, 8.0)	(7.7, 9.7)	(5.6, 6.9)
Stratified Analysis **Atezo + Bev + CP (B) vs. Bev + CP (C)**						
Hazard Ratio (95% CI) [a]		0.62 (0.52, 0.74)	--		0.71 (0.59, 0.85)	--
p-value (log-rank)		<0.0001	--		0.0002	--
Stratified Analysis **Atezo + CP (A) vs. Bev + CP (C)**						
Hazard Ratio (95% CI) [a]		--	0.94 (0.79, 1.11)		--	0.94 (0.79, 1.13)
p-value (log-rank)		--	0.450 [b]		--	0.524 [b]
ITT Population	n=400	n=400	n=402	n= 400	n=400	n=402
Patients with event (%)	331 (82.8)	267 (66.8)	311 (77.4)	296 (74.0)	269 (67.3)	286 (71.1)
Median duration of PFS (months)	6.8	8.3	6.7	7.0	8.5	6.7
95% CI	(6.0, 7.1)	(7.9, 9.8)	(5.7, 6.9)	(6.1, 7.8)	(8.1, 9.7)	(5.6, 6.9)
Stratified Analysis **Atezo + Bev + CP (B) vs. Bev + CP (C)**						
Hazard Ratio (95% CI) [a]		0.61 (0.52, 0.72)	--		0.67 (0.56, 0.79)	--
p-value (log-rank)		<0.0001	--		<0.0001	--
Stratified Analysis **Atezo + CP (A) vs. Bev + CP (C)**						
Hazard Ratio (95% CI) [a]		--	0.96 (0.82, 1.12)		--	0.92 (0.78, 1.09)
p-value (log-rank)		--	0.604 [b]		--	0.924 [b]

ITT-WT population

PFS assessed by independent review facility (PFS-IRF)

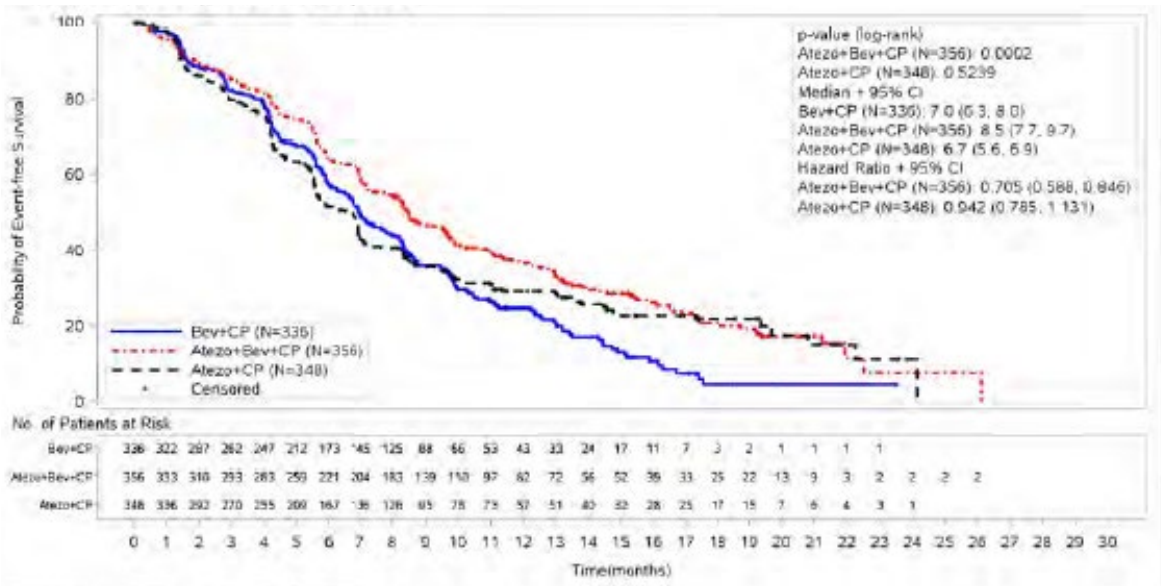


Figure 15: Kaplan-Meier plot of progression free survival per IRF with stratified analysis – WT in ITT patients (Data cut: 15 September 2017)

ITT population

PFS by independent review facility (PFS-IRF)

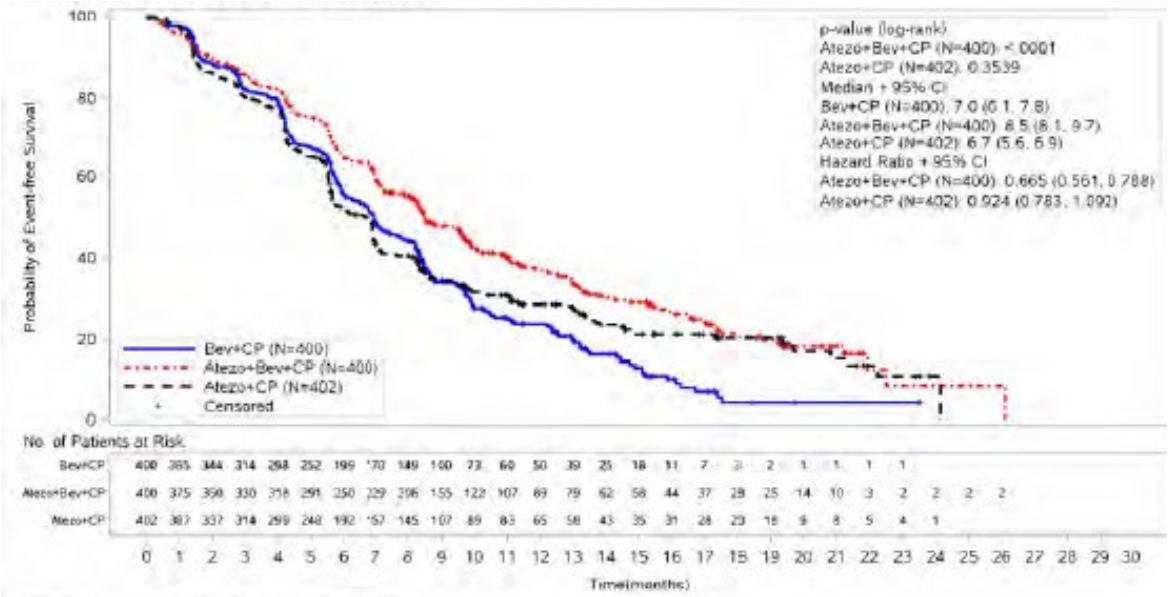
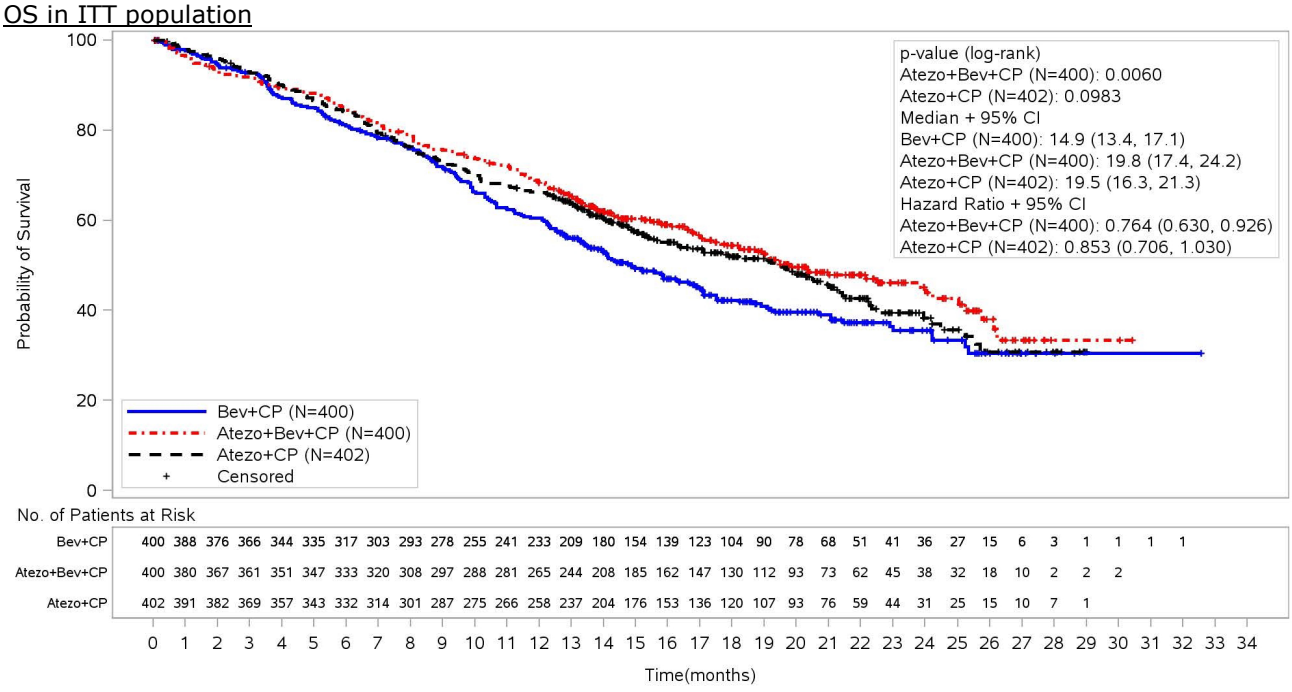


Figure 16: Kaplan-Meier plot of progression free survival per IRF with stratified analysis – ITT patients (Data cut: 15 September 2017)

OS in ITT population



Atezo=Atezolizumab, Bev=Bevacizumab, CP=Carboplatin+Paclitaxel.
Stratified by sex, liver metastasis at baseline from IxRS, and PD-L1 tumor expression by IHC from IxRS (TC3 or IC2/3 vs TC0/1/2 and IC0/1).
Randomized treatments are displayed.
Data Cut-off: 22 Jan 2018; RAVE Data Extracted: 16 Mar 2018.

Figure 17: Kaplan-Meier Plot for Overall Survival (ITT Population: CCOD 22 January 2018)

OS by PD-L1 subgroups

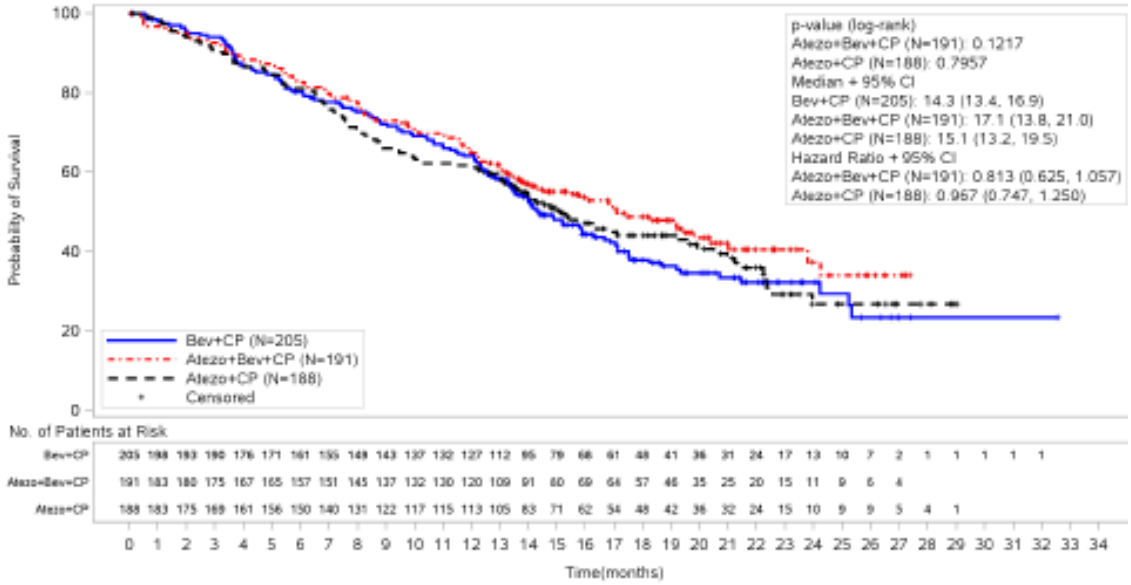


Figure 18: Kaplan-Meier plot of overall survival with stratified analysis TC0 and IC0, ITT patients (Data cut: 22 January 2018)

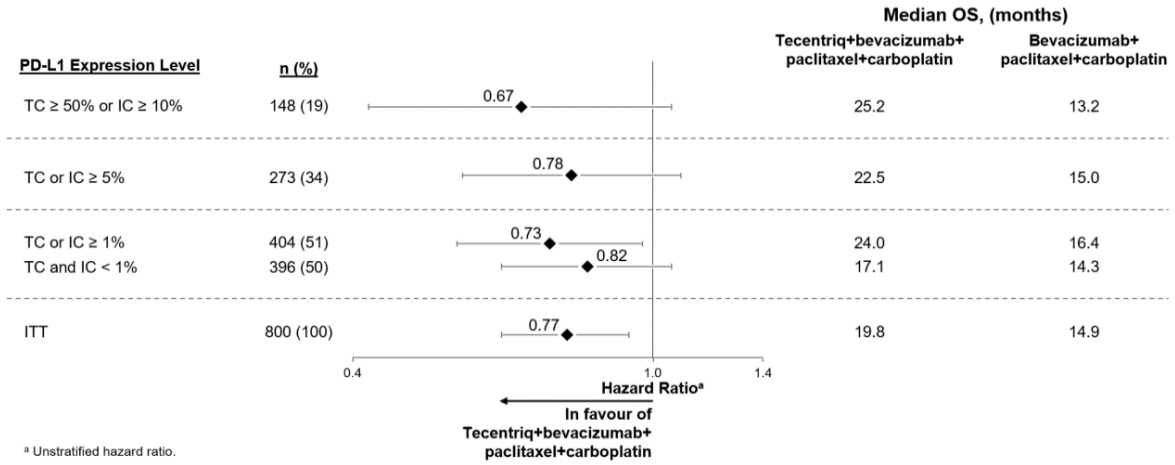


Figure 19: Forest plot of overall survival by PD-L1 expression in the ITT population, Arm B vs C (IMpower150)

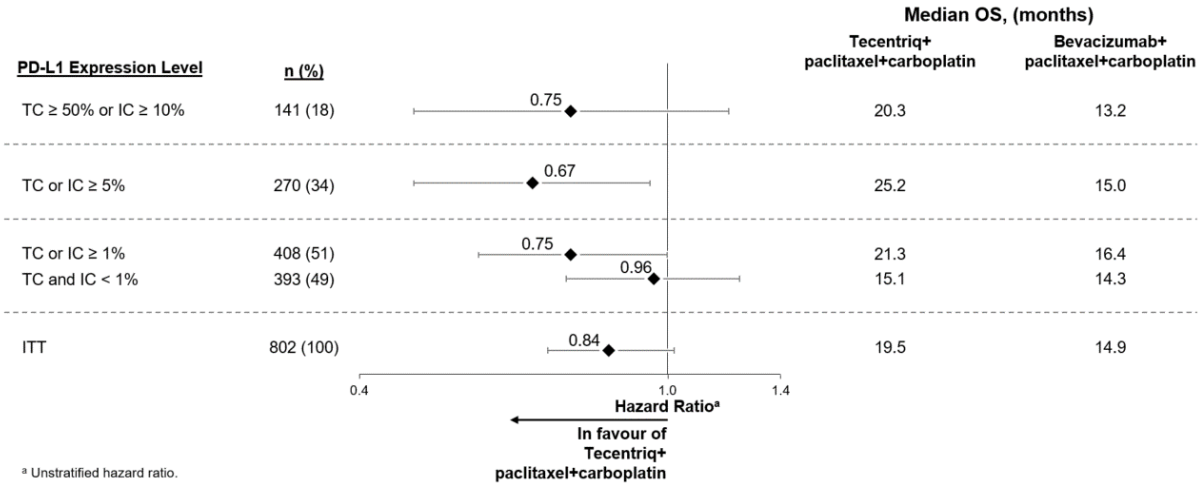


Figure 20: Forest plot of overall survival by PD-L1 expression in the ITT population, Arm A vs C (IMpower150)

Updated INV-ORR in ITT

Table 22: Best overall unconfirmed response per RECIST v1.1 – investigator measurable disease at baseline in ITT patients (Data cut: 15 September 2018)

	Bev+CP (N=393)	Atezo+Bev+CP (N=397)	Atezo+CP (N=401)
Responders	188 (47.8%)	253 (63.7%)	191 (47.6%)
Non-Responders	205 (52.2%)	144 (36.3%)	210 (52.4%)

Table 23: Investigator-Assessed Confirmed Overall Response Rate (RECIST v1.1) (Data cut: 22 January 2018)

Parameter	Bev + CP	Atezo + Bev + CP	Atezo + CP
	n = 393	n = 397	n = 401
No. of responders (%)	158 (40.2%)	224 (56.4%)	163 (40.6%)
95% CI	(35.32, 45.24)	(51.39, 61.36)	(35.80, 45.63)
No. of complete response (%)	3 (0.8%)	11 (2.8%)	8 (2.0%)
No of partial response (%)	155 (39.4%)	213 (53.7%)	155 (38.7%)

DoR in ITT population

Table 24: Duration of first response (Data cut: 15 September 2017)

	Bev+CP (Randomized) (N=188)	Atezo+Bev+CP (Randomized) (N=253)	Atezo+CP (Randomized) (N=191)
Patients with event (%)	156 (83.0%)	147 (58.1%)	119 (62.3%)
Earliest contributing event			
Death	11	21	5
Disease Progression	145	126	114
Patients without event (%)	32 (17.0%)	106 (41.9%)	72 (37.7%)
Time to Event (Months)			
Median	5.5	9.0	7.0
95% CI	(4.8, 6.0)	(7.0, 11.2)	(5.7, 8.3)
25% and 75%-ile	3.3, 8.5	4.5, 21.4	4.1, 16.1
Range	0.0* to 22.1	0.4 to 24.9*	0.0* to 22.3*

Table 25: Investigator-Assessed Duration of Response (RECIST v1.1) (Data cut: 22 January 2018)

Parameter	Bev + CP	Atezo + Bev + CP	Atezo + CP
	n = 158	n = 224	n = 163
Median in months	6.0	11.5	8.3
95% CI	(5.5, 6.9)	(8.9, 15.7)	(7.1, 11.8)

Patient reported outcomes (PROs)

The completion rates were high (>80%) for both the EORTC QLQ-C30 and LC13 across treatment arms throughout the course of treatment. At baseline, 91.4% (n = 360) in the Bev + CP arm, 90.6% (n = 357) in the Atezo + Bev + CP arm, and 92.7% (n = 370) of patients in the Atezo + CP arm completed the EORTC QLQ-C30 in the ITT population. Similar rates of baseline completion were also observed using the EORTC QLQ-LC13: 89.8% (n = 354) in the Bev + CP arm, 88.8% (n = 350) in the Atezo + Bev + CP arm, and 92.5% (n = 369) in the Atezo + CP arm.

Completion rates with both the EORTC QLQ-C30 and LC13 questionnaires remained above 70% in all arms until Cycle 20 in the Bev + CP arm, Cycle 25 in the Atezo + Bev + CP arm, and Cycle 24 in the Atezo + CP arm; most cycles in all arms had completion rates >= 80%. The latest cycle with approximately 25% of the original population remaining to complete the PRO assessments was Cycle 13 in the Bev + CP arm, Cycle 15 in the Atezo + CP arm, and Cycle 18 in the

Atezo + Bev + CP arm. Rates of completion in both the Teff-high-WT and ITT-WT populations were similar to those observed in the ITT population.

Health related quality of life (HRQoL) and function

Patients in all treatment arms reported moderately impaired HRQoL at baseline as assessed through the EORTC QLQ-C30 Global Heal Status (GHS) score with mean scores of 62.7, 62.3, and 61.5 for Atezo + CP arm, Atezo + Bev + CP arm, and Bev + CP arm, respectively. Patients in all arms reported moderate to high scores for all aspects of function (i.e., physical, role, emotional, cognitive, and social) at baseline; mean scores for physical function were 76.3, 75.9, and 75.1 for the Atezo + CP arm, Atezo + Bev + CP arm, and Bev + CP arm, respectively. Baseline scores for all functional scales were comparable between treatment arms.

Observation of change in scores over time suggests that GHS/HRQoL and Physical Function mean scores in each arm return to baseline scores following the completion of chemotherapy and numerically improve thereafter. Overall, the mean change from baseline never crossed the 10 point threshold indicating that overall, changes in GHS/HRQoL and PF are not clinically significant at any time point through Cycle 13, at which point there are fewer than 25% of patients in the baseline sample of the Bev + CP arm and comparisons between arms should be done with caution.

Mean change from baseline scores for other function domains (i.e., cognitive, emotional, social, role), follow a similar pattern at most of the post-baseline timepoints evaluated; patients in all three treatment arms report comparable scores. Mean change from baseline in GHS and function scores in both the ITT-WT (EORTC QLQ-C30 and LC13) and Teff-high WT (EORTC QLQ-C30 and LC13) populations were similar to those observed in the ITT (EORTC QLQ-C30 and LC13) population.

Treatment burden/tolerability

Patients' perspective regarding the severity of commonly experienced treatment-related symptoms (i.e., fatigue, nausea/vomiting, diarrhea, constipation, alopecia, peripheral neuropathy, sore mouth, dysphagia, hemoptysis) was captured via the EORTC QLQ-C30 and LC13 questionnaires. Initially, average change from baseline scores in fatigue, constipation, diarrhea, and nausea/vomiting scores numerically worsened in all treatment arms then returned to their baseline level following the completion of chemotherapy.

Patients in all arms, on average, did not report clinically meaningful worsening (>= 10 point increase from baseline) at any point on treatment for multiple treatment-related symptoms including fatigue, constipation, diarrhea, nausea/vomiting, hemoptysis, dysphagia, and sore mouth through Cycles 13, 15, and 18 for the Bev + CP, Atezo + CP, and Atezo + Bev + CP arms, respectively. A clinically meaningful worsening was observed across treatment arms for both patient-reported peripheral neuropathy and alopecia; large mean increases from baseline (>= 60 point increase for alopecia; >=30 point increase for peripheral neuropathy) were seen initially in all treatment arms and attenuated over time at similar time points across arms. Mean change from baseline scores were numerically lower (lower symptom severity) for patients in the Atezo + CP arm compared with patients in the Bev + CP arm for fatigue, sore mouth, constipation, and diarrhea at most time points post-baseline. Mean change from baseline results in both the ITT-WT (EORTC QLQ-C30 and LC13) and Teff-high-WT (EORTC QLQ-C30 and LC13) populations were similar to those observed in the ITT (EORTC QLQ-C30 and LC13) population.

Disease burden

No differences were observed between treatment arms in the time to deterioration of each individual lung cancer symptom, i.e., cough (ITT, ITT-WT, and Teff-high WT), dyspnea single-item (ITT, ITT-WT, and Teff-high WT), dyspnea multi-item (ITT, ITT-WT, and Teff-high WT), chest pain (ITT, ITT-WT, and Teff-high WT), and pain in arm/shoulder (ITT, ITT-WT, and Teff-high WT). Median time to deterioration were not reached in any arm across symptom scores (with the exception of pain in arm/shoulder 18.7 months in the Bev + CP arm; dyspnea 21.9 months in the Atezo + CP arm) for analyses conducted in the ITT population. Mean change from baseline in all treatment arms, on average, reported numerical improvement in multiple lung cancer symptom scores (i.e., chest pain, pain in arm/shoulder, cough,

and dyspnea single-item) for most timepoints on treatment. Results were comparable among arms at most timepoints on treatment (EORTC QLQC30 and LC13).

Ancillary analyses

Clinical efficacy in EGFR mutant/ALK+ patients

Table 26: Overview of Efficacy in the EGFR/ALK+ population (Clinical Cutoff: 22 January 2018)

Parameter	Bev + CP n = 63	Atezo + Bev + CP n = 41	Atezo + CP n = 53
Overall Survival			
Patients with event (%)	33 (52.4%)	13 (31.7%)	27 (50.9%)
Median (95% CI) duration of OS (months)	17.5 (10.4, NE)	NE (17.0, NE)	21.2 (13.6, NE)
Unstratified hazard ratio (95% CI) [a]	--	0.542 (0.285, 1.03)	0.823 (0.494, 1.37)
Progression-Free Survival			
Patients with event (%)	57 (90.5%)	28 (68.3%)	47 (88.7%)
Median (95% CI) duration of PFS (months)	6.1 (5.6, 8.4)	10.0 (7.9, 15.2)	6.9 (5.7, 7.8)
Unstratified hazard ratio (95% CI) [a]	--	0.552 (0.35, 0.87)	1.127 (0.76, 1.67)
Investigator-Assessed Unconfirmed Overall Response Rate (RECIST v1.1)	n = 61	n = 41	n = 53
No. of responders (%)	29 (47.5%)	29 (70.7%)	19 (35.8%)
95% CI	(34.60, 60.73)	(54.46, 83.87)	(23.14, 50.20)
No. of complete response (%)	2 (3.3%)	2 (4.9%)	1 (1.9%)
No of partial response (%)	27 (44.3%)	27 (65.9%)	18 (34.0%)
Investigator-Assessed Duration of Response (RECIST v1.1)[b]	n = 29	n = 29	n = 19
Patients with ongoing response	0	11 (37.9%)	3 (15.8%)
Median in months	4.4	11.1	5.6
95% CI	(4.2, 5.4)	(6.0, 18.0)	(4.2, 11.8)

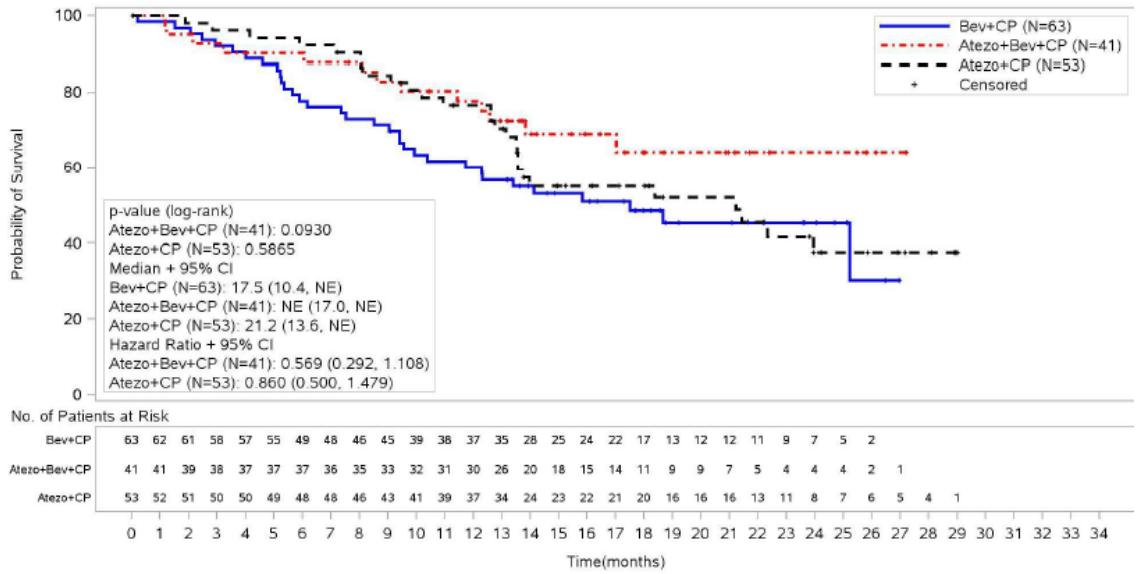


Figure 21: Kaplan-Meier plot of OS with stratified analysis EGFR/ALK+ in ITT patients (Data cut: 22 January 2018)

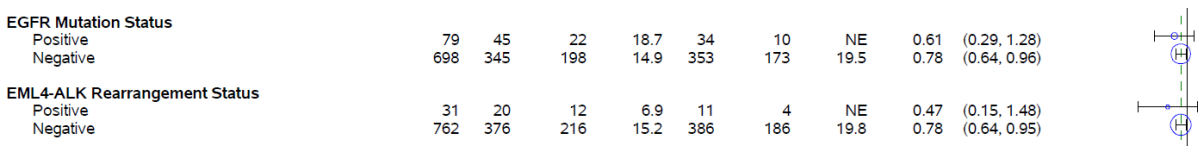


Figure 22: Forest plot – subgroup analysis of duration, overall survival Bev+CP and Atezo+Bev+CP, ITT patients (Data cut: 22 January 2018)

Missing tumour assessment

*Data not updated in 22-JAN-2018 cut-off.

Table 27: Time-to-event summary for PFS censoring for missing tumour assessments (ITT-WT population) (Data cut: 15 September 2017)

	Bev+CP (Randomized) (N=336)	Atezo+Bev+CP (Randomized) (N=356)	Atezo+CP (Randomized) (N=348)
Patients with event (%)	264 (78.6%)	227 (63.8%)	258 (74.1%)
Earliest contributing event			
Death	35	48	32
Disease Progression	229	179	226
Patients without event (%)	72 (21.4%)	129 (36.2%)	90 (25.9%)
Time to Event (Months)			
Median	6.8	8.3	6.4
95% CI	(6.0, 7.1)	(7.7, 9.8)	(5.6, 7.0)
25% and 75%-ile	4.0, 11.0	5.4, 19.2	3.4, 12.1
Range	0.0* to 23.5	0.0* to 26.1^	0.0* to 24.1*
Stratified Analysis			
p-value (log-rank)		<.0001	0.5033
Hazard Ratio		0.618	0.942
95% CI		(0.515, 0.741)	(0.790, 1.123)

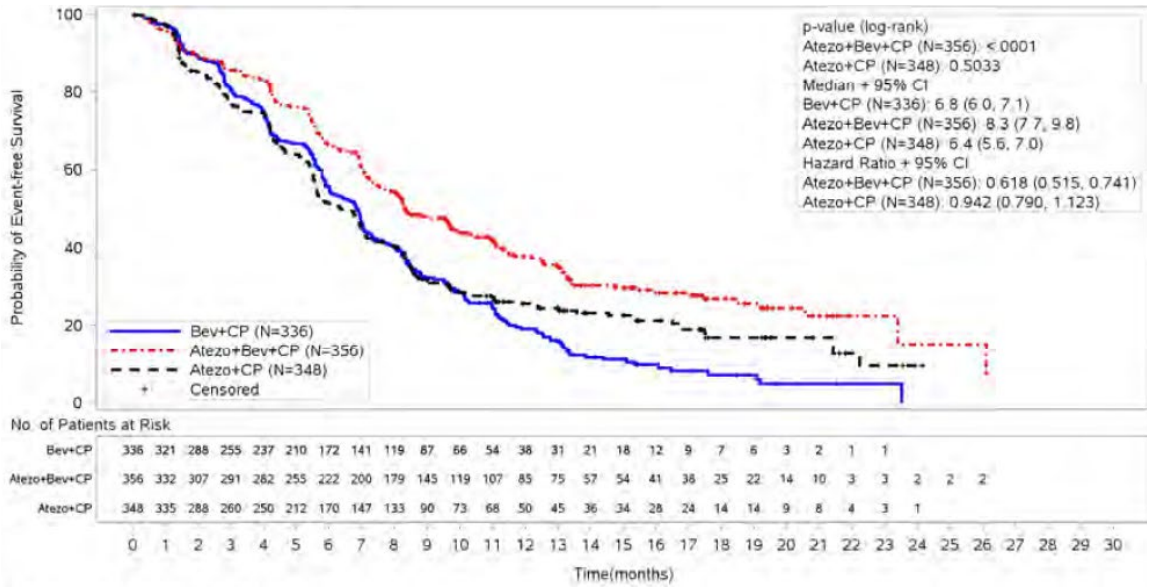
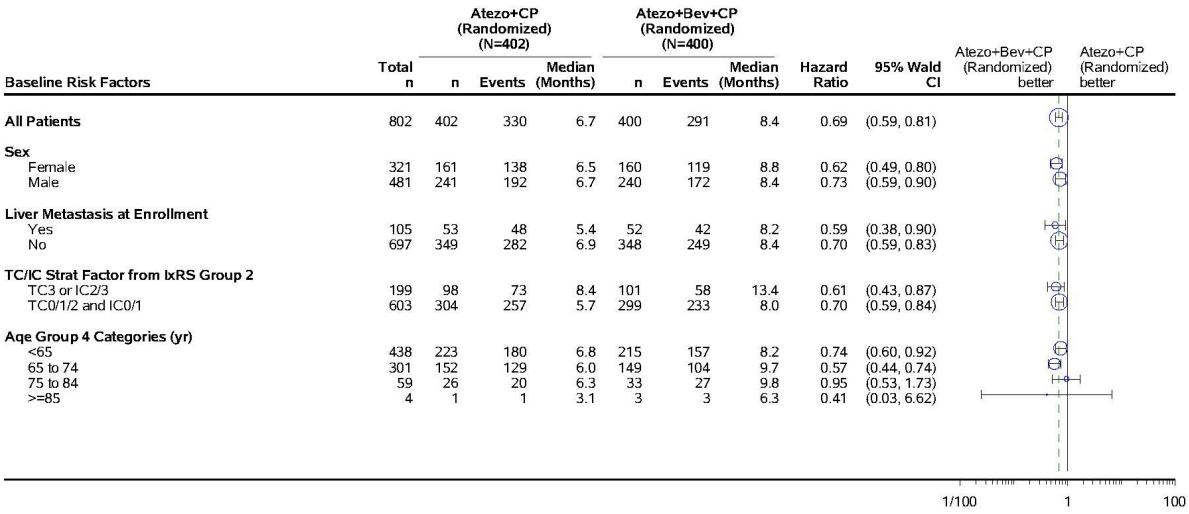


Figure 23: Kaplan-Meier plot of investigator PFS censored for missing visits with stratified analysis WT in ITT patients (Data cut: 15 September 2017)

Efficacy of the two atezolizumab-containing arms

Table 28: Summary of OS and PFS for Arm A versus Arm B in the ITT population

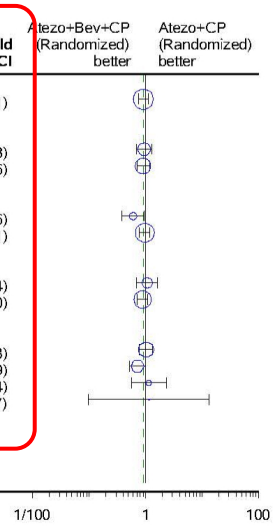
Parameter	Atezo + Bev + CP n = 400	Atezo + CP n = 402
Overall Survival		
Patients with event (%)	192 (48.0%)	206 (51.2%)
Median (95% CI) duration of survival (months)	19.8 (17.4, 24.2)	19.5 (16.3, 21.3)
Stratified hazard ratio (95% CI) [a]	0.90 (0.74, 1.10)	
p-value (log-rank)	0.3000	
Progression-Free Survival		
Patients with event (%)	291 (72.8%)	330 (82.1%)
Median (95% CI) duration of PFS (months)	8.4 (8.0, 9.9)	6.7 (5.7, 6.9)
Stratified hazard ratio (95% CI) [a]	0.67 (0.57, 0.79)	
p-value (log-rank)	<0.0001	



Atezo=Atezolizumab, Bev=Bevacizumab, CP=Carboplatin+Paclitaxel.
NE= Not estimable; Median progression-free survival was estimated from Kaplan-Meier method. Unstratified hazard ratio relative to Atezo+CP and 95% CI for the hazard ratio were estimated using Cox regression. The vertical dashed line indicates the hazard ratio for all patients. The diameter of the circle is proportional to the square root of the total number of events.
Randomized treatments are displayed.
Data Cut-off: 22 Jan 2018; RAVE Data Extracted: 16 Mar 2018.

Figure 24: Forest Plot – subgroup analysis of duration, PFS per investigator for Arm A versus Arm B (ITT population) (Data cut: 22 January 2018)

Baseline Risk Factors	Total n	Atezo+CP (Randomized) (N=402) n	Events	Median (Months)	Atezo+Bev+CP (Randomized) (N=400) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	802	402	206	19.5	400	192	19.8	0.91	(0.75, 1.11)
Sex									
Female	321	161	81	20.5	160	76	20.3	0.94	(0.69, 1.28)
Male	481	241	125	17.9	240	116	19.1	0.90	(0.70, 1.16)
Liver Metastasis at Enrollment									
Yes	105	53	41	8.9	52	31	13.3	0.60	(0.38, 0.96)
No	697	349	165	21.0	348	161	20.4	0.97	(0.78, 1.21)
TC/IC Strat Factor from IxRS Group 2									
TC3 or IC2/3	199	98	39	25.7	101	44	25.2	1.07	(0.69, 1.64)
TC0/1/2 and IC0/1	603	304	167	16.4	299	148	19.1	0.88	(0.70, 1.10)
Age Group 4 Categories (yr)									
<65	438	223	111	19.7	215	108	19.2	1.02	(0.78, 1.33)
65 to 74	301	152	81	17.9	149	63	26.1	0.72	(0.51, 0.99)
75 to 84	59	26	13	19.9	33	18	16.6	1.14	(0.56, 2.34)
>=85	4	1	1	8.7	3	3	6.3	1.14	(0.10, 13.27)



Atezo=Atezolizumab, Bev=Bevacizumab, CP=Carboplatin+Paclitaxel.
NE= Not estimable; Median survival was estimated from Kaplan-Meier method. Unstratified hazard ratio relative to Atezo+CP and 95% CI for the hazard ratio were estimated using Cox regression. The vertical dashed line indicates the hazard ratio for all patients. The diameter of the circle is proportional to the square root of the total number of events. Randomized treatments are displayed.
Data Cut-off: 22 Jan 2018; RAVE Data Extracted: 16 Mar 2018.

Figure 25: Forest Plot - subgroup analysis of duration, OS for Arm A versus Arm B (ITT population) (Data cut: 22 January 2018)

Non-protocol-specified or follow-up anti-cancer therapy

Table 29: Non-protocol concomitant medication and follow-up therapies (ITT population) (Data cut: 22 January 2018)

Types of Therapy Medication	Bev+CP (Randomized) (N=400)	Atezo+Bev+CP (Randomized) (N=400)	Atezo+CP (Randomized) (N=402)	All Patients (N=1202)
Total number of patients with at least one treatment	232 (58.0%)	158 (39.5%)	195 (48.5%)	585 (48.7%)
Total number of treatments	462	322	402	1186
Chemotherapy				
Total number of patients with at least one treatment	121 (30.3%)	127 (31.8%)	167 (41.5%)	415 (34.5%)
Total number of treatments	215	224	281	720
PEMETREXED	64 (16.0%)	71 (17.8%)	87 (21.6%)	222 (18.5%)
DOCETAXEL	39 (9.8%)	28 (7.0%)	44 (10.9%)	111 (9.2%)
CARBOPLATIN	27 (6.8%)	28 (7.0%)	33 (8.2%)	88 (7.3%)
PEMETREXED DISODIUM	16 (4.0%)	27 (6.8%)	33 (8.2%)	76 (6.3%)
CISPLATIN	15 (3.8%)	9 (2.3%)	26 (6.5%)	50 (4.2%)
GEMCITABINE	8 (2.0%)	9 (2.3%)	12 (3.0%)	29 (2.4%)
PACLITAXEL	8 (2.0%)	11 (2.8%)	5 (1.2%)	24 (2.0%)
GIMERACIL/OTERACIL POTASSIUM/TEGAFUR	4 (1.0%)	6 (1.5%)	6 (1.5%)	16 (1.3%)
VINORELBINE	4 (1.0%)	4 (1.0%)	6 (1.5%)	14 (1.2%)
GEMCITABINE HYDROCHLORIDE	4 (1.0%)	4 (1.0%)	4 (1.0%)	12 (1.0%)
ETOPOSIDE	4 (1.0%)	2 (0.5%)	4 (1.0%)	10 (0.8%)
VINORELBINE TARTRATE	3 (0.8%)	2 (0.5%)	0	5 (0.4%)
FLUOROURACIL	1 (0.3%)	2 (0.5%)	1 (0.2%)	4 (0.3%)
PACLITAXEL ALBUMIN	3 (0.8%)	1 (0.3%)	0	4 (0.3%)
METHOTREXATE	1 (0.3%)	1 (0.3%)	1 (0.2%)	3 (0.2%)
AMRUBICIN	1 (0.3%)	1 (0.3%)	0	2 (0.2%)
CYCLOPHOSPHAMIDE	1 (0.3%)	1 (0.3%)	0	2 (0.2%)
DOXORUBICIN	1 (0.3%)	1 (0.3%)	0	2 (0.2%)
IRINOTECAN	1 (0.3%)	0	1 (0.2%)	2 (0.2%)
AMRUBICIN HYDROCHLORIDE	0	0	1 (0.2%)	1 (<0.1%)
AZACITIDINE	1 (0.3%)	0	0	1 (<0.1%)
CAPECITABINE	0	0	1 (0.2%)	1 (<0.1%)
EPIRUBICIN	0	0	1 (0.2%)	1 (<0.1%)
GIMERACIL	0	1 (0.3%)	0	1 (<0.1%)
HYDROXYCARBAMIDE	0	1 (0.3%)	0	1 (<0.1%)
IFOSFAMIDE	0	1 (0.3%)	0	1 (<0.1%)
OTERACIL POTASSIUM	0	1 (0.3%)	0	1 (<0.1%)
OXALIPLATIN	0	0	1 (0.2%)	1 (<0.1%)
PLATINUM	0	0	1 (0.2%)	1 (<0.1%)
TAS-114 (CYTOSTATIC)	0	1 (0.3%)	0	1 (<0.1%)
TEGAFUR	0	1 (0.3%)	0	1 (<0.1%)
TEGAFUR/URACIL	1 (0.3%)	0	0	1 (<0.1%)
TOPOTECAN HYDROCHLORIDE	0	0	1 (0.2%)	1 (<0.1%)
VINBLASTINE	0	1 (0.3%)	0	1 (<0.1%)
Immunotherapy				
Total number of patients with at least one treatment	142 (35.5%)	24 (6.0%)	22 (5.5%)	188 (15.6%)
Total number of treatments	154	25	23	202
NIVOLUMAB	118 (29.5%)	17 (4.3%)	15 (3.7%)	150 (12.5%)
PEMBROLIZUMAB	16 (4.0%)	5 (1.3%)	5 (1.2%)	26 (2.2%)
ATEZOLIZUMAB	7 (1.8%)	2 (0.5%)	1 (0.2%)	10 (0.8%)
IPILIMUMAB	2 (0.5%)	0	0	2 (0.2%)
AMCASERTIB	0	0	1 (0.2%)	1 (<0.1%)
AVELUMAB	1 (0.3%)	0	0	1 (<0.1%)
BGB-A317 (ANTI-PD-1 MONOCLONAL ANTIBODY)	1 (0.3%)	0	0	1 (<0.1%)
DURVALUMAB	0	0	1 (0.2%)	1 (<0.1%)
PF-04518600 (ANTI-OX40 ANTIBODY)	1 (0.3%)	0	0	1 (<0.1%)
UTOMILUMAB	1 (0.3%)	0	0	1 (<0.1%)
Targeted Therapy				
Total number of patients with at least one treatment	75 (18.8%)	60 (15.0%)	77 (19.2%)	212 (17.6%)
Total number of treatments	93	72	98	263
BEVACIZUMAB	19 (4.8%)	16 (4.0%)	19 (4.7%)	54 (4.5%)
GENERIC COMPONENT(S) NOT KNOWN	8 (2.0%)	9 (2.3%)	10 (2.5%)	27 (2.2%)
RAMUCIRUMAB	7 (1.8%)	10 (2.5%)	10 (2.5%)	27 (2.2%)
ERLOTINIB	6 (1.5%)	8 (2.0%)	8 (2.0%)	22 (1.8%)
NINTEDANIB	6 (1.5%)	3 (0.8%)	11 (2.7%)	20 (1.7%)
OSIMERTINIB	8 (2.0%)	5 (1.3%)	6 (1.5%)	19 (1.6%)
AFATINIB	6 (1.5%)	3 (0.8%)	5 (1.2%)	14 (1.2%)
ERLOTINIB HYDROCHLORIDE	6 (1.5%)	3 (0.8%)	4 (1.0%)	13 (1.1%)
GEFITINIB	3 (0.8%)	1 (0.3%)	4 (1.0%)	8 (0.7%)
TRASTUZUMAB	3 (0.8%)	3 (0.8%)	0	6 (0.5%)
OSIMERTINIB MESILATE	2 (0.5%)	1 (0.3%)	1 (0.2%)	4 (0.3%)
AFATINIB DIMALEATE	1 (0.3%)	0	2 (0.5%)	3 (0.2%)
CRIZOTINIB	1 (0.3%)	1 (0.3%)	1 (0.2%)	3 (0.2%)
CERITINIB	1 (0.3%)	0	1 (0.2%)	2 (0.2%)
CUSTIRSEN	1 (0.3%)	0	1 (0.2%)	2 (0.2%)
DABRAFENIB	1 (0.3%)	0	1 (0.2%)	2 (0.2%)
GLESATINIB	1 (0.3%)	1 (0.3%)	0	2 (0.2%)
SERIBANTUMAB	0	2 (0.5%)	0	2 (0.2%)
TRAMETINIB	1 (0.3%)	0	1 (0.2%)	2 (0.2%)
ZOLEDRONIC ACID	0	1 (0.3%)	1 (0.2%)	2 (0.2%)
ABEMACICLIB	1 (0.3%)	0	0	1 (<0.1%)
AFLIBERCEPT	0	0	1 (0.2%)	1 (<0.1%)
ALECTINIB	1 (0.3%)	0	0	1 (<0.1%)
ALECTINIB HYDROCHLORIDE	1 (0.3%)	0	0	1 (<0.1%)
CAPMATINIB	0	1 (0.3%)	0	1 (<0.1%)
CHIDAMIDE	0	0	1 (0.2%)	1 (<0.1%)
CITARINOSTAT	1 (0.3%)	0	0	1 (<0.1%)
DS-6051B (TYROSINE KINASE INHIBITOR)	1 (0.3%)	0	0	1 (<0.1%)
ENTINOSTAT	0	0	1 (0.2%)	1 (<0.1%)
FLT3 LIGAND	0	0	1 (0.2%)	1 (<0.1%)
INCB050465 (PI3K-DELTA INHIBITOR)	1 (0.3%)	0	0	1 (<0.1%)
LAPATINIB	0	1 (0.3%)	0	1 (<0.1%)
LORLATINIB	0	1 (0.3%)	0	1 (<0.1%)
MOCETINOSTAT	0	0	1 (0.2%)	1 (<0.1%)
NINTEDANIB ESILATE	0	0	1 (0.2%)	1 (<0.1%)
RITUXIMAB	0	0	1 (0.2%)	1 (<0.1%)
TRASTUZUMAB EMTANSINE	0	1 (0.3%)	0	1 (<0.1%)
Unknown				
Total number of patients with at least one treatment	0	1 (0.3%)	0	1 (<0.1%)
Total number of treatments	0	1	0	1
No Coding available	0	1 (0.3%)	0	1 (<0.1%)

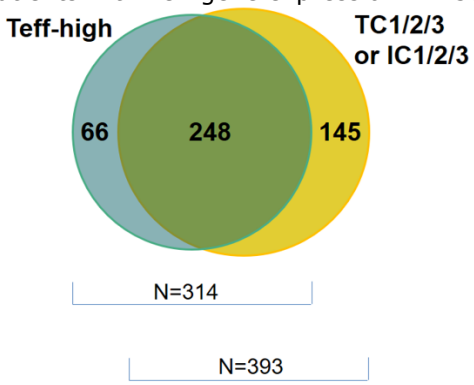
Table 30: Time-to-event summary for overall survival censoring for NPT (ITT-WT population) (Data cut: 22 January 2018)

	Bev+CP (Randomized) (N=337)	Atezo+Bev+CP (Randomized) (N=359)	Atezo+CP (Randomized) (N=349)
Patients with event (%)	91 (27.0%)	101 (28.1%)	92 (26.4%)
Earliest contributing event			
Death	91	101	92
Patients without event (%)	246 (73.0%)	258 (71.9%)	257 (73.6%)
Time to Event (Months)			
Median	24.2	26.1	NE
95% CI	(16.9, NE)	(25.8, NE)	(25.2, NE)
25% and 75%-ile	9.5, NE	11.9, NE	10.0, NE
Range	0.0* to 32.6*	0.0* to 30.4*	0.2* to 28.1*
Unstratified Analysis			
p-value (log-rank)		0.1142	0.2571
Hazard Ratio		0.794	0.845
95% CI		(0.597, 1.058)	(0.632, 1.131)
Stratified Analysis			
p-value (log-rank)		0.1671	0.4051
Hazard Ratio		0.816	0.882
95% CI		(0.612, 1.089)	(0.658, 1.184)

Concordance of PD-L1 expression and Teff gene signature

Measurement of T-Effector Gene Signature and PD-L1 Expression in Tumor Tissue

For the purpose of the primary efficacy analysis, the Teff-high population included patients with Teff gene signature expression greater than or equal to a cutoff expression of –1.91, with additional analyses in patients with Teff gene expression ≥–2.38 and ≥–2.93.

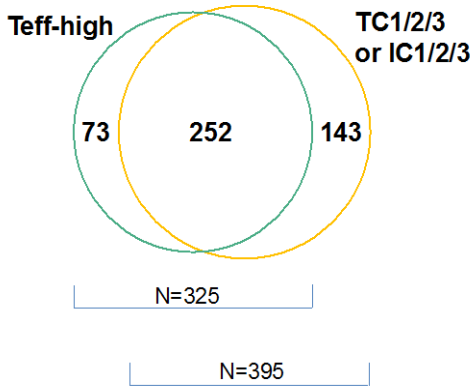


All (N=762)	TC1/2/3 or IC1/2/3 (N=393)	TC0 and IC0 (N=369)
Teff-high (N=314)	248 (32.5%)	66 (8.7%)
Teff-low (N=448)	145 (19.0%)	303 (39.8%)

Percentages are calculated based on N=762.

Teff-high are patients with Tumor Gene Expression >= - 1.91.
Data Cut-off: 15 Sep 2017; RAVE Data Extracted: 10 Nov 2017.

Figure 26: Teff Gene Signature and PD-L1 IHC Expression Patterns in IMpower150 (Atezo + Bev + CP and Bev + CP Arms in ITT population)



All (N=766)	TC1/2/3 or IC1/2/3 (N=395)	TC0 and IC0 (N=371)
Teff-high (N=325)	252 (32.9%)	73 (9.5%)
Teff-low (N=441)	143 (18.7%)	298 (38.9%)

Teff-high are patients with Tumor Gene Expression >= - 1.91.
Data Cut-off: 15 Sep 2017; RAVE Data Extracted: 10 Nov 2017.

Figure 27: Teff Gene Signature and PD-L1 IHC Expression Patterns in IMpower150 (Atezo + CP and Bev + CP Arms in ITT Population)

Table 31: OS Analysis for Overlapping and Non-Overlapping Biomarker Subgroups in the ITT-WT Population

	Bev + CP	Atezo + Bev + CP	Atezo + CP
Overlapping Subgroups			
Teff-High with TC1/2/3 or IC1/2/3 PD-L1 Expression	N=101	N=124	N=123
Median OS 95% CI Unstratified Analysis Hazard Ratio 95% CI	18.9 (10.7, NE)	25.2 (19.1, NE) 0.810 (0.548, 1.198)	21.0 (17.9, NE) 0.838 (0.566, 1.240)
Teff-Low with TC0 and IC0 PD-L1 Expression	N=131	N=125	N=119
Median OS 95% CI Unstratified Analysis Hazard Ratio 95% CI	14.4 (13.4, 16.9)	17.1 (13.7, 21.0) 0.821 (0.595, 1.131)	14.8 (10.3, 19.9) 1.005 (0.731, 1.382)
Non-Overlapping Subgroups			
Teff-Low with TC1/2/3 or IC1/2/3 PD-L1 Expression	N=58	N=63	N=56
Median OS 95% CI Unstratified Analysis Hazard Ratio 95% CI	13.2 (10.3, 21.1)	18.7 (13.8, 24.0) 0.727 (0.455, 1.161)	24.2 (15.4, 25.7) 0.576 (0.348, 0.953)
Teff-High with TC0 and IC0 PD-L1 Expression	N=28	N=32	N=39
Median OS 95% CI Unstratified Analysis Hazard Ratio 95% CI	13.4 (10.7, 17.1)	13.2 (6.8, NE) 0.936 (0.486, 1.805)	14.6 (6.8, 19.5) 1.062 (0.578, 1.953)

Subgroup analyses

OS by Demographic and Baseline Characteristics, ITT

a) Arms: Atezo+ Bev+CP (B) versus Bev+CP (C)

Baseline Risk Factors	Total n	Bev+CP (Randomized) (N=400) n	Events	Median (Months)	Atezo+Bev+CP (Randomized) (N=400) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	800	400	230	14.9	400	192	19.8	0.77	(0.63, 0.93)
Sex									
Female	321	161	87	17.1	160	76	20.3	0.82	(0.61, 1.12)
Male	479	239	143	14.1	240	116	19.1	0.73	(0.57, 0.93)
Liver Metastasis at Enrollment									
Yes	109	57	47	9.4	52	31	13.3	0.52	(0.33, 0.82)
No	691	343	183	17.0	348	161	20.4	0.82	(0.66, 1.01)
TC/IC Strat Factor from txRS Group 2									
TC3 or IC2/3	200	99	51	18.9	101	44	25.2	0.77	(0.51, 1.15)
TC0/1/2 and IC0/1	600	301	179	14.3	299	148	19.1	0.77	(0.62, 0.96)
Age Group 4 Categories (yr)									
<65	441	226	132	14.1	215	108	19.2	0.78	(0.60, 1.00)
65 to 74	281	132	75	15.8	149	63	26.1	0.69	(0.49, 0.96)
75 to 84	72	39	22	14.1	33	18	16.6	0.94	(0.50, 1.76)
>=85	6	3	1	NE	3	3	6.3	>999.99	(0.00, NE)
Race									
Asian	102	46	17	NE	56	22	24.2	1.06	(0.56, 2.00)
Black or African American	15	12	6	25.2	3	1	NE	0.84	(0.10, 7.24)
White	657	335	201	14.2	322	162	19.0	0.76	(0.62, 0.94)
Baseline ECOG									
0	338	179	75	25.2	159	55	26.1	0.75	(0.53, 1.07)
1	456	218	152	12.3	238	137	15.8	0.75	(0.59, 0.94)
Tobacco Use History v1									
Never	159	77	40	18.9	82	31	NE	0.66	(0.41, 1.05)
Current or Previous	641	323	190	14.1	318	161	18.7	0.80	(0.65, 0.98)
KRAS Mutation Status									
Positive	84	38	23	13.5	46	20	26.2	0.64	(0.35, 1.18)
Negative	137	77	45	15.8	60	22	25.8	0.59	(0.35, 1.00)
Unknown	579	285	162	14.3	294	150	19.2	0.82	(0.66, 1.03)

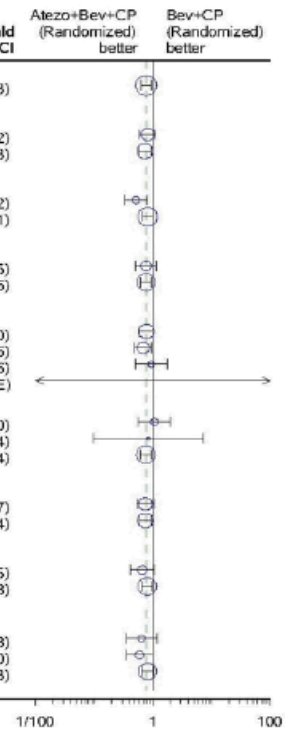


Figure 28: Subgroup analysis of OS by selected demographics and baseline disease characteristics (ITT population) (Data cut: 22 January 2018)

b) Arms: Atezo+CP (A) versus Bev+CP (C)

Baseline Risk Factors	Total n	Bev+CP (Randomized) (N=400) n	Events	Median (Months)	Atezo+CP (Randomized) (N=402) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	802	400	230	14.9	402	206	19.5	0.84	(0.70, 1.02)
Sex									
Female	322	161	87	17.1	161	81	20.5	0.88	(0.65, 1.19)
Male	480	239	143	14.1	241	125	17.9	0.82	(0.64, 1.04)
Liver Metastasis at Enrollment									
Yes	110	57	47	9.4	53	41	8.9	0.87	(0.57, 1.32)
No	692	343	183	17.0	349	165	21.0	0.84	(0.68, 1.04)
Age Group 4 Categories (yr)									
<65	449	226	132	14.1	223	111	19.7	0.76	(0.59, 0.98)
65 to 74	284	132	75	15.8	152	81	17.9	0.97	(0.71, 1.32)
75 to 84	65	39	22	14.1	26	13	19.9	0.83	(0.41, 1.65)
>=85	4	3	1	NE	1	1	8.7	>999.99	(0.00, NE)
Race									
Asian	94	46	17	NE	48	18	24.0	0.97	(0.50, 1.88)
Black or African American	21	12	6	25.2	9	6	19.0	1.12	(0.32, 3.91)
White	666	335	201	14.2	331	176	17.1	0.85	(0.69, 1.04)
Baseline ECOG									
0	359	179	75	25.2	180	68	24.2	0.85	(0.61, 1.18)
1	440	218	152	12.3	222	138	13.6	0.84	(0.67, 1.06)
Tobacco Use History v1									
Never	154	77	40	18.9	77	39	21.2	0.96	(0.62, 1.49)
Current or Previous	648	323	190	14.1	325	167	19.4	0.82	(0.66, 1.01)
KRAS Mutation Status									
Positive	74	38	23	13.5	36	18	21.0	0.89	(0.48, 1.65)
Negative	165	77	45	15.8	88	34	25.2	0.59	(0.38, 0.92)
Unknown	563	285	162	14.3	278	154	17.7	0.92	(0.74, 1.15)

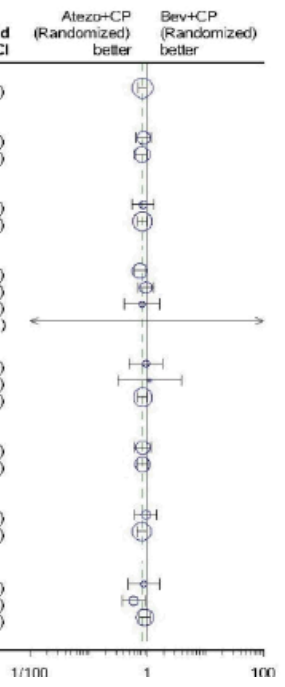


Figure 29: Subgroup analysis of OS by selected demographics and baseline disease characteristics (ITT population) (Data cut: 22 January 2018)

Table 32: Summary of updated efficacy in key subgroups (IMpower150)

Efficacy endpoint	Arm A (Atezolizumab + Paclitaxel + Carboplatin)	Arm B (Atezolizumab + Bevacizumab + Paclitaxel + Carboplatin)	Arm C (Bevacizumab + Paclitaxel + Carboplatin)
EGFR/ALK+			
Investigator-assessed PFS (RECIST v1.1) *			
Median duration (months)	6.9	10	6.1
Hazard ratio^ (95% CI)	1.13 (0.76, 1.67)	0.55 (0.35, 0.87)	---
OS interim analysis*			
Median duration (months)	21.2	NE	17.5
Hazard ratio^ (95% CI)	0.82 (0.49, 1.37)	0.54 (0.29, 1.03)	---
Liver metastases			
Investigator-assessed PFS (RECIST v1.1)*			
Median duration (months)	5.4	8.2	5.4
Hazard ratio^ (95% CI)	0.81 (0.55, 1.21)	0.41 (0.26, 0.62)	---
OS interim analysis*			
Median duration (months)	8.9	13.3	9.4
Hazard ratio^ (95% CI)	0.87 (0.57, 1.32)	0.52 (0.33, 0.82)	---
Age group < 65 (yr)			
OS interim analysis*			
Hazard ratio^ (95% CI)	0.76 (0.59, 0.98)	0.78 (0.60, 1.00)	---
Age group ≥ 65 (yr)			
OS interim analysis*			
Hazard ratio^ (95% CI)	0.96 (0.72, 1.27)	0.76 (0.57, 1.02)	---

* Updated PFS analysis and interim OS analysis at clinical cut-off 22 January 2018
^ Arm C is the comparison group for all hazard ratios.

ALK = anaplastic lymphoma kinase; CI = confidence interval; EGFR = epidermal growth factor receptor; NE = Not estimable;

OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.

Exploratory analyses

PFS, ORR and DoR per RECIST 1.1 and Modified RECIST in ITT population

Table 33: Summary of PFS, ORR, and DOR per RECIST1.1 and Modified RECIST in the ITT Population

ITT	RECIST 1.1			Modified RECIST		
	Atezo + CP	Atezo + Bev + CP	Bev + CP	Atezo + CP	Atezo + Bev + CP	Bev + CP
Median PFS, months (CI)	6.7 (5.7,6.9)	8.4 (8.0,9.9)	6.8 (6.0,7.0)	8.5 (8.1,9.7)	12.2 (11.0,13.1)	9.0 (8.2,9.9)
ORR (CI)	40% (36%,46%)	56% (51%,61%)	41% (35%,45%)	53% (19%,41%)	70% (65%,75%)	29% (19%,41%)
Median DOR, months (CI)	8.3 (1.9,26.0)	11.5 (2.0,23.1)	6.0 (1.5,23.1)	11.5 (8.3,4.0)	11.7 (10.9,16.2)	8.8 (4.2,12.7)

Impact from ADA status on efficacy (ADA Evaluable Atezolizumab Patients in Safety Evaluable Population)

The results presented in tables 36-39 suggest that persistent ADA subsets may be confounded by survivorship bias therefore, use of the persistent and transient ADA definitions in the oncology population requires careful interpretation.

Table 34: Baseline ADA Prevalence and Post-Baseline ADA Incidence in IHC and Teff Populations

	Atezo + Bev + CP (Arm B)			Atezo + CP (Arm A)		
	ADA–	ADA+	Unknown	ADA–	ADA+	Unknown
Baseline prevalence						

PD-L1 IHC TC0 or IC0	169 (89.9%)	11 (5.9%)	8 (4.3%)	172 (92.5%)	9 (4.8%)	5 (2.7%)
PD-L1 IHC TC3 or IC3	73 (98.6%)	0	1 (1.4%)	66 (97.1%)	1 (1.5%)	1 (1.5%)
Teff-low	196 (91.6%)	11 (5.1%)	7 (3.3%)	193 (92.8%)	8 (3.8%)	7 (3.4%)
Teff-high	154 (94.5%)	3 (1.8%)	6 (3.7%)	164 (92.7%)	9 (5.1%)	4 (2.3%)
Teff unknown	14 (87.5%)	2 (12.5%)	0	14 (93.3%)	1 (6.7%)	0
Post-baseline ADA incidence						
PD-L1 IHC TC0 or IC0	101 (53.7%)	72 (38.3%)	15 (8.0%)	108 (58.1%)	65 (34.9%)	13 (7.0%)
PD-L1 IHC TC3 or IC3	50 (67.6%)	19 (25.7%)	5 (6.8%)	36 (52.9%)	30 (44.1%)	2 (2.9%)
Teff-low	126 (58.9%)	73 (34.1%)	15 (7.0%)	125 (60.1%)	71 (34.1%)	12 (5.8%)
Teff-high	99 (60.7%)	51 (31.3%)	13 (8.0%)	97 (54.8%)	72 (40.7%)	8 (4.5%)
Teff unknown	7 (43.8%)	8 (50.0%)	1 (6.3%)	11 (73.3%)	3 (20.0%)	1 (6.7%)

Table 35: Demographic and baseline disease characteristics (ADA groups of interest among atezolizumab treated patients, safety evaluable patients)

	ADA-negative	Treatment-emergent ADA-positive	Treatment-induced transient ADA-positive	Treatment-induced persistent ADA-positive			
				All	positive for ≥16 weeks	positive for <16 weeks and last sample positive	only last sample positive
Atezo + Bev + CP	N=232	N=132	N=103	N=25	N=11	N=2	N=12
Sex (Male)	135 (58.2%)	89 (67.4%)	67 (65.0%)	18 (72.0%)	8 (72.7%)	2 (100.0%)	8 (66.7%)
Liver Metastasis at Enrollment (Yes)	26 (11.2%)	16 (12.1%)	10 (9.7%)	5 (20.0%)	2 (18.2%)	(100.0%)	1 (8.3%)
PD-L1 IHC Strat Factor (IxRS)							
TC0/1/2_IC0/1	168 (72.4%)	104 (78.8%)	78 (75.7%)	23 (92.0%)	11 (100.0%)	2 (100.0%)	10 (83.3%)
TC0/1/2_IC2/3	31 (13.4%)	16 (12.1%)	14 (13.6%)	1 (4.0%)	0	0	1 (8.3%)
TC3_ANY IC	33 (14.2%)	12 (9.1%)	11 (10.7%)	1 (4.0%)	0	0	1 (8.3%)
Age (years)							
Median	64.0	62.0	62.0	63.0	60.0	65.0	64.5
Min – Max	35 - 85	31 - 85	31 – 85	53 - 77	53 – 72	60 – 70	53 – 77
Race (White)	180 (77.6%)	114 (86.4%)	90 (87.4%)	20 (80.0%)	9 (81.8%)	2 (100.0%)	9 (75.0%)
Tobacco Use History (Never)	50 (21.6%)	27 (20.5%)	23 (22.3%)	4 (16.0%)	2 (18.2%)	1 (50.0%)	1 (8.3%)
EGFR Mutation Status (Positive)	21 (9.1%)	10 (7.6%)	8 (7.8%)	2 (8.0%)	1 (9.1%)	0	1 (8.3%)
EML4-ALK Rearrangement Status (Positive)	7 (3.0%)	3 (2.3%)	3 (2.9%)	0	0	0	0
KRAS Mutation Status (Positive)	27 (11.6%)	11 (8.3%)	8 (7.8%)	2 (8.0%)	1 (9.1%)	0	1 (8.3%)
Baseline ECOG (PS=1)	130 (56.3%)	80 (61.5%)	58 (57.4%)	19 (76.0%)	9 (81.8%)	1 (50.0%)	9 (75.0%)
Baseline Target Tumor Sum Longest Diameter							
Median	65.30	77.50	76.00	92.00	92.00	122.50	84.50
Min – Max	10.4 - 243.0	13.0 - 225.0	14.0 - 207.1	13.0 - 160.0	13.0 – 110.0	108.0 – 137.0	30.0 – 160.0

Table 36: IMpower150, Atezo+Bev+CP: OS and investigator-assessed PFS by ADA subgroups

	Bev + CP in the ITT	Atezo + Bev + CP						
					Treatment-induced persistent ADA-positive			
		ADA-negative	Treatment-emergent ADA-positive	Treatment-induced transient ADA-positive	All	positive for ≥16 weeks	positive for <16 weeks and last sample positive	only last sample positive
	N=400	N=232	N=132	N=103	N=25	N=11	N=2	N=12
Overall Survival								
median OS (Months)	14.9	24.0	18.7	23.8	14.5	17.1	NE	9.4
95%CI	(13.4, 17.1)	(19.2, NE)	(13.8, 25.2)	(13.8, 25.8)	(8.1, NE)	(12.2, NE)	(4.8, NE)	(1.5, 16.6)
12 month Overall Survival (%)	60.6	74.5	67.4	68.9	64.0	81.8	50.0	50.0
24 month Overall Survival (%)	35.5	50.2	44.3	47.0	36.1	49.9	NE	NE
Progression-free Survival								
median PFS (Months)	6.8	10.1	8.1	8.2	5.6	7.5	NE	2.1
95%CI	(6.0, 7.0)	(8.3, 11.6)	(7.0, 10.1)	(7.0, 10.4)	(2.8, 13.0)	(5.6, 17.3)	(4.8, NE)	(1.2, 9.6)
6 month PFS (%)	55.4	72.4	65.9	69.9	48.0	63.6	50.0	33.3
12 month PFS (%)	20.1	42.5	36.5	37.1	32.0	36.4	50.0	25.0

Table 37: IMpower150, Atezo+CP: OS and investigator-assessed PFS by ADA subgroups

	Bev + CP in the ITT	Atezo + CP						
					Treatment-induced persistent ADA-positive			
		ADA-negative	Treatment-emergent ADA-positive	Treatment-induced transient ADA-positive	All	positive for ≥16 weeks	positive for <16 weeks and last sample positive	only last sample positive
	N=400	N=233	N=146	N=110	N=31	N=8	N=12	N=11
Overall Survival								
median OS (Months)	14.9	21.3	17.1	17.1	9.9	20.3	7.4	7.2
95%CI	(13.4, 17.1)	(19.4, 24.2)	(13.0, 20.5)	(14.0, NE)	(6.7, 20.3)	(10.2, 25.7)	(4.0, NE)	(2.7, 25.2)
12 month Overall Survival (%)	60.6	73.9	60.0	64.6	43.3	75.0	33.3	30.0
24 month Overall Survival (%)	35.5	42.1	37.0	41.2	17.3	18.8	NE	30.0
Progression-free Survival								
median PFS (Months)	6.8	7.1	5.6	5.8	4.2	6.3	2.9	3.5
95%CI	(6.0, 7.0)	(6.7, 8.2)	(5.1, 6.8)	(5.3, 7.1)	(1.7, 6.8)	(1.4, 8.3)	(1.7, 5.6)	(1.5, 6.8)
6 month PFS (%)	55.4	58.4	44.8	49.1	33.3	50.0	25.0	30.0
12 month PFS (%)	20.1	28.1	20.4	24.2	6.7	12.5	8.3	NE

Table 38: Hazard ratio of overall survival by ADA status in the comparison of Atezo+Bev+CP (Arm B) versus Bev+CP (Arm C)

Analysis Approach	HR (95% CI)	
	Week 4 ADA-positive Atezo+Bev+CP (n=96) vs. Bev+CP (n=372)	Week 4 ADA-negative Atezo+Bev+CP (n=256) vs. Bev+CP (n=372)
IPW2	0.67 (0.49,0.91)	0.74 (0.59, 0.93)
Propensity Score Matching 2	0.59 (0.38, 0.94)	0.62 (0.44, 0.86)

IPW=inverse probability of treatment weight.

Summary of main study

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

Table 39: Summary of Efficacy for trial IMpower150

Title: A Phase III, open-label, randomized study of atezolizumab (anti–PD-L1 antibody) in combination with carboplatin + paclitaxel with or without bevacizumab compared with carboplatin + paclitaxel + bevacizumab in chemotherapy-naïve patients with stage IV non-squamous non-small cell lung cancer (IMpower150).			
Study identifier	GO29436		
Design	Phase III, open-label, randomized, three treatment arms		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Approximately 2.5 years First patient randomized: 31 March 2015 Last patient randomized: 30 December 2016 Data cutoff date: 22 January 2018
Hypothesis	Superiority		
Treatments groups	Arm A (Atezo + CP)		Atezolizumab+carboplatin+paclitaxel (induction: four or six 21-day cycles); atezolizumab (maintenance: 21-day cycles). 402 patients randomized.
	Arm B (Atezo + Bev + CP)		Atezolizumab+bevacizumab+carboplatin+paclitaxel (induction: four or six 21-day cycles); atezolizumab+bevacizumab (maintenance: 21-day cycles). 400 patients randomized.
	Arm C (Bev + CP)		Bevacizumab+carboplatin+paclitaxel (induction: four or six 21-day cycles); bevacizumab (maintenance: 21-day cycles). 400 patients randomized.
	Co-Primary endpoints	PFS ITT-WT	Progression free survival according to RECIST v1.1 in the intent-to-treat (ITT)–WT population
		OS ITT-WT	Overall survival (OS) in the ITT–WT population
Database lock	22 January 2018		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat wild type (ITT-WT)			
Descriptive statistics and estimate variability	Treatment group	Arm A (Atezo + CP)	Arm B (Atezo + bev + CP)	Arm C (Bev + CP)
	Number of subject	349	359	337
	Median PFS, months	6.3	8.3	6.8
	95% CI	5.6, 7.0	7.7, 9.8	6.0, 7.1
	Median OS, months	19.4	19.2	14.7
	95% CI	15.7, 21.3	17.0, 23.8	13.3, 16.9
	ORR, % 95% CI	42.0 36.7, 47.3	55.3 50.0, 60.6	40.4 35.0, 45.9

Effect estimate per comparison	PFS ITT-WT	Comparison groups	Arm B vs. Arm C
		Stratified HR	0.59
		95% CI	0.50, 0.70
		P-value	<0.0001
	PFS ITT-WT	Comparison groups	Arm A vs. Arm C
		Stratified HR	0.88
		95% CI	0.75, 1.04
		P-value	0.1445
	OS ITT-WT	Comparison groups	Arm B vs. Arm C
		Stratified HR	0.78
		95% CI	0.64, 0.96
		P-value	0.0164
	OS ITT-WT	Comparison groups	Arm A vs. Arm C
		Stratified HR	0.88
		95% CI	0.72, 1.08
		P-value	0.2041

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

N/A

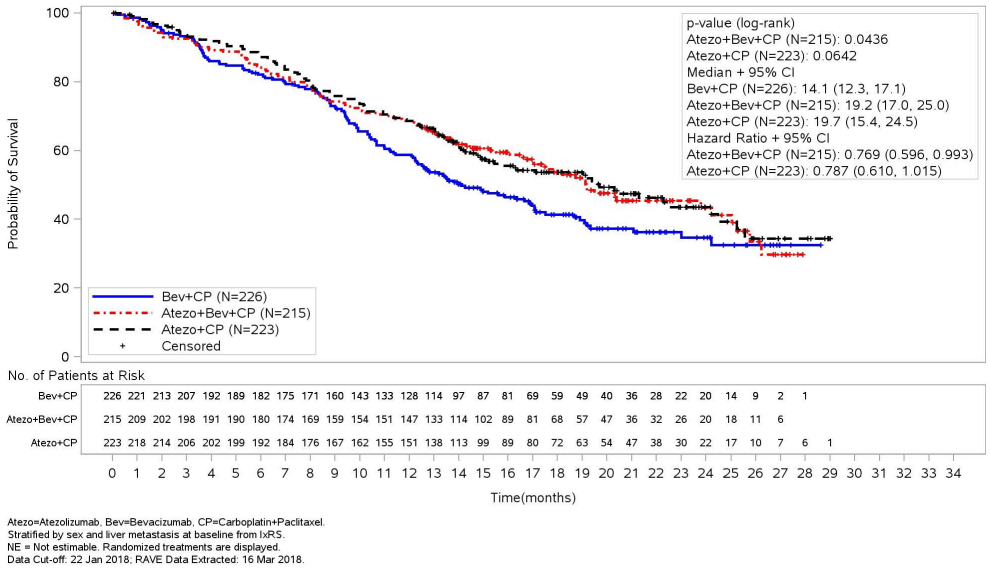
Clinical studies in special populations

Efficacy data by age subgroups

Table 40: PFS and OS by Age Group and for the Overall ITT Population

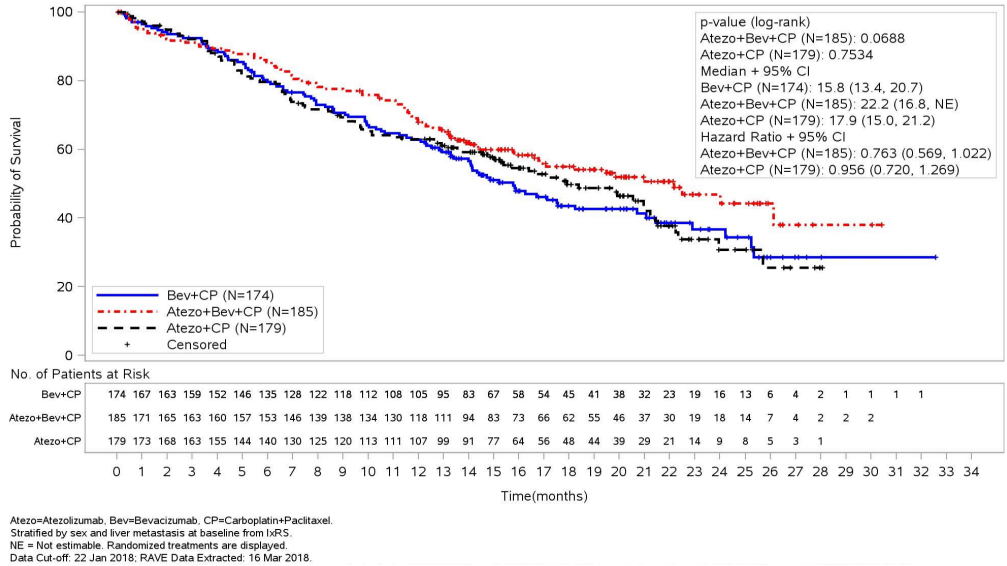
Patient Groups	<65 Years		≥65 Years		ITT	
Efficacy	**Bev+CP**	**Atezo +Bev+CP**	**Bev+CP**	**Atezo +Bev+CP**	**Bev+CP**	**Atezo +Bev+CP**
median OS, months	14.1 (12.3, 17.1)	19.2 (17.0, 25)	15.8 (13.4, 20.7)	22.2 (16.8, NE)	14.9 (13.4, 17.1)	19.8 (17.4, 24.2)
OS HR (95% CI)	0.776 (0.602, 1.001)		0.760 (0.568, 1.017)		0.760 (0.63, 0.93)	
median PFS, months	6.5 (5.8, 7.0)	8.1 (7.1, 9.6)	6.9 (6.0, 8.0)	9.7 (8.2, 11.0)	6.8 (6.0, 7.0)	8.4 (8.0, 9.9)
PFS HR (95% CI)	0.609 (0.490, 0.759)		0.602 (0.470, 0.771)		0.586 (0.50, 0.69)	

a) Less than 65 years of age



Atezo=Atezolizumab, Bev=Bevacizumab, CP=Carboplatin+Paclitaxel.
Stratified by sex and liver metastasis at baseline from IxRS.
NE = Not estimable. Randomized treatments are displayed.
Data Cut-off: 22 Jan 2018; RAVE Data Extracted: 16 Mar 2018.

b) Greater or equal to 65 years of age



Atezo=Atezolizumab, Bev=Bevacizumab, CP=Carboplatin+Paclitaxel.
Stratified by sex and liver metastasis at baseline from IxRS.
NE = Not estimable. Randomized treatments are displayed.
Data Cut-off: 22 Jan 2018; RAVE Data Extracted: 16 Mar 2018.

Figure 30: KM Plot of OS by Age Groups (ITT Population) (Data cut: 22 January 2018)

2.4.3. Discussion on clinical efficacy

The proposed indication is: *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). Patients with EGFR mutant or ALK-positive NSCLC should have received targeted therapy if clinically indicated prior to receiving Tecentriq.*

The proposed posed posology is 1200 mg administered by IV infusion q3w. Treatment should be continued as long as clinical benefit is observed or until it is no longer tolerated by the patient.

Design and conduct of clinical studies

The MAH has provided data from the first interim analysis (data cut-off 15 September 2017) and second interim analysis (data cut-off 22 January 2018) from G029426 (IMpower150) to support this application.

1202 patients were randomized in a 1:1:1 ratio to receive Atezo + CP (arm A), Atezo + Bev + CP (arm B) or Bev + CP (arm C). Dosing and schedule for drugs in all three arms was based on previously approved indications and hence endorsed. Randomization was stratified by sex, presence of liver metastases at baseline, and PD-L1 expression by immunohistochemistry (IHC).

The control group (Arm C) is currently a standard of care for the first-line treatment of NSCLC based on the results of the ECOG 4599 study, which showed a significant improvement in OS (12.3 months vs. 10.3 months [Hazard Ratio (HR) = 0.80; p < 0.003]), PFS (6.4 months vs. 4.8 months [HR = 0.65; p < 0.0001]), and ORR (35% [133 of 381 patients] vs. 15% [59 of 392 patients]; p < 0.001) in patients treated with bevacizumab q3w in combination with carboplatin + paclitaxel compared with carboplatin - paclitaxel alone.No crossover was permitted from the control arm (Arm C) to either of the experimental arms. This is acceptable, since OS is one of the primary efficacy endpoints. Patients randomized to arms containing atezolizumab (A and B) were allowed to keep maintenance treatment beyond progression, but those randomized to the arm containing bevacizumab without atezolizumab (Arm C) were not.

The study was originally designed to demonstrate an overall survival benefit of Atezo + Bev + CP in an all-comer population (ITT). However, emerging data from 2L+ non-small cell lung cancer (NSCLC) studies with monotherapy PD-1/PD-L1 inhibitors demonstrated that patients with EGFR mutations did not

derive significant clinical benefit from these drugs. In consequence, the hierarchical testing scheme was adjusted in version 6 of the protocol, such that ITT population could not be formally tested if arm A did not show statistically significant OS benefit as compared to arm C. After such amendments, the co-primary efficacy endpoints were investigator-assessed PFS per RESIST 1.1 in the Teff-high WT population (Teff-high patients without an activating EGFR mutation or ALK translocation) and the ITT-WT population (defined as the ITT population excluding patients with an activating EGFR mutation or ALK translocation) and overall survival in the ITT-WT population. The method to control the type 1 error for the two co-primary endpoints and for the comparisons of Arms A vs. C and B vs. C was considered adequate in general.

Numerous inclusion and exclusion criteria conditioned the randomisation of about 55% (1202 out of 2166) of screened patients. From the non-participating patients, 44% were excluded due to issues regarding lack of PD-L1 status, prior treatment for stage IV NSCLC or CNS metastases that did not fulfill inclusion/exclusion criteria. The enrolled population seems in line with expectations for the 1L setting in metastatic NSCLC patients.

ITT population was subdivided into multiple subpopulations according to diverse parameters (presence or absence of EGFR mutations/ALK translocations, Teff gene signature score, PD-L1 staining) as a way to optimally select the group of patients with most benefit.

Being this a study of three arms, most of the comparisons (OS, PFS, ORR, DOR, etc.) were performed between the experimental arms (B and A) against the control arm (C), that is, B vs. C and A vs. C. However, to define the added benefit of bevacizumab to Atezo + CP, the MAH was also requested to perform OS and PFS comparisons of arm B vs. A for the ITT population (the sought indication is in all-comers).

Baseline characteristics are well balanced among the three arms of treatment. As expected, since PD-L1 status was a stratification factor, distribution of its subcategories across the three arms in the ITT population is fair. It is remarkable that almost half (48.6%) of all randomized patients are PD-L1 negative (TC0 and IC0).

In the second interim analysis there was a minor variation of the numbers analysed, as 2 patients originally categorised as EGFR positive and 3 patients originally ALK positive were recategorised as having no mutations.

Overall, the main criticism to the design and conduct of this study is the modification of primary efficacy objectives and populations in subsequent protocol amendments, however the validity of the study is not questioned.

Efficacy data and additional analyses

Primary efficacy endpoints:

ITT-WT PFS: Final PFS analysis in ITT-WT population (co-primary endpoint) was done in the first interim analysis (data cut off 15-SEP-2017) when about 781 PFS events had happened in 1040 WT patients, about 75.1%. With data cut off of 22-JAN-2018, about 80.8% PFS events (855 in 1045 WT patients) have occurred and the median PFS remains identical for all three arms, including their 95% CIs: median PFS in ITT-WT population was 6.3 months in arm A, 8.3 months in arm B and 6.8 months in arm C. The updated data cutoff maintained the statistically significant PFS advantage for the comparison of arm B vs. C: stratified HR (0.62 → 0.59) and p-value (<.0001 → <.0001).

Considering the comparison of arms B and C, the study met its first co-primary efficacy endpoint, since the median duration of PFS was greater in the Atezo + Bev + CP arm (8.3 months, 95% CI: 7.7, 9.8) compared with the Bev + CP arm (6.8 months, 95% CI: 6.0, 7.1). This renders a stratified HR of 0.62 (95% CI: 0.52, 0.74; $p < 0.0001$) and confers a statistically significant and clinically relevant advantage

to the combination of Atezo + Bev + CP in WT patients. The comparison of arms A and C, delivers a HR of 0.88 (95% CI: 0.75, 1.04; p: 0.14).

Teff-high WT PFS: 447 out of 1202 patients (37.2%) were classified as Teff-high WT. When these patients are selected, PFS benefit from Atezo + Bev + CP (arm B) is increased: median PFS in arms A and C was similar to ITT-WT population (6.7 and 6.8 months, respectively), but notably higher for arm B (11.4 months). In Teff-high WT population there are scarcely any differences in PFS between first and second interim analyses. Arm B maintains a statistically significant PFS advantage as compared to arm C, whereas arm A and C are not statistically different. However, to all appearances, the newly introduced Teff-biomarker did not distinguish satisfactorily between responders and non-responders. Comparison between Teff-high and low subgroups in the control arm (Bev+CP) suggests that Teff expression does not appear to be a predictive factor in this study. These data are supported by comparing Teff-high and low subgroups in 2L NSCLC (OAK). Overall, PD-L1 appeared to identify a broader patient population with similar treatment effect compared with Teff gene signature (i.e. PD-L1 IHC appeared to be a more adequate predictive biomarker, since there is obviously a subgroup of patients with Teff gene signature low but positive PD-L1 expression who derived a benefit by PD-L1 directed treatment).

ITT-WT OS: With an event rate of 53% in ITT-WT population, median OS was 19.4 months in arm A, 19.2 months in arm B and 14.7 months in arm C. When considering the complete study period (the whole curve, not just the median), even if there is a borderline statistical difference in OS between arm B (Atezo + Bev + CP) and C (Bev + CP), this difference is not clinically relevant. From a clinical point of view and based on the KM for OS plots and the estimates for median survival time, the difference between arms B (Atezo + Bev + CP) and A (Atezo + CP) is negligible. This is even more pronounced in the PD-L1 positive (TC3/IC3) population, where actually no meaningful differences in the KM plots could be detected. Evolution of the OS comparison –per stratified HR- of arm B vs. arm C in ITT-WT population is static [0.78 (0.62, 0.97) → 0.78 (0.64, 0.96)], whereas the comparison of A vs. C varies minimally [0.92 (0.74, 1.15) → 0.88 (0.72, 1.08)]. However, comparisons of hazard ratios might be questionable given the non-proportional hazards and using survival rates at specific landmarks might prove more sensible: at 12 months, 61% of patients were alive in arm C, as compared to 67% in arm B and 65% in arm A; at 24 months, 34% of patients were alive in arm C, compared to 43% in arm B and 39% in arm A. However, as OS data are not mature at 24 months, no conclusion can be drawn at this stage.

Secondary efficacy endpoints:

Results of *PFS in ITT population* were similar to ITT-WT: median PFS was 6.7 months in arm A, 8.4 months in arm B and 6.8 months in arm C. Median PFS in arm C (Bev + CP) is comparable to the result established by the pivotal trial NCT00021060 (6.2 months). The stratified HR for the comparison of arms B and C was 0.59 (95% CI: 0.50, 0.69), indicating a clinically meaningful benefit with Atezo + Bev + CP as compared with Bev + CP. PFS between arms A and C is similar, although not yet formally tested (stratified HR of 0.91, 95% CI 0.78, 1.06).

PFS benefit from treatment in arms B or A, as compared to arm C, was much higher for patients with increasing *PD-L1* IHC positivity (TC2/3 or IC2/3). However, subgroup analysis suggests a small clinical advantage (PFS and OS) from Atezo + Bev + CP as compared to Bev + CP also in the PD-L1 negative subgroup (TC0/IC0), albeit with a late crossing of the OS curves after months 12.

EGFR/ALK+ patients: The number of subjects with EGFR mutations and ALK translocations in IMpower150 is limited; OS data are not fully mature yet and a statistical significance in the ITT population could not be provided due to the hierarchical multiple testing sequence. Nonetheless, the provided data support the assumption of a clinically meaningful benefit for the addition of atezolizumab + bevacizumab to carboplatin + paclitaxel in the EGFR/ALK+ subpopulation of the trial. Given the unmet medical need for this subpopulation of patients after failure of TKI therapies, its inclusion in the indication is supported by the preliminary OS and PFS data. There are no data on the efficacy of atezolizumab in combination with

bevacizumab, paclitaxel and carboplatin in EGFR+ patients who have progressed previously on erlotinib+bevacizumab and this has been reflected in section 4.4 of the SmPC.

Patients with liver metastases: in Arm B as compared to Arm C, pre-specified subgroup analyses from the interim OS analysis showed an OS improvement for patients with liver metastases: HR of 0.52.

ORR: In ITT population, confirmation of response by the Investigator has brought upon a significant decrease of the previously reported response rates (7-8% in each arm), but arm B (56.4%) keeps a considerable advantage over arms C (40.2%) and A (40.6%).

DoR: Regarding ITT population, arm B exhibited a significantly longer median response (11.5 months, 95% CI 8.9, 15.7) than arm C (6.0 months, 95% CI 5.5, 6.9). Responders from arm A had a median DoR of 7.0 months, but the 95% CI (5.7, 8.3) overlaps with that from arm B, so the difference in DoR between arms B and A is not significant.

Concordance between PD-L1 and Teff gene signature: PD-L1 IHC appeared to identify a broader patient population with similar treatment effect compared with Teff gene signature in the IMpower150 study.

8.7% of patients (66 of 762) who were Teff-high were found to have PD-L1 status of TC0 and IC0 by SP142 PD-L1 IHC- 19% of patients (145 of 762) who were found to be Teff-low were considered TC1/2/3 or IC1/2/3 by SP142 IHC. Analysis of these non-overlapping biomarker subgroups clearly revealed that the PD-L1 marker is better to distinguish between responders and non(worse)-responders.

Benefit from adding bevacizumab to Atezo + CP (Arm B vs. Arm A): Although the study was not statistically powered for these comparisons, their values provide insight into the benefit from adding bevacizumab to Atezo + CP. PFS benefit from arm B (mPFS 8.4 months) is clear and regarding arm A (mPFS 6.7 months) significant: descriptive HR 0.67 (95% CI 0.57-0.79, p-value < 0.0001). Nonetheless, HR for OS in ITT population when comparing arms B (mOS 19.8 months) and A (mOS 19.5 months) is 0.90 (95% CI 0.74-1.10, p-value 0.30). A similar result comes out when comparing such arms in ITT-WT population: 0.90 (CI and p-value not provided), slightly favoring arm B, even when mOS was higher in arm A (19.4 months) than arm B (19.2 months). On the same line, OS benefit from Atezo+Bev+CP vs. Atezo + CP in EGFR/ALK+ patients is doubtful as well: HR 0.66 (95% CI 0.34-1.28, p-value not provided).

Atezolizumab ADA status: There was a high rate (30-40%) of ADA conversion (negative to positive) in both arms (A and B). In treatment-induced ADA-persistent patients (all subsets), lower median OS and median PFS were observed compared with ADA-negative and ADA-transient patients. Although these differences might in part be confounded by the imbalances in baseline characteristics, the reduced efficacy of ADA-positive patients in the Atezo + CP arm could be clinically meaningful. This issue will be addressed post-approval.

Efficacy by age subgroups: Dividing the ITT population in <65 and ≥65 years of age did now show PFS or OS differences between these subgroups when comparing arms B and C, but it did suggest slightly diminished efficacy in older individuals when arms A and C where compared. The limitations regarding data in elderly patients have been reflected in section 5.1 of the SmPC.

PROs: The results show that the 4-drug combination did not have any major effect on QoL. However, having in mind the worse safety profile of Atezo+beva+CP compared to atezo+CP and the open-label design, these data should be interpreted with caution.

2.4.4. Conclusions on the clinical efficacy

Efficacy results of the second interim analysis from IMpower150 show that both co-primary endpoints have been met, thus confirming superiority from Atezo + Bev + CP over Bev + CP in terms of PFS in ITT-WT/Teff-high WT population and OS in ITT-WT population. ITT population cannot be formally tested because of the statistical amendments introduced in the last version of the protocol. Arm A (Atezo + CP)

versus Arm C (Bev + CP) efficacy boundary was not crossed and Arm A (Atezo + CP) will be re-tested at the time of the final OS analysis,, but its overall OS benefit is similar to arm B (Atezo + Bev + CP).

Subgroup analysis demonstrates PFS benefit from Atezo + Bev + CP vs. Bev + CP in EGFR/ALK+ patients and in patients with liver metastases, supported by a clinically meaningful OS benefit (formal statistical testing was not planned).

Teff gene signature did not prove to be a useful biomarker to distinguish from responders and non-responders in this trial: PD-L1 IHC appeared to identify a broader population with beneficial effect from Atezo + Bev + CP.

In order to address the uncertainties in relation to ADA, the MAH is recommended:

-To submit and discuss the neutralising ADA data for both atezolizumab monotherapy and when co-administered with Carboplatin-paclitaxel with or without bevacizumab in IMpower150.

- To submit an assessment of the effect of atezolizumab ADAs on PK and efficacy endpoints including OS, PFS, and ORR in NSCLC Studies POPLAR, OAK, IMpower150, IMpower130, IMpower131, and IMpower132.

2.5. Clinical safety

Introduction

Study IMpower150: The safety population included all treated patients, defined as randomized patients who received any amount of any component of study treatment. For the safety analyses, patients were grouped according to whether any amount of atezolizumab was received, including when atezolizumab was received in error. Specifically for patients randomized to the Bev + CP arm, if atezolizumab was received in error in addition to Bev + CP treatment, the patients were grouped with the Atezo + Bev + CP arm for the safety analyses.

Accordingly, safety evaluable population consisted of 400 patients from arm A, 393 patients from arm B and 394 patients from arm C.

Atezolizumab Monotherapy: In addition, safety data on single-agent atezolizumab from seven studies (OAK, IMvigor211, IMvigor 210, POPLAR, FIR, BIRCH and PCD4989g) are presented for 3075 atezolizumab-treated safety-evaluable patients (all patients who received any amount of atezolizumab) of whom 1636 (53.2%) are patients with NSCLC.

Table 41: Safety summary atezolizumab-treated patients

Atezolizumab-Treated Patients
Protocols: GO27831 (All Cohorts), GO28625, GO28753, GO28754, GO29293, GO28915, GO29294

	All Patients (N=3075)
Total number of patients with at least one adverse event	2949 (95.9%)
Total number of events	32075
Total number of patients with at least one	
Serious Adverse Events	1274 (41.4%)
Serious AE leading to withdrawal from treatment	176 (5.7%)
Serious AE leading to dose interruption	437 (14.2%)
Serious AE related to treatment	338 (11.0%)
AE leading to withdrawal from treatment	219 (7.1%)
AE leading to dose interruption	853 (27.7%)
Related AE	2082 (67.7%)

Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v20.1. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. AEs collected after first treatment dose are included.
Grade 5 AEs due to PD are excluded for studies GO27831 and GO28625.
GO27831=PCD4989g; GO28625=FIR; GO28753=POPLAR; GO28754=BIRCH; GO29293=IMvigor 210; GO28915=OAK; GO29294=IMvigor 211.
Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO29293:04JUL2016, GO28915:07JUL2016, GO29294:13MAR2017.

The update of the monotherapy dataset has had minor impact in the known safety profile of atezolizumab. Noticeable changes seen at the SmPC include hyperthyroidism with all-grades incidence of 0.9% (from "common" to "uncommon") and urinary tract infections (10.8%) now classified as "very common".

Patient exposure

Table 42: Exposure to atezolizumab and bevacizumab treatment (safety evaluable population)

	Bevacizumab Exposure		Atezolizumab Exposure	
	Bev+CP (N=394)	Atezo+Bev+CP (N=393)	Atezo+Bev+CP (N=393)	Atezo+CP (N=400)
Number of doses received				
n	393	393	393	400
Mean (SD)	9.6 (7.2)	12.2 (9.5)	14.2 (10.1)	12.2 (9.5)
Median	8.0	10.0	12.0	10.0
Min–Max	1–38	1–44	1–44	1–43
Treatment duration (M)				
n	393	393	393	400
Mean (SD)	6.4 (5.2)	8.4 (7.0)	9.7 (7.3)	8.2 (6.8)
Median	5.1	6.7	8.3	6.4
Min–Max	0–26	0–30	0–30	0–29
Treatment duration (M)				
n	393	393	393	400
0 to ≤3 months	124 (31.6%)	112 (28.5%)	86 (21.9%)	98 (24.5%)
>3 months to ≤6 months	101 (25.7%)	61 (15.5%)	53 (13.5%)	86 (21.5%)
>6 months to ≤12 months	105 (26.7%)	103 (26.2%)	112 (28.5%)	106 (26.5%)
>12 months	63 (16.0%)	117 (29.8%)	142 (36.1%)	110 (27.5%)
Dose Intensity (%)				
n	393	393	393	400
Mean (SD)	94.4 (7.8)	93.8 (8.2)	94.0 (8.3)	94.6 (8.2)
Median	97.3	96.8	96.9	97.7
Min–Max	44–105	51–105	51–108	46–102
Total cumulative dose (mg)				
n	393	393	393	400
Mean (SD)	10264.0 (8187.7)	13113.4 (10676.3)	16990.3 (12171.7)	14599.3 (11389.4)
Median	8070.0	10260.0	14400.0	12000.0
Min–Max	585–43265	560–49035	1200–52800	260–51600

Table 43: Summary of Exposure to Atezolizumab Treatment Beyond PD, Atezo+CP

Study Drug Exposure On or After First Disease Progression, Atezolizumab Infusion
Atezo+CP, Atezolizumab, Reported Disease Progression, Safety Evaluable Patients
Protocol: GO29436 (Data Cut: 22 Jan 2018)

	Atezo Treated On or After First PD (N=122)
Number of doses received	
n	122
Mean (SD)	5.5 (5.9)
Median	3.0
Min - Max	1 - 34
Treatment duration (M)	
n	122
Mean (SD)	3.2 (4.2)
Median	1.4
Min - Max	0 - 23
Treatment duration (M)	
n	122
0 to <= 3 months	79 (64.8%)
>3 months to <= 6 months	19 (15.6%)
>6 months to <= 12 months	18 (14.8%)
>12 months	6 (4.9%)
Total cumulative dose (mg)	
n	122
Mean (SD)	6590.2 (7061.9)
Median	3600.0
Min - Max	1200 - 40800

Atezo=Atezolizumab, Bev=Bevacizumab, CP=Carboplatin+Paclitaxel.
PD = Progression of Disease.
M=Months. Duration is months from date of last treatment received to date of earliest treatment received on or after first disease progression plus 1. Data Cut-off: 22 Jan 2018; RAVE Data Extracted: 16 Mar 2018.

Table 44: Summary of Exposure to Atezolizumab Treatment Beyond PD, Atezo+Bev+CP

Study Drug Exposure On or After First Disease Progression, Atezolizumab Infusion
Atezo+Bev+CP, Atezolizumab, Reported Disease Progression, Safety Evaluable Patients
Protocol: GO29436 (Data Cut: 22 Jan 2018)

	Atezo Treated On or After First PD (N=97)
Number of doses received	
n	97
Mean (SD)	5.3 (5.1)
Median	3.0
Min - Max	1 - 24
Treatment duration (M)	
n	97
Mean (SD)	3.0 (3.6)
Median	1.4
Min - Max	0 - 16
Treatment duration (M)	
n	97
0 to <= 3 months	68 (70.1%)
>3 months to <= 6 months	13 (13.4%)
>6 months to <= 12 months	13 (13.4%)
>12 months	3 (3.1%)
Total cumulative dose (mg)	
n	97
Mean (SD)	6346.4 (6106.5)
Median	3600.0
Min - Max	1200 - 28800

Atezo=Atezolizumab, Bev=Bevacizumab, CP=Carboplatin+Paclitaxel.
PD = Progression of Disease.
M=Months. Duration is months from date of last treatment received to date of earliest treatment received on or after first disease progression plus 1. Data Cut-off: 22 Jan 2018; RAVE Data Extracted: 16 Mar 2018.

Adverse events

Common adverse events

Table 45: Adverse events with an incidence rate of at least 10% by system organ class and preferred term (data cut: 22 January 2018)

	Overall (N=1187)		
MedDRA System Organ Class MedDRA Preferred Term	Bev+CP (Actual) (N=394)	Atezo+Bev+CP (Actual) (N=393)	Atezo+CP (Actual) (N=400)
Overall total number of patients with at least one Adverse Events[1]	380 (96.4%)	375 (95.4%)	378 (94.5%)
GASTROINTESTINAL DISORDERS			
Total number of patients with at least one Adverse Events[1]	229 (58.1%)	263 (66.9%)	230 (57.5%)
NAUSEA	125 (31.7%)	154 (39.2%)	128 (32.0%)
CONSTIPATION	92 (23.4%)	117 (29.8%)	99 (24.8%)
DIARRHOEA	97 (24.6%)	126 (32.1%)	79 (19.8%)
VOMITING	69 (17.5%)	73 (18.6%)	65 (16.3%)
STOMATITIS	25 (6.3%)	51 (13.0%)	23 (5.8%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Total number of patients with at least one Adverse Events[1]	202 (51.3%)	229 (58.3%)	229 (57.3%)
ALOPECIA	180 (45.7%)	187 (47.6%)	179 (44.8%)
RASH	26 (6.6%)	65 (16.5%)	71 (17.8%)
PRURITUS	24 (6.1%)	50 (12.7%)	44 (11.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Total number of patients with at least one Adverse Events[1]	198 (50.3%)	238 (60.6%)	202 (50.5%)
FATIGUE	107 (27.2%)	130 (33.1%)	105 (26.3%)
ASTHENIA	80 (20.3%)	81 (20.6%)	71 (17.8%)
PYREXIA	34 (8.6%)	73 (18.6%)	53 (13.3%)
NERVOUS SYSTEM DISORDERS			
Total number of patients with at least one Adverse Events[1]	182 (46.2%)	226 (57.5%)	205 (51.3%)
NEUROPATHY PERIPHERAL	68 (17.3%)	93 (23.7%)	103 (25.8%)
PERIPHERAL SENSORY NEUROPATHY	56 (14.2%)	65 (16.5%)	58 (14.5%)
HEADACHE	51 (12.9%)	61 (15.5%)	38 (9.5%)
PARAESTHESIA	42 (10.7%)	50 (12.7%)	36 (9.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Total number of patients with at least one Adverse Events[1]	182 (46.2%)	210 (53.4%)	178 (44.5%)
ARTHRALGIA	86 (21.8%)	103 (26.2%)	86 (21.5%)
MYALGIA	54 (13.7%)	65 (16.5%)	63 (15.8%)
BACK PAIN	41 (10.4%)	48 (12.2%)	38 (9.5%)
PAIN IN EXTREMITY	32 (8.1%)	45 (11.5%)	39 (9.8%)
MUSCULOSKELETAL PAIN	34 (8.6%)	43 (10.9%)	30 (7.5%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Total number of patients with at least one Adverse Events[1]	178 (45.2%)	193 (49.1%)	188 (47.0%)
ANAEMIA	107 (27.2%)	115 (29.3%)	144 (36.0%)
NEUTROPENIA	70 (17.8%)	73 (18.6%)	61 (15.3%)
THROMBOCYTOPENIA	47 (11.9%)	53 (13.5%)	49 (12.3%)
FEBRILE NEUTROPENIA	26 (6.6%)	40 (10.2%)	29 (7.3%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Total number of patients with at least one Adverse Events[1]	166 (42.1%)	157 (39.9%)	131 (32.8%)
COUGH	74 (18.8%)	77 (19.6%)	67 (16.8%)
DYSPNOEA	62 (15.7%)	53 (13.5%)	86 (21.5%)
EPISTAXIS	87 (22.1%)	66 (16.8%)	15 (3.8%)
METABOLISM AND NUTRITION DISORDERS			
Total number of patients with at least one Adverse Events[1]	101 (25.6%)	136 (34.6%)	122 (30.5%)
DECREASED APPETITE	83 (21.1%)	113 (28.8%)	95 (23.8%)
HYPOMAGNESAEMIA	23 (5.8%)	51 (13.0%)	35 (8.8%)
INVESTIGATIONS			
Total number of patients with at least one Adverse Events[1]	100 (25.4%)	117 (29.8%)	79 (19.8%)
PLATELET COUNT DECREASED	45 (11.4%)	55 (14.0%)	40 (10.0%)
NEUTROPHIL COUNT DECREASED	35 (8.9%)	48 (12.2%)	33 (8.3%)
WEIGHT DECREASED	41 (10.4%)	49 (12.5%)	25 (6.3%)
VASCULAR DISORDERS			
Total number of patients with at least one Adverse Events[1]	87 (22.1%)	99 (25.2%)	14 (3.5%)
HYPERTENSION	87 (22.1%)	99 (25.2%)	14 (3.5%)
RENAL AND URINARY DISORDERS			
Total number of patients with at least one Adverse Events[1]	59 (15.0%)	63 (16.0%)	7 (1.8%)
PROTEINURIA	59 (15.0%)	63 (16.0%)	7 (1.8%)
PSYCHIATRIC DISORDERS			
Total number of patients with at least one Adverse Events[1]	37 (9.4%)	39 (9.9%)	47 (11.8%)
INSOMNIA	37 (9.4%)	39 (9.9%)	47 (11.8%)
ENDOCRINE DISORDERS			
Total number of patients with at least one Adverse Events[1]	11 (2.8%)	45 (11.5%)	30 (7.5%)
HYPOTHYROIDISM	11 (2.8%)	45 (11.5%)	30 (7.5%)

Table 46: Overview of Adverse Events by Treatment Phase (Safety Evaluable Population) (data cut: 22 January 2018)

	Bev+CP			Atezo+Bev+CP			Atezo+CP		
		Maintenance			Maintenance			Maintenanc	
	Induction (N=394)	Follow-up (N=270)	Overall (N=394)	Induction (N=393)	Follow-up (N=312)	Overall (N=393)	Induction (N=400)	e Follow-up (N=305)	Overall (N=400)
Total number of events	3457	1099	4630	3950	2405	6419	3277	1516	4851
Total number of patients with at least one:									
Adverse event	389 (98.7%)	219 (81.1%)	390 (99.0%)	380 (96.7%)	289 (92.6%)	386 (98.2%)	382 (95.5%)	260 (85.2%)	391 (97.8%)
Treatment-related AE	375 (95.2%)	147 (54.4%)	377 (95.7%)	362 (92.1%)	221 (70.8%)	370 (94.1%)	365 (91.3%)	172 (56.4%)	377 (94.3%)
Grade 3-4 AE	204 (51.8%)	61 (22.6%)	230 (58.4%)	211 (53.7%)	115 (36.9%)	250 (63.6%)	199 (49.8%)	68 (22.3%)	230 (57.5%)
Treatment-related Grade 3-4 AE			191 (48.5%)			223 (56.7%)			172 (43.0%)
Grade 5 AE	11 (2.8%)	9 (3.3%)	21 (5.3%)	15 (3.8%)	8 (2.6%)	24 (6.1%)	6 (1.5%)	4 (1.3%)	10 (2.5%)
Treatment-related Grade 5 AE	5 (1.3%)	3 (1.1%)	9 (2.3%)	10 (2.5%)	1 (0.3%)	11 (2.8%)	1 (0.3%)	3 (1.0%)	4 (1.0%)
Serious AE	104 (26.4%)	35 (13.0%)	135 (34.3%)	112 (28.5%)	82 (26.3%)	174 (44.3%)	113 (28.3%)	61 (20.0%)	157 (39.3%)
Treatment-Related Serious AE	68 (17.3%)	9 (3.3%)	78 (19.8%)	76 (19.3%)	31 (9.9%)	103 (26.2%)	65 (16.3%)	18 (5.9%)	78 (19.5%)
AE leading to any dose modification/ interruption	167 (42.4%)	44 (16.3%)	188 (47.7%)	198 (50.4%)	118 (37.8%)	246 (62.6%)	179 (44.8%)	57 (18.7%)	207 (51.8%)

Note: The denominator for the maintenance/follow up phase is adjusted to patients who received at least one dose of study treatment during the maintenance phase. Therefore, the total number of events or patients with Grade 5 or events leading to treatment withdrawal for each treatment phase does not add up to the overall number.

Comparison between IMpower150 Atezo + Bev + CP Arm and Monotherapy

Almost all patients in the Atezo + Bev+ CP arm and atezolizumab monotherapy population experienced at least one AE of any grade (98.0% Atezo + Bev + CP vs. 95.9% monotherapy population). The most common SOCs (≥ 30% of patients in either Atezo + Bev + CP arm or monotherapy population) in which AEs were reported were:

- General disorders and administration site conditions (72.5% vs. 68.7%)
- Gastrointestinal disorders (72.0% vs. 60.4%)
- Nervous system disorders (70.7% vs. 32.9%)
- Skin and subcutaneous tissue disorders (64.9% vs. 34.7%)
- Musculoskeletal and connective tissue disorders (59.0% vs. 47.7%)
- Respiratory, thoracic and mediastinal disorders (56.5% vs. 49.9%)
- Infections and infestations (53.2% vs. 42.6%)
- Blood and lymphatic system disorders (49.9% vs. 21.2%)
- Metabolism and nutrition disorders (48.1% vs. 42.5%)
- Investigations (43.8% vs. 27.6%)

- Vascular disorders (34.9% vs. 13.9%)

Treatment-related AEs

Table 47: Treatment-related adverse events reported in ≥10% patients in any treatment arm (Safety evaluable patients) (data cut: 22 January 2018)

	Overall (N=1187)		
MedDRA System Organ Class MedDRA Preferred Term	Bev+CP (Actual) (N=394)	Atezo+Bev+CP (Actual) (N=393)	Atezo+CP (Actual) (N=400)
Overall total number of patients with at least one Adverse Events[1]	361 (91.6%)	358 (91.1%)	362 (90.5%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Total number of patients with at least one Adverse Events[1]	188 (47.7%)	221 (56.2%)	209 (52.3%)
ALOPECIA	175 (44.4%)	185 (47.1%)	175 (43.8%)
RASH	20 (5.1%)	55 (14.0%)	45 (11.3%)
PRURITUS	13 (3.3%)	42 (10.7%)	34 (8.5%)
GASTROINTESTINAL DISORDERS			
Total number of patients with at least one Adverse Events[1]	179 (45.4%)	223 (56.7%)	189 (47.3%)
NAUSEA	110 (27.9%)	135 (34.4%)	107 (26.8%)
DIARRHOEA	60 (15.2%)	84 (21.4%)	61 (15.3%)
CONSTIPATION	48 (12.2%)	66 (16.8%)	56 (14.0%)
VOMITING	56 (14.2%)	58 (14.8%)	39 (9.8%)
STOMATITIS	22 (5.6%)	47 (12.0%)	22 (5.5%)
NERVOUS SYSTEM DISORDERS			
Total number of patients with at least one Adverse Events[1]	153 (38.8%)	193 (49.1%)	181 (45.3%)
NEUROPATHY PERIPHERAL	66 (16.8%)	88 (22.4%)	100 (25.0%)
PERIPHERAL SENSORY NEUROPATHY	56 (14.2%)	65 (16.5%)	56 (14.0%)
PARAESTHESIA	37 (9.4%)	44 (11.2%)	32 (8.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Total number of patients with at least one Adverse Events[1]	153 (38.8%)	163 (41.5%)	162 (40.5%)
ANAEMIA	94 (23.9%)	97 (24.7%)	126 (31.5%)
NEUTROPENIA	68 (17.3%)	72 (18.3%)	57 (14.3%)
THROMBOCYTOPENIA	45 (11.4%)	52 (13.2%)	42 (10.5%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Total number of patients with at least one Adverse Events[1]	146 (37.1%)	156 (39.7%)	136 (34.0%)
FATIGUE	89 (22.6%)	104 (26.5%)	87 (21.8%)
ASTHENIA	63 (16.0%)	58 (14.8%)	52 (13.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Total number of patients with at least one Adverse Events[1]	88 (22.3%)	101 (25.7%)	100 (25.0%)
ARTHRALGIA	59 (15.0%)	69 (17.6%)	63 (15.8%)
MYALGIA	47 (11.9%)	53 (13.5%)	56 (14.0%)
METABOLISM AND NUTRITION DISORDERS			
Total number of patients with at least one Adverse Events[1]	58 (14.7%)	89 (22.6%)	68 (17.0%)
DECREASED APPETITE	58 (14.7%)	89 (22.6%)	68 (17.0%)
INVESTIGATIONS			
Total number of patients with at least one Adverse Events[1]	60 (15.2%)	80 (20.4%)	57 (14.3%)
PLATELET COUNT DECREASED	44 (11.2%)	54 (13.7%)	39 (9.8%)
NEUTROPHIL COUNT DECREASED	35 (8.9%)	48 (12.2%)	33 (8.3%)
VASCULAR DISORDERS			
Total number of patients with at least one Adverse Events[1]	70 (17.8%)	78 (19.8%)	3 (0.8%)
HYPERTENSION	70 (17.8%)	78 (19.8%)	3 (0.8%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Total number of patients with at least one Adverse Events[1]	68 (17.3%)	54 (13.7%)	5 (1.3%)
EPISTAXIS	68 (17.3%)	54 (13.7%)	5 (1.3%)
RENAL AND URINARY DISORDERS			
Total number of patients with at least one Adverse Events[1]	53 (13.5%)	58 (14.8%)	1 (0.3%)
PROTEINURIA	53 (13.5%)	58 (14.8%)	1 (0.3%)

Grade 3/4 AEs

Table 48: Grade 3/4 AEs reported in ≥5% of patients in any treatment arm (safety evaluable population) (Data cut 22 January 2018)

Overall		(N=1187)		
MedDRA System Organ Class MedDRA Preferred Term	Grade	Bev+CP (Actual) (N=394)	Atezo+Bev+CP (Actual) (N=393)	Atezo+CP (Actual) (N=400)
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
- Overall -	- Any Grade -	186 (47.2%)	198 (50.4%)	194 (48.5%)
	3 - 4	106 (26.9%)	110 (28.0%)	93 (23.3%)
ANAEMIA	- Any Grade -	107 (27.2%)	115 (29.3%)	144 (36.0%)
	3 - 4	26 (6.6%)	28 (7.1%)	40 (10.0%)
NEUTROPENIA	- Any Grade -	70 (17.8%)	73 (18.6%)	61 (15.3%)
	3 - 4	47 (11.9%)	55 (14.0%)	36 (9.0%)
FEBRILE NEUTROPENIA	- Any Grade -	26 (6.6%)	40 (10.2%)	29 (7.3%)
	3 - 4	26 (6.6%)	35 (8.9%)	25 (6.3%)
INFECTIONS AND INFESTATIONS				
- Overall -	- Any Grade -	157 (39.8%)	220 (56.0%)	177 (44.3%)
	3 - 4	35 (8.9%)	63 (16.0%)	47 (11.8%)
PNEUMONIA	- Any Grade -	29 (7.4%)	39 (9.9%)	29 (7.3%)
	3 - 4	13 (3.3%)	21 (5.3%)	14 (3.5%)
INVESTIGATIONS				
- Overall -	- Any Grade -	147 (37.3%)	177 (45.0%)	145 (36.3%)
	3 - 4	44 (11.2%)	75 (19.1%)	46 (11.5%)
PLATELET COUNT DECREASED	- Any Grade -	45 (11.4%)	55 (14.0%)	40 (10.0%)
	3 - 4	9 (2.3%)	20 (5.1%)	7 (1.8%)
NEUTROPHIL COUNT DECREASED	- Any Grade -	35 (8.9%)	48 (12.2%)	33 (8.3%)
	3 - 4	25 (6.3%)	34 (8.7%)	23 (5.8%)
VASCULAR DISORDERS				
- Overall -	- Any Grade -	114 (28.9%)	140 (35.6%)	67 (16.8%)
	3 - 4	39 (9.9%)	47 (12.0%)	15 (3.8%)
HYPERTENSION	- Any Grade -	87 (22.1%)	99 (25.2%)	14 (3.5%)
	3 - 4	33 (8.4%)	36 (9.2%)	5 (1.3%)

AEs of special interest

Atezolizumab

Table 49: Summary of adverse events of special interest to atezolizumab (safety evaluable population) (Data cut 15 September 2017)

	Overall (N=1187)		
	Bev+CP (Actual) (N=394)	Atezo+Bev+CP (Actual) (N=393)	Atezo+CP (Actual) (N=400)
Total number of patients with at least one AESI	108 (27.4%)	199 (50.6%)	184 (46.0%)
Total number of Special Interest events	161	392	318
Total number of patients with at least one			
Treatment-related AESI	69 (17.5%)	172 (43.8%)	150 (37.5%)
Grade 3-4 AESI	13 (3.3%)	45 (11.5%)	37 (9.3%)
Treatment-related Grade 3-4 AESI	8 (2.0%)	37 (9.4%)	33 (8.3%)
Grade 5 AESI	0	0	2 (0.5%)
Treatment-related Grade 5 AESI	0	0	1 (0.3%)
Serious Special Interest Adverse Event	4 (1.0%)	25 (6.4%)	26 (6.5%)
Treatment-Related Serious AESI	2 (0.5%)	20 (5.1%)	25 (6.3%)
AESI leading to withdrawal from any treatment	3 (0.8%)	24 (6.1%)	19 (4.8%)
AESI leading to any dose modification/interruption	15 (3.8%)	48 (12.2%)	43 (10.8%)
AESI Medical Concepts: patients with at least one			
Immune-Related Rash	52 (13.2%)	113 (28.8%)	114 (28.5%)
Immune-Related Hepatitis	29 (7.4%)	54 (13.7%)	39 (9.8%)
Immune-Related Hepatitis (Lab Abnormal)	29 (7.4%)	47 (12.0%)	34 (8.5%)
Immune-Related Hypothyroidism	15 (3.8%)	50 (12.7%)	30 (7.5%)
Infusion-Related Reactions	11 (2.8%)	13 (3.3%)	16 (4.0%)
Immune-Related Pneumonitis	5 (1.3%)	11 (2.8%)	21 (5.3%)
Immune-Related Hyperthyroidism	5 (1.3%)	16 (4.1%)	11 (2.8%)
Immune-Related Colitis	2 (0.5%)	9 (2.3%)	3 (0.8%)
Immune-Related Hepatitis (Diagnosis)	0	8 (2.0%)	6 (1.5%)
Immune-Related Severe Cutaneous Reaction	1 (0.3%)	4 (1.0%)	3 (0.8%)
Immune-Related Adrenal Insufficiency	3 (0.8%)	2 (0.5%)	2 (0.5%)
Immune-Related Pancreatitis	0	5 (1.3%)	2 (0.5%)
Immune-Related Nephritis	0	3 (0.8%)	1 (0.3%)
Immune-Related Ocular Inflammatory Toxic	0	3 (0.8%)	1 (0.3%)
Immune-Related Myositis	1 (0.3%)	2 (0.5%)	0
Immune-Related Vasculitis	1 (0.3%)	1 (0.3%)	1 (0.3%)
Immune-Related Hypophysitis	0	3 (0.8%)	0
Immune-Related Diabetes Mellitus	0	1 (0.3%)	1 (0.3%)
Autoimmune Hemolytic Anemia	1 (0.3%)	1 (0.3%)	0
Immune-Related Meningoencephalitis	0	1 (0.3%)	0
Immune-Related Encephalitis	0	1 (0.3%)	0

Table 50: Summary of Safety Information for Important AESIs for Atezolizumab (IMpower150 Safety Evaluable Patients) (data cut: 22 January 2018)

Important AESI (Atezo +Bev+CP N=394, Atezo +CP N=393)	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)	
	Atezo +Bev+CP	Atezo +CP	Atezo +Bev+CP	Atezo +CP	Atezo +Bev+CP	Atezo +CP	Atezo +Bev+CP	Atezo +CP
Immune-Related								
Hepatitis (Diagnosis & Laboratory Abnormality)	2.7 (0.2-17.3)	0.8 (0.3-23.1)	1.0 (0.1-12.3*)	0.9 (0.1-15.1*)	7 (1.8%)	3 (0.8%)	12 (3.1%)	5 (1.3%)
Hepatitis (Diagnosis)	3.0 (0.4-6.8)	2.4 (0.6-16.9)	1.7 (0.1-12.3*)	0.5 (0.1-7.1*)	3 (0.8%)	1 (0.3%)	4 (1.0%)	1 (0.3%)
Hepatitis (Laboratory Abnormality)	2.7 (0.2-17.3)	0.7 (0.3-23.1)	1.2 (0.1-12.1*)	0.9 (0.2-15.1*)	4 (1.0%)	2 (0.5%)	8 (2.0%)	4 (1.0%)
Hypothyroidism	5.3 (1.4-15.4)	4.5 (2.0-9.0)	NE (0.3-24.1*)	NE (0.3-17.2*)	1 (0.3%)	0	0	0
Hyperthyroidism	3.2 (1.4-7.6)	2.3 (0.7-16.7)	3.0 (0.7-16.7*)	1.4 (0.3-8.2*)	1 (0.3%)	0	2 (0.5%)	2 (0.5%)
Adrenal Insufficiency	6.9 (3.4-10.4)	8.4 (6.7-10.1)	NE (0.7-10.5*)	NE (6.1*-7.7*)	0	1 (0.3%)	2 (0.5%)	2 (0.5%)
Pneumonitis	3.3 (0.3-13.1)	4.3 (0.5-19.3)	1.2 (0.2-10.6*)	4.2 (0.2-16.2*)	8 (2.0%)	8 (2.0%)	9 (2.3%)	18 (4.5%)
Colitis	2.6 (0.3-16.3)	4.3 (0.2-13.4)	2 (0.8-23.1*)	0.3 (0.1*-0.3)	1 (0.3%)	0	6 (1.5%)	2 (0.5%)
Guillain-Barré	N/A	N/A	N/A	N/A	0	0	0	0
Myasthenia Gravis	N/A	N/A	N/A	N/A	0	0	0	0
Meningoencephalitis	0.5 (0.5-0.5)	N/A	6.4 (6.4-6.4)	N/A	0	0	1 (0.3%)	0
Pancreatitis	4.4 (0.7-9.4)	11.3 (5.5-17.1)	2.3 (0.4*-4.1*)	0.3 (0.2-0.4)	1 (0.3%)	0	1 (0.3%)	0
Diabetes Mellitus	5.5 (5.5-5.5)	9.9 (9.9-9.9)	NE (6.8*-6.8*)	NE (10.2*-10.2*)	0	0	0	0
Hypophysitis	7.7 (5.0-8.8)	N/A	NE (0.3*-1.9*)	N/A	1 (0.3%)	0	3 (0.8%)	0
Myocarditis	N/A	N/A	N/A	N/A	0	0	0	0
Infusion-Related Reactions	0.8 (0.0-3.7)	0.7 (0.0-3.0)	0.03 (0.03-0.2)	0.03 (0.03-0.3)	0	1 (0.3%)	7 (1.8%)	10 (2.5%)

AESIs requiring corticosteroid treatment

Among the AESIs related to atezolizumab, 20.6% of patients in the Atezo+Bev+CP arm, 7.6% of patients in the Bev+CP arm, and 23.3% of patients in the Atezo+CP arm experienced AESIs requiring corticosteroid treatment. The majority of AESIs requiring corticosteroid treatment were of Grade 1-2 severity; 8.7% of patients in the Atezo+Bev+CP arm, 0.8% of patients in the Bev+CP arm, and 6.5% of patients in the Atezo+CP arm experienced a Grade 3-4 AESI requiring corticosteroid treatment.

Selected AESIs to Atezolizumab

Table 51: Summary of safety information for important AESIs for atezolizumab (safety evaluable patients) (data cut: 22 January 2018)

Important AESI (Atezo+Bev+CP N=393, Atezo+CP N=400)	Intensity						Resolved All Grades [a]		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 +Bev+CP	Atezo +CP	Atezo +Bev+CP	Atezo +CP	Atezo +Bev+CP	Atezo +CP	Atezo +Bev+CP	Atezo +CP	Atezo +Bev+CP	Atezo +CP	Atezo +Bev+CP	Atezo +CP	Atezo +Bev+CP	Atezo +CP	Atezo +Bev+CP	Atezo +CP
Immune-Related																
Hepatitis (Diagnosis & Laboratory Abnormality)	54 (13.7%)	42 (10.5%)	20 (5.1%)	12 (3.0%)	0	1 (0.3%)	42 (10.7%)	33 (8.3%)	2.73 (0.2–17.3)	1.72 (0.3–23.1)	1.18 (0.13–16.53*)	0.87 (0.13–19.32*)	7 (1.8%)	3 (0.8%)	21 (5.3%)	10 (2.5%)
Hepatitis (Diagnosis)	7 (1.8%)	7 (1.8%)	3 (0.8%)	2 (0.5%)	0	1 (0.3%)	4 (1.0%)	5 (1.3%)	3.32 (0.4–6.8)	2.69 (0.6–16.9)	2.23 (0.13–16.53*)	0.72 (0.13–13.31*)	3 (0.8%)	1 (0.3%)	4 (1.0%)	0
Hepatitis (Laboratory Abnormality)	48 (12.2%)	36 (9.0%)	18 (4.6%)	10 (2.5%)	0	0	38 (9.7%)	29 (7.3%)	2.61 (0.2–17.3)	1.10 (0.3–23.1)	1.18 (0.13–16.33*)	0.87 (0.16–19.32*)	4 (1.0%)	2 (0.5%)	18 (4.6%)	10 (2.5%)
Hypothyroidism	56 (14.2%)	34 (8.5%)	1 (0.3%)	1 (0.3%)	0	0	21 (5.3%)	13 (3.3%)	5.86 (1.4–15.4)	5.17 (2.0–15.9)	NE (0.26–28.29*)	NE (0.56*–21.39*)	1 (0.3%)	0	4 (1.0%)	6 (1.5%)
Hyperthyroidism	16 (4.1%)	11 (2.8%)	1 (0.3%)	0	0	0	11 (2.8%)	11 (2.8%)	3.22 (1.4–7.6)	2.30 (0.7–16.7)	3.19 (0.72–20.90*)	1.02 (0.26–3.38)	1 (0.3%)	0	2 (0.5%)	3 (0.8%)
Adrenal Insufficiency	2 (0.5%)	4 (1.0%)	1 (0.3%)	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)	5.54 (0.7–10.4)	10.86 (6.7–13.5)	NE (0.69–17.51*)	NE (0.23–10.38)	0	1 (0.3%)	2 (0.5%)	4 (1.0%)
Pneumonitis	13 (3.3%)	23 (5.8%)	6 (1.5%)	8 (2.0%)	0	1 (0.3%)	9 (2.3%)	11 (2.8%)	3.58 (0.3–17.2)	4.30 (0.5–23.1)	1.31 (0.20–10.64*)	4.24 (0.20–20.44*)	8 (2.0%)	8 (2.0%)	11 (2.8%)	22 (5.5%)

Table 52: Patients Hospitalised with Any-Grade Pneumonitis

Patient ID	Highest NCI-CTCAE Grade	Serious Criteria	Outcome
Atezo + Bev + CP			
10082	3	Hospitalized	recovered
10984	2	Hospitalized	recovered
12423	3	Hospitalized	recovered
12686	2	Hospitalized	recovered
13082	3	Hospitalized	Recovered
13381	4	Life-threatening (hospitalized)	Recovered
13483	3	Hospitalized	not recovered
Atezo + CP			
13105	3	Hospitalized	Recovered
11481	3	Hospitalized	not recovered
11562	4	Life-threatening (hospitalized)	Recovered
12351	3	Hospitalized	Recovered
11071	2	Hospitalized	not recovered
14044	4	Life-threatening (hospitalized)	Recovered
10543	3	Hospitalized	not recovered
14661	3	Hospitalized	Recovered

Bevacizumab

Table 53: Summary of Bleeding/Haemorrhage AESIs (Safety Evaluable Population) (Data Cut: 22 Jan 2018)

AE of Special Interest Medical Concept MedDRA Preferred Term	Bev+CP (Actual) (N=394)	Atezo+Bev+CP (Actual) (N=393)	Atezo+CP (Actual) (N=400)
Bleeding / Haemorrhage			
Total number of patients with at least one adverse event	123 (31.2%)	127 (32.3%)	58 (14.5%)
Total number of events	178	195	81
EPISTAXIS	87 (22.1%)	66 (16.8%)	15 (3.8%)
HAEMOPTYSIS	20 (5.1%)	27 (6.9%)	14 (3.5%)
HAEMATURIA	7 (1.8%)	13 (3.3%)	11 (2.8%)
GINGIVAL BLEEDING	8 (2.0%)	7 (1.8%)	0
CONTUSION	2 (0.5%)	4 (1.0%)	4 (1.0%)
CEREBROVASCULAR ACCIDENT	1 (0.3%)	6 (1.5%)	2 (0.5%)
RECTAL HAEMORRHAGE	1 (0.3%)	7 (1.8%)	1 (0.3%)
PULMONARY HAEMORRHAGE	6 (1.5%)	2 (0.5%)	0
HAEMATOCHEZIA	1 (0.3%)	6 (1.5%)	0
HAEMORRHOIDAL HAEMORRHAGE	1 (0.3%)	5 (1.3%)	1 (0.3%)
HAEMATOMA	1 (0.3%)	1 (0.3%)	2 (0.5%)
MOUTH HAEMORRHAGE	3 (0.8%)	1 (0.3%)	0
BLOOD URINE PRESENT	0	1 (0.3%)	2 (0.5%)
CONJUNCTIVAL HAEMORRHAGE	1 (0.3%)	0	2 (0.5%)
GASTROINTESTINAL HAEMORRHAGE	0	1 (0.3%)	2 (0.5%)
PETECHIAE	1 (0.3%)	1 (0.3%)	1 (0.3%)
PURPURA	1 (0.3%)	1 (0.3%)	1 (0.3%)
ANAL HAEMORRHAGE	1 (0.3%)	1 (0.3%)	0
BONE CONTUSION	0	0	2 (0.5%)
HAEMORRHAGE	0	1 (0.3%)	1 (0.3%)
HAEMORRHAGE INTRACRANIAL	0	1 (0.3%)	1 (0.3%)
VAGINAL HAEMORRHAGE	0	2 (0.5%)	0
CATHETER SITE HAEMATOMA	1 (0.3%)	0	0
CEREBRAL HAEMORRHAGE	1 (0.3%)	0	0
DISSEMINATED INTRAVASCULAR COAGULATION	0	1 (0.3%)	0
ECCHYMOSIS	1 (0.3%)	0	0
GASTRIC HAEMORRHAGE	0	1 (0.3%)	0
INCREASED TENDENCY TO BRUISE	0	1 (0.3%)	0
INJECTION SITE BRUISING	0	1 (0.3%)	0
INTESTINAL HAEMORRHAGE	0	1 (0.3%)	0
LARGE INTESTINAL HAEMORRHAGE	1 (0.3%)	0	0
MELAENA	0	1 (0.3%)	0
MENORRHAGIA	1 (0.3%)	0	0
METRORRHAGIA	0	0	1 (0.3%)
MUSCLE HAEMORRHAGE	0	0	1 (0.3%)
OCCULT BLOOD POSITIVE	1 (0.3%)	0	0
PERIORBITAL HAEMATOMA	0	1 (0.3%)	0
POST PROCEDURAL HAEMATURIA	0	0	1 (0.3%)
POST PROCEDURAL HAEMORRHAGE	1 (0.3%)	0	0
RETINAL HAEMORRHAGE	1 (0.3%)	0	0
SUBCUTANEOUS HAEMATOMA	0	1 (0.3%)	0
SUBDURAL HAEMATOMA	0	1 (0.3%)	0
TUMOUR HAEMORRHAGE	0	1 (0.3%)	0
UPPER GASTROINTESTINAL HAEMORRHAGE	0	1 (0.3%)	0

Selected AESIs to Bevacizumab

Table 54: Summary of hypertension AESIs reported in at least 1% of patients (safety evaluable population) (Data Cut: 22 Jan 2018)

	Overall (N=1187)		
AE of Special Interest Medical Concept MedDRA Preferred Term	Bev+CP (Actual) (N=394)	Atezo+Bev+CP (Actual) (N=393)	Atezo+CP (Actual) (N=400)
Hypertension			
Total number of patients with at least one adverse event	89 (22.6%)	105 (26.7%)	14 (3.5%)
Total number of events	106	141	14
HYPERTENSION	87 (22.1%)	99 (25.2%)	14 (3.5%)
HYPERTENSIVE CRISIS	2 (0.5%)	4 (1.0%)	0

Table 55: Summary of thromboembolic event – arterial AESIs reported in at least 1% of patients (safety evaluable population) (Data Cut: 22 Jan 2018)

AE of Special Interest Medical Concept MedDRA Preferred Term	Overall (N=1187) Bev+CP (Actual) (N=394)	Atezo+Bev+CP (Actual) (N=393)	Atezo+CP (Actual) (N=400)
Thromboembolic Event - Arterial			
Total number of patients with at least one adverse event	20 (5.1%)	30 (7.6%)	27 (6.8%)
Total number of events	21	34	31
THROMBOSIS	4 (1.0%)	3 (0.8%)	3 (0.8%)
CEREBROVASCULAR ACCIDENT	1 (0.3%)	6 (1.5%)	2 (0.5%)

Table 56: Summary of thromboembolic event – venous AESIs reported in at least 1% of patients (safety evaluable population) (Data Cut: 22 Jan 2018)

AE of Special Interest Medical Concept MedDRA Preferred Term	Overall (N=1187) Bev+CP (Actual) (N=394)	Atezo+Bev+CP (Actual) (N=393)	Atezo+CP (Actual) (N=400)
Thromboembolic Event - Venous			
Total number of patients with at least one adverse event	23 (5.8%)	27 (6.9%)	25 (6.3%)
Total number of events	26	28	28
PULMONARY EMBOLISM	16 (4.1%)	14 (3.6%)	10 (2.5%)
DEEP VEIN THROMBOSIS	6 (1.5%)	6 (1.5%)	10 (2.5%)
THROMBOPHLEBITIS SUPERFICIAL	1 (0.3%)	0	5 (1.3%)

Table 57: Summary of Arterial Thromboembolic Event –AESIs Reported in the Safety Evaluable Population (Data Cut: 22 Jan 2018)

AE of Special Interest Medical Concept MedDRA Preferred Term	Bev+CP (Actual) (N=394)	Atezo+Bev+CP (Actual) (N=393)	Atezo+CP (Actual) (N=400)
Thromboembolic Event - Arterial or Venous			
Total number of patients with at least one adverse event	40 (10.2%)	55 (14.0%)	47 (11.8%)
Total number of events	47	62	59
PULMONARY EMBOLISM	16 (4.1%)	14 (3.6%)	10 (2.5%)
DEEP VEIN THROMBOSIS	6 (1.5%)	6 (1.5%)	10 (2.5%)
THROMBOSIS	4 (1.0%)	3 (0.8%)	3 (0.8%)
CEREBROVASCULAR ACCIDENT	1 (0.3%)	6 (1.5%)	2 (0.5%)
EMBOLISM	2 (0.5%)	2 (0.5%)	3 (0.8%)
ISCHAEMIC STROKE	3 (0.8%)	2 (0.5%)	2 (0.5%)
MYOCARDIAL INFARCTION	2 (0.5%)	2 (0.5%)	2 (0.5%)
THROMBOPHLEBITIS SUPERFICIAL	1 (0.3%)	0	5 (1.3%)
ACUTE MYOCARDIAL INFARCTION	2 (0.5%)	2 (0.5%)	1 (0.3%)
CEREBRAL INFARCTION	1 (0.3%)	2 (0.5%)	2 (0.5%)
CEREBRAL ISCHAEMIA	1 (0.3%)	3 (0.8%)	1 (0.3%)
TRANSIENT ISCHAEMIC ATTACK	2 (0.5%)	2 (0.5%)	1 (0.3%)
VENOUS THROMBOSIS LIMB	0	3 (0.8%)	1 (0.3%)
DEVICE OCCLUSION	0	1 (0.3%)	2 (0.5%)
THROMBOPHLEBITIS	0	2 (0.5%)	1 (0.3%)
THROMBOSIS IN DEVICE	0	2 (0.5%)	1 (0.3%)
DEVICE RELATED THROMBOSIS	1 (0.3%)	0	1 (0.3%)
PARESIS	0	0	2 (0.5%)
ARTERIAL OCCLUSIVE DISEASE	0	0	1 (0.3%)
ATRIAL THROMBOSIS	0	1 (0.3%)	0
CAROTID ARTERY OCCLUSION	0	0	1 (0.3%)
CENTRAL VENOUS CATHETERISATION	0	1 (0.3%)	0
CEREBRAL ARTERY EMBOLISM	1 (0.3%)	0	0
DISSEMINATED INTRAVASCULAR COAGULATION	0	1 (0.3%)	0
EMBOLISM VENOUS	0	1 (0.3%)	0
HAEMORRHOIDS THROMBOSED	0	0	1 (0.3%)
INTESTINAL INFARCTION	0	0	1 (0.3%)
LACUNAR INFARCTION	0	0	1 (0.3%)
PARAPARESIS	0	0	1 (0.3%)
PELVIC VENOUS THROMBOSIS	0	0	1 (0.3%)
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE	0	0	1 (0.3%)
PERIPHERAL ARTERY THROMBOSIS	0	1 (0.3%)	0
PORTAL VEIN THROMBOSIS	1 (0.3%)	0	0
PULMONARY ARTERY THROMBOSIS	0	1 (0.3%)	0
SPLENIC INFARCTION	1 (0.3%)	0	0
SUPERIOR VENA CAVA SYNDROME	1 (0.3%)	0	0
VENA CAVA THROMBOSIS	0	1 (0.3%)	0

Adverse drug reactions

Table 58: ADRs for the atezolizumab monotherapy and combination safety data sets

Atezolizumab monotherapy (n=3075)		**System Organ Class ADR**	Atezolizumab in combination therapy (n=793)	
Frequency (All Grades)	Incidence % (All Grades)		Frequency (All Grades)	Incidence % (All Grades)
Infections and infestations				
very common	360 (11.7%)	Urinary tract infection [a]		
Blood and Lymphatic System Disorders				
-	-	Anaemia	very common	259 (32.7%)
-	-	Neutropenia [b]	very common	257 (32.4%)
common	113 (3.7%)	Thrombocytopenia [c]	very common	190 (24.0%)
Immune System Disorders				
common	35 (1.1%)	Hypersensitivity		
Endocrine Disorders				
uncommon	12 (0.4%)	Adrenal insufficiency [d]		
uncommon	10 (0.3%)	Diabetes mellitus [e]		
uncommon	28 (0.9%)	Hyperthyroidism [f]		
rare	1 (<0.1%)	Hypophysitis		
common	149 (4.8%)	Hypothyroidism [g]	very common	90 (11.3%)
Metabolism and nutrition disorders				
very common	799 (26.0%)	Decreased appetite	very common	208 (26.2%)
common	137 (4.5%)	Hypokalemia	common	60 (7.6%)
-	-	Hypomagnesaemia	very common	86 (10.8%)
common	163 (5.3%)	Hyponatremia	common	38 (4.8%)
Nervous System Disorders				
uncommon	5 (0.2%)	Guillain-Barré syndrome [h]	-	-
uncommon	12 (0.4%)	Meningoencephalitis [i]		1 (0.1%)
rare	1 (<0.1%)	Myasthenic syndrome	-	-
-	-	Peripheral neuropathy[j]	very common	338 (42.6%)
Cardiac Disorders				
rare	1 (<0.1%)	Myocarditis [k]	-	-
Vascular Disorders				
common	102 (3.3%)	Hypotension		
Respiratory, Thoracic, and Mediastinal Disorders				
very common	637 (20.7%)	Cough		
very common	635 (20.7%)	Dyspnoea	very common	
common	72 (2.3%)	Hypoxia		
common	92 (3.0%)	Nasal congestion		
common	86 (2.8%)	Pneumonitis [l]		
Gastrointestinal Disorders				
common	261 (8.5%)	Abdominal pain		
common	34 (1.1%)	Colitis [m]		
-	-	Constipation	very common	216 (27.2%)
very common	609 (19.8%)	Diarrhoea [n]	very common	206 (26.0%)
common	82 (2.7%)	Dysphagia		
very common	728 (23.7%)	Nausea	very common	282 (35.6%)
uncommon	16 (0.5%)	Pancreatitis [o]		
-	-	Stomatitis	common	74 (9.3%)
very common	471 (15.3%)	Vomiting		
Hepatobiliary Disorders				
common	160 (5.2%)	ALT increased		
common	173 (5.6%)	AST increased		
common	62 (2.0%)	Hepatitis [p]		
Skin and Subcutaneous Tissue Disorders				
very common	385 (12.5%)	Pruritus	very common	94 (11.9%)
very common	590 (19.2%)	Rash [q]	very common	236 (29.8%)
Musculoskeletal and Connective Tissue Disorders				
very common	428 (13.9%)	Arthralgia	very common	189 (23.8%)
very common	471 (15.3%)	Back pain		
common	233 (7.6%)	Musculoskeletal pain		73 (9.2%)
Renal Disorders				
rare	1 (<0.1%)	Nephritis[r]		
General Disorders and Administration				
very common	454 (14.8%)	Asthenia		
common	199 (6.5%)	Chills		

Atezolizumab monotherapy (n=3075)		**System Organ Class ADR**	Atezolizumab in combination therapy (n=793)	
Frequency (All Grades)	Incidence % (All Grades)		Frequency (All Grades)	Incidence % (All Grades)
very common	1093 (35.5%)	Fatigue	very common	235 (29.6%)
common	180 (5.9%)	Influenza like illness		
common	30 (1.0%)	Infusion related reactions[s]		
very common	613 (19.9%)	Pyrexia	very common	126 (15.9%)

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 neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic sepsis.
c. Includes reports of thrombocytopenia and platelet count decreased.
d. Includes reports of adrenal insufficiency, primary adrenal insufficiency.
e. Includes reports of diabetes mellitus, type 1 diabetes mellitus, diabetic ketoacidosis and ketoacidosis.
f. Includes reports of hyperthyroidism, endocrine ophthalmopathy, exophthalmus.
g. Includes reports of hypothyroidism, blood thyroid stimulating hormone increased, thyroiditis, autoimmune thyroiditis, blood thyroid stimulating hormone decreased, autoimmune hypothyroidism, euthyroid sick syndrome, myxoedema, thyroid function test abnormal, thyroiditis acute, thyroxine decreased, goitre.
h. Includes reports of Guillain Barré syndrome and demyelinating polyneuropathy.
i. Includes reports of encephalitis, meningitis, photophobia.
j. Includes reports of neuropathy peripheral, peripheral sensory neuropathy, polyneuropathy, herpes zoster, peripheral motor neuropathy, neuralgic amyotrophy, peripheral sensorimotor neuropathy, toxic neuropathy.
k. Reported in studies outside the pooled dataset. The frequency is based on the program wide exposure.
l. Includes reports of pneumonitis, lung infiltration, bronchiolitis, interstitial lung disease, radiation pneumonitis.
m. Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic, colitis ulcerative.
n. Includes reports of diarrhoea, frequent bowel movements, and gastrointestinal hypermotility.
o. Includes reports of pancreatitis, pancreatitis acute, lipase increased and amylase increased.
p. 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.
q. Includes reports of acne, eczema, erythema, erythema of eyelid, erythema multiforme, generalised erythema, exfoliative rash, eyelid rash, folliculitis, furuncle, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis exfoliative, drug eruption, 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, eczema infected.
r. Includes report of Henoch-Schonlein Purpura nephritis.
s. Includes infusion-related reaction and cytokine release syndrome.

Serious adverse event/deaths/other significant events

Table 59: Serious adverse events reported in ≥2% of patients in either treatment arm (safety evaluable population) (Data Cut: 22 Jan 2018)

	Overall (N=1187)		
MedDRA System Organ Class MedDRA Preferred Term	Bev+CP (Actual) (N=394)	Atezo+Bev+CP (Actual) (N=393)	Atezo+CP (Actual) (N=400)
Total number of patients with at least one adverse event	135 (34.3%)	174 (44.3%)	157 (39.3%)
Overall total number of events	213	346	254
INFECTIONS AND INFESTATIONS			
Total number of patients with at least one adverse event	32 (8.1%)	58 (14.8%)	53 (13.3%)
Total number of events	38	69	59
PNEUMONIA	17 (4.3%)	24 (6.1%)	17 (4.3%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Total number of patients with at least one adverse event	28 (7.1%)	35 (8.9%)	32 (8.0%)
Total number of events	33	42	37
PULMONARY EMBOLISM	8 (2.0%)	5 (1.3%)	7 (1.8%)
PNEUMONITIS	0	7 (1.8%)	8 (2.0%)
HAEMOPTYSIS	2 (0.5%)	9 (2.3%)	2 (0.5%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Total number of patients with at least one adverse event	29 (7.4%)	38 (9.7%)	19 (4.8%)
Total number of events	31	47	21
FEBRILE NEUTROPENIA	17 (4.3%)	27 (6.9%)	13 (3.3%)
GASTROINTESTINAL DISORDERS			
Total number of patients with at least one adverse event	20 (5.1%)	32 (8.1%)	21 (5.3%)
Total number of events	20	47	27
DIARRHOEA	3 (0.8%)	10 (2.5%)	8 (2.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Total number of patients with at least one adverse event	14 (3.6%)	19 (4.8%)	9 (2.3%)
Total number of events	16	20	9
PYREXIA	1 (0.3%)	8 (2.0%)	5 (1.3%)

Table 60: Deaths and causes of death (safety evaluable population) (Data Cut: 22 Jan 2018)

	Bev+CP (Actual) (N=394)	Atezo+Bev+CP (Actual) (N=393)	Atezo+CP (Actual) (N=400)	All Patients (N=1187)
All Deaths	226 (57.4%)	189 (48.1%)	205 (51.3%)	620 (52.2%)
Adverse Event	21 (5.3%)	24 (6.1%)	10 (2.5%)	55 (4.6%)
Progressive Disease	197 (50.0%)	153 (38.9%)	181 (45.3%)	531 (44.7%)
Other*	8 (2.0%)	12 (3.1%)	14 (3.5%)	34 (2.9%)

* Includes fatal events that are unrelated to study treatment and occur outside the reporting period.

Table 61: Adverse events leading to death (safety evaluable population) (Data Cut: 22 Jan 2018)

	Overall (N=1187)		
MedDRA System Organ Class MedDRA Preferred Term	Bev+CP (Actual) (N=394)	Atezo+Bev+CP (Actual) (N=393)	Atezo+CP (Actual) (N=400)
Total number of patients with at least one adverse event	21 (5.3%)	24 (6.1%)	10 (2.5%)
Overall total number of events	21	24	10
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Total number of patients with at least one adverse event	5 (1.3%)	9 (2.3%)	4 (1.0%)
Total number of events	5	9	4
HAEMOPTYSIS	1 (0.3%)	3 (0.8%)	1 (0.3%)
PULMONARY EMBOLISM	2 (0.5%)	2 (0.5%)	0
PULMONARY HAEMORRHAGE	2 (0.5%)	2 (0.5%)	0
ACUTE RESPIRATORY FAILURE	0	0	1 (0.3%)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0	1 (0.3%)	0
INTERSTITIAL LUNG DISEASE	0	0	1 (0.3%)
PNEUMONIA ASPIRATION	0	1 (0.3%)	0
PULMONARY OEDEMA	0	0	1 (0.3%)
INFECTIONS AND INFESTATIONS			
Total number of patients with at least one adverse event	6 (1.5%)	1 (0.3%)	2 (0.5%)
Total number of events	6	1	2
PNEUMONIA	3 (0.8%)	1 (0.3%)	2 (0.5%)
SEPSIS	2 (0.5%)	0	0
RESPIRATORY TRACT INFECTION	1 (0.3%)	0	0
CARDIAC DISORDERS			
Total number of patients with at least one adverse event	3 (0.8%)	2 (0.5%)	1 (0.3%)
Total number of events	3	2	1
CARDIAC ARREST	0	2 (0.5%)	1 (0.3%)
ACUTE MYOCARDIAL INFARCTION	1 (0.3%)	0	0
MYOCARDIAL INFARCTION	1 (0.3%)	0	0
PERICARDITIS	1 (0.3%)	0	0
NERVOUS SYSTEM DISORDERS			
Total number of patients with at least one adverse event	2 (0.5%)	3 (0.8%)	1 (0.3%)
Total number of events	2	3	1
CEREBROVASCULAR ACCIDENT	0	2 (0.5%)	0
HAEMORRHAGE INTRACRANIAL	0	1 (0.3%)	1 (0.3%)
CEREBRAL INFARCTION	1 (0.3%)	0	0
POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME	1 (0.3%)	0	0
GASTROINTESTINAL DISORDERS			
Total number of patients with at least one adverse event	2 (0.5%)	3 (0.8%)	0
Total number of events	2	3	0
INTESTINAL PERFORATION	2 (0.5%)	0	0
INTESTINAL ANGINA	0	1 (0.3%)	0
INTESTINAL ISCHAEMIA	0	1 (0.3%)	0
INTESTINAL OBSTRUCTION	0	1 (0.3%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Total number of patients with at least one adverse event	2 (0.5%)	2 (0.5%)	1 (0.3%)
Total number of events	2	2	1
DEATH	2 (0.5%)	2 (0.5%)	1 (0.3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Total number of patients with at least one adverse event	0	3 (0.8%)	0
Total number of events	0	3	0
FEBRILE NEUTROPENIA	0	3 (0.8%)	0

VASCULAR DISORDERS			
Total number of patients with at least one adverse event	1 (0.3%)	1 (0.3%)	0
Total number of events	1	1	0
AORTIC DISSECTION	0	1 (0.3%)	0
THROMBOSIS	1 (0.3%)	0	0
HEPATOBILIARY DISORDERS			
Total number of patients with at least one adverse event	0	0	1 (0.3%)
Total number of events	0	0	1
HEPATITIS ACUTE	0	0	1 (0.3%)

Laboratory findings

Table 62: Summary of clinically relevant laboratory shifts from baseline (safety evaluable population)

	Bev+CP	Atezo+Bev+CP	Atezo+CP
Hematology			
CD4 Cells, Abs (Low)	7/138 (5.1%)	11/115 (9.6%)	7/129 (5.4%)
Hemoglobin (High)	5/379 (1.3%)	3/378 (0.8%)	2/379 (0.5%)
Hemoglobin (Low)	26/379 (6.9%)	29/378 (7.7%)	37/379 (9.8%)
Lymphocytes Abs (High)	0/378 (0.0%)	0/377 (0.0%)	0/378 (0.0%)
Lymphocytes Abs (Low)	37/378 (9.8%)	50/377 (13.3%)	50/378 (13.2%)
Platelet (Low)	22/379 (5.8%)	33/378 (8.7%)	18/379 (4.7%)
Neutrophils, Total, Abs (Low)	88/379 (23.2%)	105/377 (27.9%)	67/378 (17.7%)
International Normalized Ratio (High)	1/11 (9.1%)	0/21 (0.0%)	1/18 (5.6%)
Activated Partial Thromboplastin Time (High)	0/10 (0.0%)	0/18 (0.0%)	0/12 (0.0%)
White Blood Cell Count (High)	0/379 (0.0%)	0/378 (0.0%)	0/379 (0.0%)
White Blood Cell Count (Low)	49/379 (12.9%)	58/378 (15.3%)	41/379 (10.8%)
Chemistry			
Albumin (Low)	4/373 (1.1%)	8/370 (2.2%)	6/374 (1.6%)
Alkaline Phosphatase (High)	2/377 (0.5%)	5/377 (1.3%)	5/376 (1.3%)
SGPT/ALT (High)	1/379 (0.3%)	16/375 (4.3%)	10/374 (2.7%)
SGOT/AST (High)	2/378 (0.5%)	9/373 (2.4%)	5/373 (1.3%)
Bilirubin (High)	1/378 (0.3%)	3/377 (0.8%)	0/374 (0.0%)
Calcium (High)	3/379 (0.8%)	2/376 (0.5%)	1/374 (0.3%)
Calcium (Low)	7/379 (1.8%)	8/376 (2.1%)	5/374 (1.3%)
Creatinine (High)	1/380 (0.3%)	5/377 (1.3%)	2/377 (0.5%)
Glucose (Low)	0/374 (0.0%)	6/376 (1.6%)	3/376 (0.8%)
Magnesium (High)	6/364 (1.6%)	5/365 (1.4%)	5/362 (1.4%)
Magnesium (Low)	5/364 (1.4%)	8/365 (2.2%)	4/362 (1.1%)
Phosphorus (Low)	11/360 (3.1%)	15/358 (4.2%)	11/354 (3.1%)
Potassium (High)	6/380 (1.6%)	8/377 (2.1%)	4/376 (1.1%)
Potassium (Low)	9/380 (2.4%)	19/377 (5.0%)	8/376 (2.1%)
Sodium (High)	1/380 (0.3%)	0/377 (0.0%)	0/376 (0.0%)
Sodium (Low)	24/380 (6.3%)	30/377 (8.0%)	22/376 (5.9%)

Safety in special populations

Age

Table 63: Atezolizumab monotherapy: safety by age (all patient population)

	All Patients (n=3075)	<65 Years (n=1553)	65–74 Years (n=1073)	75–84 Years (n=452)	≥85 Years (n=20)
Any AE	2949 (94.9%)	1463 (95.8%)	1028 (95.8%)	438 (96.9%)	20 (100%)
Grade 3–4 AEs	1440 (46.9%)	700 (45.8%)	506 (47.2%)	224 (49.5%)	10 (50.0%)
SAEs	1273 (41.4%)	620 (40.5%)	430 (40.9%)	201 (44.5%)	13 (65.0%)
Grade 5 AEs	120 (3.9%)	59 (3.9%)	39 (3.6%)	21 (4.6%)	1 (5.0%)
AEs leading to study drug withdrawal	219 (7.1%)	107 (7.0%)	67 (6.2%)	43 (9.5%)	2 (10.0%)
AESIs	966 (31.4%)	460 (30.1%)	363 (33.8%)	141 (31.2%)	2 (10.0%)

AE=adverse event; AESI=adverse event of special interest; SAE=serious adverse event.
Note: Clinical cutoff dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO29293:04JUL2016, GO28915:07JUL2016, GO29294:13MAR2017.

Table 64: System organ class reported with difference of ≥10% with age in all patients population (monotherapy)

MedDRA SOC	All Patients (n=3075)	<65 Years (n=1553)	65–74 Years (n=1073)	75–84 Years (n=452)	≥85 Years (n=20)
Gastrointestinal disorders	1856 (60.4%)	900 (58.8%)	661 (61.6%)	285 (63.1%)	10 (50.0%)
Respiratory, thoracic, and mediastinal disorders	1533 (49.9%)	740 (48.4%)	541 (50.4%)	243 (53.8%)	9 (45.0%)
Infections and infestations	1311 (42.6%)	635 (41.5%)	457 (42.6%)	213 (47.1%)	6 (30.0%)
Renal and urinary disorders	468 (15.2%)	192 (12.5%)	182 (17.0%)	89 (19.7%)	5 (25.0%)
Injury, poisoning, and procedural complications	318 (10.3%)	120 (8.5%)	118 (11.0%)	65 (14.4%)	5 (25.0%)

SOC=System Organ Class.
Note: Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO29293:04JUL2016, GO28915:07JUL2016, GO29294:13MAR2017.

Table 65: Overview of safety by age (safety-evaluable patients – IMpower150)

	Bev+CP		Atezo+Bev+CP		Atezo+CP	
	<65 (n=221)	≥65 (n=173)	<65 (n=212)	≥65 (n=181)	<65 (n=222)	≥65 (n=178)
Total number of patients with at least one						
Adverse Event	219 (99.1%)	171 (98.8%)	209 (98.6%)	176 (97.2%)	217 (97.7%)	172 (96.6%)
Treatment-related[a] AE	211 (95.5%)	165 (95.4%)	201 (94.8%)	170 (93.9%)	208 (93.7%)	164 (92.1%)
Grade 3-4 AE	122 (55.2%)	108 (65.4%)	122 (57.5%)	120 (66.3%)	123 (55.4%)	103 (57.9%)
Treatment-related[a] Grade 3-4 AE	102 (46.2%)	86 (49.7%)	104 (49.1%)	115 (63.5%)	94 (42.3%)	76 (42.7%)
Grade 5 AE	9 (4.1%)	12 (6.9%)	8 (3.8%)	15 (8.3%)	5 (2.3%)	5 (2.8%)
Treatment-related[a] Grade 5 AE	4 (1.8%)	5 (2.9%)	5 (2.4%)	6 (3.3%)	1 (0.5%)	2 (1.1%)
Serious Adverse Event	62 (28.1%)	72 (41.6%)	79 (37.3%)	86 (47.5%)	83 (37.4%)	72 (40.4%)
Treatment-Related[a] SAE	35 (15.8%)	41 (23.7%)	47 (22.2%)	53 (29.3%)	42 (18.9%)	35 (19.7%)
AE leading to withdrawal from any treatment	49 (22.2%)	49 (28.3%)	57 (26.9%)	71 (39.2%)	28 (12.6%)	28 (15.7%)
AE leading to any dose modification/interruption	100 (45.2%)	89 (51.4%)	115 (54.2%)	120 (66.3%)	112 (50.5%)	91 (51.1%)
AESI[b]	65 (29.4%)	43 (24.9%)	108 (50.9%)	91 (50.3%)	104 (46.8%)	80 (44.9%)
Grade 3-4 AESI[b]	8 (3.6%)	5 (2.9%)	20 (9.4%)	25 (13.8%)	23 (10.4%)	14 (7.9%)
Grade 5 AESI[b]	0	0	0	0	0	2 (1.1%)

ECOG PS

Table 66: Safety summary by ECOG at baseline (IMpower150) (Data cut: 22 January 2018)

	Bev+CP (Actual) (N=394)			Atezo+Bev+CP (Actual) (N=393)			Atezo+CP (Actual) (N=400)	
	0 (N=177)	1 (N=214)	Unknown (N=3)	0 (N=158)	1 (N=232)	Unknown (N=3)	0 (N=179)	1 (N=221)
Total number of patients with at least one adverse event	176 (99.4%)	211 (98.6%)	3 (100.0%)	155 (98.1%)	228 (98.3%)	3 (100.0%)	175 (97.8%)	216 (97.7%)
Total number of events	2300	2305	25	2718	3663	38	2316	2535
Total number of patients with at least one								
Treatment-related AE	173 (97.7%)	201 (93.9%)	3 (100.0%)	149 (94.3%)	218 (94.0%)	3 (100.0%)	172 (96.1%)	205 (92.8%)
Grade 3-4 AE	102 (57.6%)	125 (58.4%)	3 (100.0%)	99 (62.7%)	151 (65.1%)	0	97 (54.2%)	133 (60.2%)
Treatment-related Grade 3-4 AE	85 (48.0%)	103 (48.1%)	3 (100.0%)	88 (55.7%)	135 (58.2%)	0	79 (44.1%)	93 (42.1%)
Grade 5 AE	6 (3.4%)	15 (7.0%)	0	6 (3.8%)	18 (7.8%)	0	2 (1.1%)	8 (3.6%)
Treatment-related Grade 5 AE	3 (1.7%)	6 (2.8%)	0	3 (1.9%)	8 (3.4%)	0	1 (0.6%)	3 (1.4%)
Serious Adverse Event	58 (32.8%)	76 (35.5%)	1 (33.3%)	62 (39.2%)	112 (48.3%)	0	69 (38.5%)	88 (39.8%)
Treatment-Related Serious Adverse Event	35 (19.8%)	42 (19.6%)	1 (33.3%)	34 (21.5%)	69 (29.7%)	0	41 (22.9%)	37 (16.7%)
AE leading to withdrawal from any treatment	41 (23.2%)	55 (25.7%)	2 (66.7%)	51 (32.3%)	81 (34.9%)	1 (33.3%)	21 (11.7%)	32 (14.5%)
AE leading to any dose modification/interruption	93 (52.5%)	93 (43.5%)	2 (66.7%)	95 (60.1%)	150 (64.7%)	1 (33.3%)	101 (56.4%)	106 (48.0%)

Atezo=Atezolizumab, Bev=Bevacizumab, CP=Carboplatin+Paclitaxel.
Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v20.1. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. AEs collected after first treatment dose are included.
Data Cut-off: 22 Jan 2018; RAVE Data Extracted: 16 Mar 2018.

Gender

Table 67: Overview of safety to atezolizumab monotherapy by gender

	All Patients (n=3075)	
	Men (n=1955)	Women (n=1120)
Any AE	1869 (95.6%)	1080 (96.4%)
Grade 3–4 AE	897 (45.9%)	543 (48.5%)
SAEs	825 (42.2%)	449 (40.1%)
Grade 5 AEs	84 (4.3%)	36 (3.2%)
AEs leading to treatment withdrawal	147 (7.5%)	72 (6.4%)
AESI	625 (32.0%)	341 (30.4%)

AE=adverse event; AESI=adverse event of special interest.
Note: Clinical cutoff dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO29293:04JUL2016, GO28915:07JUL2016, GO29294:13MAR2017.

Table 68: Safety summary by gender, adverse event profile without 30-day window in all patients population (monotherapy)

	Male (N=1955)	Female (N=1120)	Total (N=3075)
Total number of patients with at least one adverse event	1869 (95.6%)	1080 (96.4%)	2949 (95.9%)
Total number of events	19557	12518	32075
Total number of patients with at least one			
Serious Adverse Events	825 (42.2%)	449 (40.1%)	1274 (41.4%)
Serious Related Adverse Events	226 (11.6%)	112 (10.0%)	338 (11.0%)
Serious AE leading to withdrawal from treatment	118 (6.0%)	58 (5.2%)	176 (5.7%)
Serious AE leading to dose interruption	282 (14.4%)	155 (13.8%)	437 (14.2%)
AE leading to withdrawal from treatment	147 (7.5%)	72 (6.4%)	219 (7.1%)
AE leading to dose interruption	549 (28.1%)	304 (27.1%)	853 (27.7%)
Related AE	1317 (67.4%)	765 (68.3%)	2082 (67.7%)
Adverse Events of Special Interest	625 (32.0%)	341 (30.4%)	966 (31.4%)
Immune Mediated Adverse Events	214 (10.9%)	96 (8.6%)	310 (10.1%)

Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v20.1. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. AEs collected after first treatment dose are included.
Grade 5 AEs due to PD are excluded for studies GO27831 and GO28625.
GO27831=PCD4989g; GO28625=FIR; GO28753=POPLAR; GO28754=BIRCH; GO29293=IMvigor 210; GO28915=OAK; GO29294=IMvigor 211.
Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO29293:04JUL2016, GO28915:07JUL2016, GO29294:13MAR2017.

Race

Table 69: Safety by race – IMpower150 atezolizumab-containing arms (arms A and B) (data cut: 15 September 2017)

	Atezo + Bev + CP (Arm B)		Atezo + CP (Arm A)	
	Asian (n=55)	Caucasian (n=316)	Asian (n=48)	Caucasian (n=329)
Total number of patients with at least one				
Adverse Event	55 (100.0%)	308 (97.5%)	48 (100.0%)	318 (96.7%)
Treatment–related[a] AE	54 (98.2%)	300 (94.9%)	47 (97.9%)	303 (92.1%)
Grade 3–4 AE	46 (83.6%)	184 (58.2%)	37 (77.1%)	174 (52.9%)
Treatment–related[a] Grade 3–4 AE	45 (81.8%)	165 (52.2%)	36 (75.0%)	122 (37.1%)
Grade 5 AE	3 (5.5%)	18 (5.7%)	0	10 (3.0%)
Treatment–related[a] Grade 5 AE	2 (3.6%)	9 (2.8%)	0	3 (0.9%)
Serious Adverse Event	29 (52.7%)	129 (40.8%)	19 (39.6%)	126 (38.3%)
Treatment–Related[a] SAE	21 (38.2%)	75 (23.7%)	16 (33.3%)	55 (16.7%)
AE leading to withdrawal from any treatment	26 (47.3%)	98 (31.0%)	12 (25.0%)	43 (13.1%)
AE leading to any dose modification/interruption	40 (72.7%)	186 (58.9%)	26 (54.2%)	164 (49.8%)
AESI[b]	39 (70.9%)	151 (47.8%)	33 (68.8%)	143 (43.5%)
Grade 3–4 AESI[b]	11 (20.0%)	34 (10.8%)	10 (20.8%)	26 (7.9%)
Grade 5 AESI[b]	0	0	0	2 (0.6%)

AE=adverse event; AESI=adverse event of special interest; Atezo=atezolizumab; Bev=bevacizumab; CP=carboplatin and paclitaxel; SAE=serious adverse event.

[a] Refers to any drug component of the respective combination treatments.

[b] AESI to atezolizumab.

Table 70: Overview of Safety by Race - IMpower150 (data cut: 15 September 2017)

	Bev+CP				Atezo+Bev+CP				Atezo+CP			
	Asian (n=46)	Black (n=12)	White (n=329)	Other (n=7)	Asian (n=55)	Black (n=3)	White (n=316)	Other (n=19)	Asian (n=48)	Black (n=9)	White (n=329)	Other (n=14)
Total number of patients with at least one												
Adverse Event	46 (100.0%)	12 (100.0%)	325 (98.8%)	7 (100.0%)	55 (100.0%)	3 (100.0%)	308 (97.5%)	19 (100.0%)	48 (100.0%)	9 (100.0%)	318 (96.7%)	14 (100.0%)
Treatment–related[a] AE	45 (97.8%)	12 (100.0%)	312 (94.8%)	7 (100.0%)	54 (98.2%)	2 (66.7%)	300 (94.9%)	15 (78.9%)	47 (97.9%)	9 (100.0%)	303 (92.1%)	13 (92.9%)
Grade 3–4 AE	34 (73.9%)	10 (83.3%)	182 (55.3%)	4 (57.1%)	46 (83.6%)	1 (33.3%)	184 (58.2%)	11 (57.9%)	37 (77.1%)	6 (66.7%)	174 (52.9%)	9 (64.3%)
Treatment–related[a] Grade 3–4 AE	31 (67.4%)	9 (75.0%)	145 (44.1%)	3 (42.9%)	45 (81.8%)	1 (33.3%)	165 (52.2%)	8 (42.1%)	36 (75.0%)	4 (44.4%)	122 (37.1%)	8 (57.1%)
Grade 5 AE	0	0	21 (6.4%)	0	3 (5.5%)	1 (33.3%)	18 (5.7%)	1 (5.3%)	0	0	10 (3.0%)	0
Treatment–related[a] Grade 5 AE	0	0	9 (2.7%)	0	2 (3.6%)	0	9 (2.8%)	0	0	0	3 (0.9%)	0
Serious Adverse Event	8 (17.4%)	3 (25.0%)	120 (36.5%)	3 (42.9%)	29 (52.7%)	2 (66.7%)	129 (40.8%)	5 (26.3%)	19 (39.6%)	5 (55.6%)	126 (38.3%)	5 (35.7%)
Treatment–Related[a] SAE	2 (4.3%)	1 (8.3%)	71 (21.6%)	2 (28.6%)	21 (38.2%)	1 (33.3%)	75 (23.7%)	3 (15.8%)	16 (33.3%)	2 (22.2%)	55 (16.7%)	4 (28.6%)
AE leading to withdrawal from any treatment	7 (15.2%)	4 (33.3%)	84 (25.5%)	3 (42.9%)	26 (47.3%)	2 (66.7%)	98 (31.0%)	2 (10.5%)	12 (25.0%)	0	43 (13.1%)	1 (7.1%)
AE leading to any dose modification/interruption	23 (50.0%)	4 (33.3%)	160 (48.6%)	2 (28.6%)	40 (72.7%)	0	186 (58.9%)	9 (47.4%)	26 (54.2%)	5 (55.6%)	164 (49.8%)	8 (57.1%)
AESI[b]	14 (30.4%)	3 (25.0%)	91 (27.7%)	0	39 (70.9%)	1 (33.3%)	151 (47.8%)	8 (42.1%)	33 (68.8%)	3 (33.3%)	143 (43.5%)	5 (35.7%)
Grade 3–4 AESI[b]	2 (4.3%)	0	11 (3.3%)	0	11 (20.0%)	0	34 (10.8%)	0	10 (20.8%)	1 (11.1%)	26 (7.9%)	0
Grade 5 AESI[b]	0	0	0	0	0	0	0	0	0	0	2 (0.6%)	0

Increased haematologic toxicities were observed in Asian patients.

Extrinsic factors

Region

Table 71: Overview of Safety by Region - IMpower150, 15 Sep 17clinical cut date

	Bev+CP					Atezo+Bev+CP					Atezo+CP				
	Asia-Pacific (n=43)	Australia (n=28)	North America (n=87)	Central or South America (n=38)	Europe (n=198)	Asia-Pacific (n=49)	Australia (n=27)	North America (n=95)	Central or South America (n=31)	Europe (n=191)	Asia-Pacific (n=43)	Australia (n=33)	North America (n=84)	Central or South America (n=30)	Europe (n=210)
Total number of patients with at least one															
Adverse Event	43 (100.0%)	28 (100.0%)	87 (100.0%)	37 (97.4%)	195 (98.5%)	49 (100.0%)	27 (100.0%)	93 (97.9%)	31 (100.0%)	185 (96.9%)	43 (100.0%)	32 (97.0%)	84 (100.0%)	30 (100.0%)	200 (95.2%)
Treatment-related[a] AE	42 (97.7%)	27 (96.4%)	82 (94.3%)	35 (92.1%)	190 (96.0%)	48 (98.0%)	27 (100.0%)	91 (95.8%)	27 (87.1%)	178 (93.2%)	42 (97.7%)	31 (93.9%)	81 (96.4%)	29 (96.7%)	189 (90.0%)
Grade 3-4 AE	32 (74.4%)	14 (50.0%)	58 (66.7%)	21 (55.3%)	105 (53.0%)	41 (83.7%)	19 (70.4%)	63 (66.3%)	10 (32.3%)	109 (57.1%)	33 (76.7%)	21 (63.6%)	54 (64.3%)	16 (53.3%)	102 (48.6%)
Treatment-related[a] Grade 3-4 AE	29 (67.4%)	11 (39.3%)	47 (54.0%)	15 (39.5%)	86 (43.4%)	40 (81.6%)	17 (63.0%)	56 (58.9%)	10 (32.3%)	96 (50.3%)	32 (74.4%)	13 (39.4%)	36 (42.9%)	12 (40.0%)	77 (36.7%)
Grade 5 AE	0	0	6 (6.9%)	3 (7.9%)	12 (6.1%)	3 (6.1%)	0	8 (8.4%)	6 (19.4%)	6 (3.1%)	0	0	1 (1.2%)	2 (6.7%)	7 (3.3%)
Treatment-related[a] Grade 5 AE	0	0	3 (3.4%)	1 (2.6%)	5 (2.5%)	2 (4.1%)	0	1 (1.1%)	3 (9.7%)	5 (2.6%)	0	0	0	1 (3.3%)	2 (1.0%)
Serious Adverse Event	7 (16.3%)	10 (35.7%)	37 (42.5%)	10 (26.3%)	70 (35.4%)	24 (49.0%)	14 (51.9%)	48 (50.5%)	8 (25.8%)	71 (37.2%)	15 (34.9%)	18 (54.5%)	39 (46.4%)	10 (33.3%)	73 (34.8%)
Treatment-Related[a] SAE	1 (2.3%)	7 (25.0%)	21 (24.1%)	6 (15.8%)	41 (20.7%)	19 (38.8%)	7 (25.9%)	20 (21.1%)	6 (19.4%)	48 (25.1%)	13 (30.2%)	8 (24.2%)	15 (17.9%)	3 (10.0%)	38 (18.1%)
AE leading to withdrawal from any treatment	5 (11.6%)	4 (14.3%)	31 (35.6%)	7 (18.4%)	51 (25.8%)	22 (44.9%)	9 (33.3%)	36 (37.9%)	10 (32.3%)	51 (26.7%)	11 (25.6%)	2 (6.1%)	12 (14.3%)	4 (13.3%)	27 (12.9%)
AE leading to any dose modification/interruption	23 (53.5%)	13 (46.4%)	47 (54.0%)	16 (42.1%)	90 (45.5%)	34 (69.4%)	18 (66.7%)	61 (64.2%)	15 (48.4%)	107 (56.0%)	23 (53.5%)	16 (48.5%)	50 (59.5%)	19 (63.3%)	95 (45.2%)
AESI[b]	13 (30.2%)	6 (21.4%)	24 (27.6%)	14 (36.8%)	51 (25.8%)	34 (69.4%)	19 (70.4%)	47 (49.5%)	15 (48.4%)	84 (44.0%)	28 (65.1%)	20 (60.6%)	39 (46.4%)	11 (36.7%)	86 (41.0%)
Grade 3-4 AESI[b]	2 (4.7%)	0	5 (5.7%)	1 (2.6%)	5 (2.5%)	10 (20.4%)	3 (11.1%)	12 (12.6%	0	20 (10.5%)	9 (20.9%)	4 (12.1%	5 (6.0%)	1 (3.3%	18 (8.6%)
Grade 5 AESI[b]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (1.0%)

Tobacco Use History

Table 72: Overview of Safety by Tobacco Use History - IMpower150 (data cut: 15 September 2017)

	Bev+CP		Atezo+Bev+CP		Atezo+CP	
	Never (n=76)	Current Previous (n=318)	Never (n=80)	Current Previous (n=313)	Never (n=77)	Current Previous (n=323)
Total number of patients with at least one						
Adverse Event	75 (98.7%)	315 (99.1%)	78 (97.5%)	307 (98.1%)	73 (94.8%)	316 (97.8%)
Treatment-related[a] AE	73 (96.1%)	303 (95.3%)	76 (95.0%)	295 (94.2%)	67 (87.0%)	305 (94.4%)
Grade 3-4 AE	45 (59.2%)	185 (58.2%)	44 (55.0%)	198 (63.3%)	45 (58.4%)	181 (56.0%)
Treatment-related[a] Grade 3-4 AE	38 (50.0%)	150 (47.2%)	43 (53.8%)	176 (56.2%)	37 (48.1%)	133 (41.2%)
Grade 5 AE	3 (3.9%)	18 (5.7%)	2 (2.5%)	21 (6.7%)	0	10 (3.1%)
Treatment-related[a] Grade 5 AE	1 (1.3%)	8 (2.5%)	1 (1.3%)	10 (3.2%)	0	3 (0.9%)
Serious Adverse Event	20 (26.3%)	114 (35.8%)	24 (30.0%)	141 (45.0%)	23 (29.9%)	132 (40.9%)
Treatment-Related[a] SAE	10 (13.2%)	66 (20.8%)	19 (23.8%)	81 (25.9%)	13 (16.9%)	64 (19.8%)
AE leading to withdrawal from any treatment	12 (15.8%)	86 (27.0%)	23 (28.8%)	105 (33.5%)	12 (15.6%)	44 (13.6%)
AE leading to any dose modification/interruption	35 (46.1%)	154 (48.4%)	43 (53.8%)	192 (61.3%)	36 (46.8%)	167 (51.7%)
AESI[b]	28 (36.8%)	80 (25.2%)	43 (53.8%)	156 (49.8%)	36 (46.8%)	148 (45.8%)
Grade 3-4 AESI[b]	4 (5.3%)	9 (2.8%)	8 (10.0%)	37 (11.8%)	11 (14.3%)	26 (8.0%)
Grade 5 AESI[b]	0	0	0	0	0	2 (0.6%)

Safety related to drug-drug interactions and other interactions

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

Discontinuation due to adverse events

Table 73: Treatment discontinuations due to adverse events by treatment phase (safety evaluable population) (data cut: 22 January 2018)

	Bev+CP			Atezo+Bev+CP			Atezo+CP		
	Induction (N=394)	Maintenance Follow-up (N=270)	Overall (N=394)	Induction (N=393)	Maintenance Follow-up (N=312)	Overall (N=393)	Induction (N=400)	Maintenance Follow-up (N=305)	Overall (N=400)
Total number of patients with at least 1 AE resulting in treatment discontinuation from									
Any study treatment	70 (17.8%)	29 (10.7%)	98 (24.9%)	88 (22.4%)	56 (17.9%)	133 (33.8%)	38 (9.5%)	17 (5.6%)	53 (13.3%)
Atezolizumab	N/A	N/A	N/A	30 (7.6%)	26 (8.3%)	59 (15.0%)	18 (4.5%)	14 (4.6%)	34 (8.5%)
Bevacizumab	45 (11.4%)	25 (9.3%)	71 (18.0%)	53 (13.5%)	41 (13.1%)	96 (24.4%)	N/A	N/A	N/A
Only carboplatin and paclitaxel	20 (5.1%)	5 (1.9%)	24 (6.1%)	22 (5.6%)	4 (1.3%)	24 (6.1%)	12 (3.0%)	2 (0.7%)	13 (3.3%)
All study treatments	21 (5.3%)	0	22 (5.6%)	22 (5.6%)	0	23 (5.9%)	13 (3.3%)[a]	0	14 (3.5%)

Atezo=atezolizumab; Bev=bevacizumab; CP=carboplatin and paclitaxel; N/A=not applicable.

Note: The denominator for the maintenance/follow up phase is adjusted to patients who received at least one dose of study treatment during the maintenance phase. Therefore, the total number of events or patients with events leading to treatment withdrawal for each treatment phase does not add up to the overall number.

[a] Population includes Atezo + CP patient (No. ##280268−11103) who did not receive CP and did not enter induction period.

Comparison of key safety results between first and second interim analysis

A comparison of the key safety results from the first and second interim analyses is provided in the table below. No new safety signals are identified and the safety profile is consistent between the two cutoffs. The key findings were as follows:

- Median exposure to study drug remained consistent with the previous clinical cutoff date (CCOD).
- The proportion of patients with at least one adverse event (AE; any grade) remained consistent with the primary clinical study report (CSR) and was similar between treatment arms (Bev + CP: 99.0% Atezo + Bev + CP: 98.2%; Atezo + CP: 97.8%). Overall, the AEs with an incidence rate of at least 10% observed with atezolizumab in combination with chemotherapy with or without bevacizumab were those events known to occur with an incidence of at least 10% for each individual study treatment.
- Since the previous CCOD, a larger increase in the number of AEs was observed in Atezo + Bev + CP (additional 334 events) and Atezo + CP (additional 229 events) compared with Bev + CP (additional 90 events).
- Grade 3-4 AEs were comparable between treatment arms (Bev + CP: 58.4% Atezo + Bev + CP: 63.6%; Atezo + CP: 57.5%). Grade 3-4 AEs related to any study treatment remained higher in the Atezo + Bev + CP arm (56.7%) compared with the Bev + CP arm (48.5%) and Atezo + CP arm (43.0%).
- The proportion of patients experiencing serious AEs (SAEs) remained higher in Atezo + Bev + CP (44.3%) compared with Bev + CP (34.3%) and Atezo + CP (39.3%).
- Since the previous CCOD, two new Grade 5 events were reported in the Atezo + Bev + CP arm, including 1 event of intestinal ischemia and 1 event of unexplained death. One additional Grade 5 event ("death" considered unrelated to atezolizumab), reported in a patient in the Atezo + CP arm at the previous CCOD, was reclassified subsequent follow-up review to interstitial lung disease (ILD; considered related to atezolizumab treatment).
- The proportion of patients experiencing AEs considered by the investigator as related to any study treatment remained comparable between treatment arms (Bev + CP: 95.7%, Atezo + Bev + CP: 94.1%; Atezo + CP: 94.3%).

- The incidence of AEs of special interest (AESIs) for atezolizumab was consistent with the primary analysis as well as the known safety profile of atezolizumab, with the exception of immune-mediated pancreatitis and meningoencephalitis. Pancreatitis has since been added to the table of adverse drug reactions (ADRs) since this medical concept reached the threshold of what is deemed to be clinically different from monotherapy, and meningoencephalitis (including non-infective encephalitis) was removed from the table of ADRs as this medical concept no longer meets the threshold of what is deemed to be clinically different from monotherapy.
- The majority of atezolizumab AESIs were mild or moderate in severity.
- The incidence of AESIs for bevacizumab remained consistent with that reported at the earlier CCOD as well as the known safety profile of bevacizumab.

Table 74: Comparison of safety data from study IMpower150 (safety evaluable population)

	15 September 2017			22 January 2018		
	Bev + CP (N=394)	Atezo + Bev + CP (N=393)	Atezo + CP (N=400)	Bev + CP (N=394)	Atezo + Bev + CP (N=393)	Atezo + CP (N=400)
Total number of events	4540	6085	4622	4630	6419	4851
Total number of patients with at least one						
Adverse event	390 (99.0%)	385 (98.0%)	389 (97.3%)	390 (99.0%)	386 (98.2%)	391 (97.8%)
Treatment-related AE	376 (95.4%)	371 (94.4%)	372 (93.0%)	377 (95.7%)	370 (94.1%)	377 (94.3%)
Grade 3–4 AE	230 (58.4%)	242 (61.6%)	226 (56.5%)	230 (58.4%)	250 (63.6%)	230 (57.5%)
Treatment-related Grade 3–4 AE	188 (47.7%)	219 (55.7%)	170 (42.5%)	191 (48.5%)	223 (56.7%)	172 (43.0%)
Grade 5 AE	21 (5.3%)	23 (5.9%)	10 (2.5%)	21 (5.3%)	24 (6.1%)	10 (2.5%)
Treatment-related Grade 5 AE	9 (2.3%)	11 (2.8%)	3 (0.8%)	9 (2.3%)	11 (2.8%)	4 (1.0%)
Serious AE	134 (34.0%)	165 (42.0%)	155 (38.8%)	135 (34.3%)	174 (44.3%)	157 (39.3%)
Treatment-Related Serious AE	76 (19.3%)	100 (25.4%)	77 (19.3%)	78 (19.8%)	103 (26.2%)	78 (19.5%)
AE leading to withdrawal from any treatment	98 (24.9%)	128 (32.6%)	56 (14.0%)	98 (24.9%)	133 (33.8%)	53 (13.3%)
AE leading to any dose modification/interruption	189 (48.0%)	235 (59.8%)	203 (50.8%)	188 (47.7%)	246 (62.6%)	207 (51.8%)

AE=adverse event; Atezo=atezolizumab; Bev=bevacizumab; CP=carboplatin and paclitaxel; CSR=clinical study report.
Only events reported in the Adverse Events Form are included. Investigator text for AEs encoded using MedDRA v20.1. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. AEs collected after first treatment dose are included.

Post marketing experience

No new safety signals were identified in the post-marketing setting for atezolizumab used as a monotherapy (see Periodic Benefit Risk Evaluation Report [PBRER] data lock point of 17 November 2017). As of 17 November 2017, 15,888 patients had been exposed to atezolizumab in the post-marketing setting. The combination regimens administrated in Study IMpower150 are not approved yet.

2.5.1. Discussion on clinical safety

Safety evaluable population in study IMpower150 consisted of 400 patients from arm A, 393 patients from arm B and 394 patients from arm C.

Exposure pattern of atezolizumab (number of doses received, treatment duration, dose intensity, total cumulative dose) is slightly higher in arm B than A. The same can be said about bevacizumab, with higher exposure in arm B than C. Arms B and A were allowed to keep treatment beyond progression whereas arm C was not. 122 patients from the Atezo + CP arm and 97 patients from the Atezo + Bev + CP arm received a mean of 3 doses of atezolizumab after progression. From these patients, a higher proportion

of patients from arm B had bulky progression than those from arm A. On the same line, patients who continued atezolizumab after progression in arm A lived longer (mOS 13.5 months) than those from arm B (mOS 11.1 months).

As expected, the majority of patients (95%) experienced one or more AEs through the study. Overall, the frequency of any AEs, G3-4, G5, serious AEs and AEs leading to dose modification/interruption was higher in the induction phase than in the maintenance phase for all 3 arms of treatment. The trend of higher toxicity from the 4-drug regimen (as compared to both 3-drug regimens) is evident in both phases. The frequency of G3-4 AEs in the induction phase in all 3 arms is around 50%. However, in the maintenance phase, about 23% of patients from one-drug arms (arm A = atezolizumab, arm C = bevacizumab) had G3-4 AEs, as compared to 37% from the 2-drug arm (arm B = atezolizumab + bevacizumab). Immune-related endocrinopathies in atezolizumab-containing arms were more frequent in the maintenance than in the induction phase.

In general, arm B had higher incidence of AEs than the other two arms. AEs with higher incidence in arm B than arms A and C were nausea, diarrhea, stomatitis, gastroesophageal reflux, dysphagia, fatigue, pyrexia, mucosal inflammation, headache, musculoskeletal pain, epistaxis, haemoptysis, dysphonia, febrile neutropenia, pneumonia, upper respiratory tract infection, bronchitis, diverticulitis, decreased appetite, hypomagnesaemia, hypokalaemia, dehydration, hyponatraemia, hyperglycaemia, platelet count decreased, neutrophil count decreased, weight decreased, aspartate aminotransferase increased, alanine aminotransferase increased, WBC count decreased, hypertension, hypertensive crisis, proteinuria, hypothyroidism and hyperthyroidism.

Epistaxis, hypertension and proteinuria were equally common in bevacizumab-containing arms and almost absent in arm A. When AEs were selected if considered treatment-related, they also occurred more frequently in arm B than in the other arms.

Grade 3-4 AEs were overall frequent in all three arms of treatment, being registered in 59% (698 out of 1187) of patients from the safety population. G3/4 AEs occurred with 5% higher frequency in the Atezo + Bev + CP arm (61.6%), as compared to the Atezo + CP arm (56.5%).

AESIs: AESIs (any grade and G3/4) were more common in arm B than in arms A and C. Discontinuation due to an AESI followed the same pattern. Immune-related hepatitis and colitis were more common in arm B than the other arms. Hypothyroidism and rash –more easily manageable than the previous– were more frequent in arms A and B. All other immune-mediated AE had an incidence comparable to atezolizumab monotherapy and were clinically manageable. Less frequent immune-related AESIs (meningoencephalitis, pancreatitis, hypophyisitis) were rare. As compared to atezolizumab monotherapy (34%), AESIs of any grade were also much more frequent in atezolizumab-containing arms (51% in arm B and 46% in arm A). This difference is mostly driven by AESIs that are clinically manageable such as hepatitis (lab abnormal), hypothyroidism and rash. AESIs that required corticosteroid treatment in IMpower150 occurred in about 20% of each of the atezolizumab-containing arms, and they had similar efficacy outcomes to the overall ITT population.

Atezolizumab AESIs: Any-grade immune-related pneumonitis occurred in 29 patients: 3 (0.8%) patients in arm C, 10 (2.5%) in arm B and 16 (4.0%) in arm A –in this last group with median duration of 4.2 months. Overall, nearly 2% of patients that received atezolizumab required hospitalisation for autoimmune pneumonitis, but there were no G5 AEs from pneumonitis. Frequency of immune-related hepatitis was much higher in arm B (5.1%) than arm A (3.0%), as were hypothyroidism and hyperthyroidism.

Bevacizumab AESIs: Incidence of haemorrhagic events is significantly higher in bevacizumab containing arms: 32.3% and 31.2% in arms B and C, respectively, as compared to 14.5% in arm A. Incidence of haemoptysis in arm B (27 out of 393 patients, 6.9%) doubles that of arm A (14 out of 400 patients,

3.5%). Out of 61 patients who presented haemoptysis, 13 required hospitalisation for such AE and 5 of them died as a direct consequence. Of the 13 hospitalised patients, 12 (92%) had received bevacizumab either in arm B or C. All 5 patients who died from haemoptysis had received the 4-drug regimen (Atezo + Bev + CP) in arm B. 4 patients exposed to bevacizumab (2 in arm B and 2 in arm C) died from fatal pulmonary haemorrhage, which prompted modification of criteria to exclude patients with clear tumour infiltration into the thoracic great vessels or cavitation of pulmonary lesions.

Incidence of hypertension was significantly higher in arms B and C (24.6%) than arm A (3.5%), and comparable to its incidence in all previous bevacizumab studies. No relevant differences on incidence of hypertension are seen between arms B and C.

Cerebrovascular accident occurred in 6 patients from arm B (1.5%), two of which died. Incidence of pulmonary thromboembolism in bevacizumab-containing arms was higher than arm A (3.8% vs. 2.5%), and more likely associated to fatality: all 4 patients that died from pulmonary thromboembolism were in bevacizumab-containing arms (2 patients in arm B and 2 in arm C). The increased risk of cerebrovascular accidents is reflected in section 4.8 of the SmCP.

Overall, complications associated to bevacizumab, in particular in the 4-drug regimen, cannot be underestimated: G5 events from pulmonary thromboembolism, myocardial infarctions, haemoptysis, cerebrovascular accidents and pulmonary haemorrhage accounted for 9 patients in arm B and 7 patients in arm C. In comparison, only 1 patient died from any of these AEs in the Atezo + CP arm.

Serious AEs were more common in arm B (44.3%) as compared to either arm C (34.3%) or A (39.3%). Excluding pneumonia (6.1% in arm B vs. 3.1% in atezolizumab monotherapy), incidence of serious AEs was in general comparable to atezolizumab monotherapy population. Febrile neutropenia attributable to treatment was also more frequent in arm B (6.9%) regarding arms A (3.3%) or C (4.3%).

Deaths: The most common cause of death in all treatment arms was progressive disease: 531 out of 620 deaths (86%). Incidence of G5 AEs was relevantly lower in arm A (10 patients, 2.5%) as compared to arms B (24 patients, 6.1%) and C (21 patients, 5.3%), and even compared to atezolizumab monotherapy population (3.9%).

A large proportion of G5 AEs appeared to be possibly related to bevacizumab treatment and this has already been highlighted in bevacizumab-related AEs. Overall, most common G5 AEs were haemoptysis, pneumonia, pulmonary embolism and febrile neutropenia. While deaths from thoracic disorders were more common in arm B (9 events), deaths from infections were more common in arm C (6 events).

Special populations: A worse safety profile was generally observed in patients aged ≥65 years, compared with patients <65 years in the bevacizumab-containing arms. The worse safety profile in elderly patients has been reflected in section 4.8 of the SmPC. The most pronounced differences in safety between patients with ECOG PS 0 or 1 were noticed in the Atezo + Bev + CP arm. A tendency towards a worse safety profile for female vs. male patients can be observed across all treatment arms.

Due to increased hematologic toxicities observed in Asian patients in IMpower150, it is recommended that the starting dose of paclitaxel should be 175 mg/m2 every three weeks (see section 4.2 and 5.1 of the SmPC).

Discontinuation: Most of the withdrawals of any study treatment were attributable to withdrawals of bevacizumab in both the induction and the maintenance phase. In the bevacizumab-containing arms numerically higher rates of discontinuation of only chemotherapy and all study treatments were observed in the induction phase compared to the Atezo+CP arm (5.3%, 5.6% and 3.3% withdrawals of all study treatments for Bev+CP, Atezo+Bev+CP and Atezo+CP, respectively). These data underline the relevant contribution of bevacizumab to the toxicity profile and the (worse) tolerability of the combination therapies.

Updated safety results: The Atezo + Bev + CP arm has manifested a worse toxicity profile with longer follow-up. Since the previous data cutoff, a larger increase in the number of AEs was observed in the Atezo + Bev + CP (additional 334 events) and Atezo + CP arms (additional 229 events) compared with the Bev + CP arm (additional 90 events). The same trend (with largest numerical increases in AEs in the Atezo + Bev + CP since the first analyses) was observed for grade 3-4 AEs, serious AEs, AEs leading to withdrawal from any treatment and AE leading to any dose modification/interruption.

Since atezolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected. Based on PK data from IMpower150, there is no evidence of a PK drug-drug interaction with the coadministration of atezolizumab and/or bevacizumab with carboplatin and paclitaxel.

The use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of atezolizumab. However, systemic corticosteroids or other immunosuppressants can be used to treat immune-related adverse reactions after starting atezolizumab.

2.5.2. Conclusions on clinical safety

The combination of Atezo + Bev + CP was found to be tolerable but showed a clearly worse safety profile than the other two arms in IMpower150. This 4-drug regimen exhibited higher toxicity compared to the other treatment arms as observed with the higher incidence of any, G3/4, serious and G5 AEs. However, arms A and B had comparable incidence and outcome for immune-related AEs as for atezolizumab monotherapy, whereas bevacizumab-related AEs had significantly high incidence and fatality, in particular in the Atezo + Bev + CP arm.

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 4.2 is acceptable.

No changes to the list of safety concerns, pharmacovigilance plan and risk minimisations measures were required as a result of this extension of indication

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 4.2 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 Diabetes mellitus Immune-related Hypothyroidism Immune-related Hyperthyroidism Immune-related Adrenal insufficiency Immune-related Hypophysitis Immune-related Guillain-Barré syndrome Immune-related Myasthenic syndrome / myasthenia gravis Immune related meningoencephalitis Infusion-related reactions Immune-related myocarditis Immune-related nephritis
Important potential risks	Anti-therapeutic 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

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 authorisation or a marketing authorisation under exceptional circumstances				
There are no Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation 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 ATAs against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy	Anti-therapeutic antibodies	Final CSR	Q1 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 bacillus Calmette-Guérin 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 Planned	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

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
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, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, myocarditis, nephritis, and infusion-related reactions Planned	The overall objective is to evaluate the effectiveness of the HCP brochure designed to mitigate important immune-related risks in patients receiving atezolizumab 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	Immune-related hepatitis Immune-related pneumonitis Immune-related colitis Immune-related pancreatitis Immune-related Diabetes mellitus Immune-related Hypothyroidism Immune-related Hyperthyroidism Immune-related Adrenal insufficiency Immune-related Hypophysitis Immune-related Guillain-Barré syndrome Immune-related Myasthenic syndrome / myasthenia gravis Immune related meningoencephalitis Infusion-related reactions Immune-related myocarditis immune-related nephritis	Protocol submission Interim report Final Report	February 2018 December 2020 December 2022

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:** 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, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, 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:** 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, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, 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 measures:** • Educational materials for HCPs • Patient alert cards**.**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 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, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Observational Study Evaluation of the effectiveness of HCP

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Precautions for Use Section 4.8 Undesirable effects **Additional risk minimization 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, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, myocarditis, nephritis, and infusion-related reactions.
Immune-Related Diabetes Mellitus	**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:** 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, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, myocarditis, nephritis, and infusion-related reactions.
Immune-Related Hypothyroidism	**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:** 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, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, myocarditis, nephritis, and infusion-related reactions.
Immune-Related Hyperthyroidism	**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:** 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, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, myocarditis, nephritis, and infusion-related reactions.

Safety concern	Risk minimization measures	Pharmacovigilance activities
Immune-Related Adrenal Insufficiency	**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:** 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, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, myocarditis, nephritis, and infusion-related reactions.
Immune-Related 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:** 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, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, myocarditis, nephritis, and infusion-related reactions.
Immune-Related Guillain-Barre Syndrome	**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:** 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, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, myocarditis, nephritis, and infusion-related reactions.
Immune-Related Myasthenic Syndrome / 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**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Observational Study Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important

Safety concern	Risk minimization measures	Pharmacovigilance activities
	measures: • Educational materials for HCPs • Patient alert cards**.**	immune-related risks: Pneumonitis, hepatitis, colitis, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, myocarditis, nephritis, and infusion-related reactions.
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:** 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, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, 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:** 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, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, 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:** 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, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, myocarditis, nephritis, and infusion-related reactions.

Safety concern	Risk minimization measures	Pharmacovigilance activities
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:** 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, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, myocarditis, nephritis, and infusion-related reactions.
Anti-therapeutic 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
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:** No specific text in E.U. SmPC **No Additional risk minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study WO29635

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 6.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, changes related to section 4.8 of the SmPC have been implemented in order to update the monotherapy safety data and reflect the largest pooled monotherapy population available (now including also data from study IMvigor211 and from all cohorts for study PCD4989g). In addition, small corrections and formatting changes have been implemented throughout the SmPC.

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 metastatic non-squamous NSCLC), with no significant age difference.
- Moreover, the posology proposed in this application is the same as the currently approved indication.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication as considered by the CHMP is for 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 (see section 5.1).

Lung cancer remains the leading cause of cancer death worldwide. This disease is the most common cancer in men worldwide and accounts for the highest absolute number of cancer deaths globally. Non-small cell lung cancer (NSCLC) is the predominant subtype, accounting for approximately 85% of all. NSCLC can be divided into two major histologic types: non-squamous and squamous cell carcinoma. Non-squamous histology accounts for more than half of all NSCLC, whereas squamous histology accounts for approximately 30%.

Genetic changes that have prognostic and predictive significance in NSCLC include EGFR mutations (10-40%) and ALK traslocations (2-6%).

The aim of therapy in the metastatic setting of NSCLC is to prolong progression free survival and overall survival, with no addition of major treatment-related toxicity.

3.1.2. Available therapies and unmet medical need

For patients who have metastatic NSCLC without an oncogenic driver mutation (such as EGFR mutations or ALK translocations), first-line standard of care is platinum-based chemotherapy, partnered with agents such as taxanes (paclitaxel, docetaxel), vinorelbine, gemcitabine, and pemetrexed, or platinum-based chemotherapy +/- bevacizumab. For both EGFR mutant patients and patients with ALK translocation, the standard of care after failure of tyrosine kinase inhibitors is platinum based chemotherapy.

Over the last few years, immune checkpoint inhibitors, such as PD-1/PD-L1 blocking antibodies, have emerged as effective 2L+ treatment in NSCLC: nivolumab, pembrolizumab and atezolizumab have demonstrated superiority over docetaxel as monotherapy.

Since these patients usually undergo rapid clinical deterioration during disease progression, many of them do not receive second line treatment.

3.1.3. Main clinical studies

IMpower150 (GO29436) is a phase III trial comparing the efficacy and safety of atezolizumab in combination with carboplatin + paclitaxel with or without bevacizumab, versus carboplatin + paclitaxel + bevacizumab, in metastatic non-squamous NSCLC in the first-line setting. The current submission supports the use of atezolizumab in combination with bevacizumab, carboplatin, and paclitaxel for the treatment of chemotherapy-naïve patients with metastatic, non-squamous NSCLC, including patients with EGFR mutations or ALK translocations who have failed targeted therapy. This variation is being submitted at this time because the protocol-specified first interim analysis has been conducted, with a clinical cut-off date of 15 September 2017.

3.2. Favourable effects

The updated data was submitted from the second interim analysis of IMpower150 with data cut-off of 22 January 2018. Both co-primary efficacy endpoints of the study have been met.

In ITT-WT population, median PFS was 6.7 months in arm A, 8.4 months in arm B and 6.8 months in arm C. Stratified HR of 0.59 ($p < 0.0001$) confers a statistically significant advantage to Atezo + Bev + CP as compared to Bev + CP. There was no significant difference between the numbers, percentages and comparisons on PFS in Teff-high WT population compared to the first interim analysis, but PD-L1 expression appears to identify a broader population with similar treatment effects as compared to the Teff gene signature.

Median OS in ITT-WT population was 19.4 months in arm A, 19.2 months in arm B and 14.7 months in arm C. A statistically significant benefit from arm B over arm C is demonstrated from a stratified HR of 0.78 ($p = 0.0164$).

Subgroup analysis showed that patients with liver metastases at enrolment obtained the highest OS benefit in ITT population (arm B vs. C): HR of 0.52.

EGFR/ALK+ patients also had clinical benefit from treatment following progression from TKIs: median PFS was 10 months in arm B, 6.9 months in arm A and 6.1 months in arm C, whereas median OS was 21.2 months in arm A, not reached in arm B and 17.5 months in arm C.

Most secondary endpoints were consistent with the clinical benefit from arm B shown across subpopulations. ORR in ITT population, although certainly decreased after confirmation of response, was 56% in arm B, 41% in arm A and 40% in arm C. In the same population, median duration of response was 11.5 months in arm B, 7.0 months in arm A and 6.0 months in arm C.

3.3. Uncertainties and limitations about favourable effects

Taking into account a significant atezolizumab ADA conversion rate, it remains unknown whether the emergence of these antibodies has a clear impact on efficacy of atezolizumab in combination with CP +/- bevacizumab. The MAH is recommended to conduct an assessment (post-approval) of the effect of atezolizumab ADAs on PK and efficacy endpoints including OS, PFS, and ORR in NSCLC Studies POPLAR, OAK, IMpower150, IMpower130, IMpower131, and IMpower132.

Due to the limited sample size, the magnitude of the benefit of atezolizumab in combination with chemotherapy +/- bevacizumab in patients aged ≥ 75 years is difficult to characterise (see section 5.1 of the SmPC)

3.4. Unfavourable effects

In IMpower150, an overall higher frequency of adverse events was observed in the four-drug regimen of atezolizumab, bevacizumab, paclitaxel, and carboplatin compared to atezolizumab, paclitaxel and carboplatin, including Grade 3 and 4 events (63.6% compared to 57.5%), Grade 5 events (6.1% compared to 2.5%), adverse events of special interest to atezolizumab (52.4% compared to 48.0%), as well as adverse events leading to withdrawal of any study treatment (33.8% compared to 13.3%). Nausea, diarrhoea, stomatitis, fatigue, pyrexia, mucosal inflammation, decreased appetite, weight decreased, hypertension and proteinuria were reported higher (≥5% difference) in patients receiving atezolizumab in combination with bevacizumab, paclitaxel and carboplatin. Other clinically significant adverse events which were observed more frequently in the atezolizumab, bevacizumab, paclitaxel, and carboplatin arm were epistaxis, haemoptysis, cerebrovascular accident, including fatal events.

In IMpower150, age ≥ 65 was associated with an increased risk of developing adverse events in patients receiving atezolizumab in combination with bevacizumab, carboplatin and paclitaxel.

3.5. Uncertainties and limitations about unfavourable effects

Data for patients ≥75 years of age are too limited to draw conclusions on this population (see section 4.8 of the SmPC).

3.6. Effects Table

Table 75: Effects Table for Tecentriq in combination with bevacizumab, paclitaxel and carboplatin in 1st line treatment of patients with metastatic non-squamous NSCLC (data cut-off: 22 January 2018)

Effect	Unit	Atezo+CP (arm A)	Atezo+Bev+CP (arm B)	Bev+CP (arm C)	Uncertainties / Strength of evidence
Favourable Effects					
PFS ITT	Months	6.7	8.4	6.8	B vs. C HR 0.59 p<0.0001 A vs. C HR 0.91 p 0.2194
*PFS ITT-WT	Months	6.3	8.3	6.8	B vs. C HR 0.59 p<0.0001 A vs. C HR 0.88 p 0.1445
*PFS Teff-high WT	Months	6.7	11.4	6.8	B vs. C HR 0.49 p <0.0001 A vs. C HR 0.80 p 0.1000
PFS EGFR/ALK+	Months	6.9	10.0	6.1	B vs. C HR 0.55 p 0.0167 A vs. C HR 1.13 p 0.4186
OS ITT	Months	19.5	19.8	14.9	B vs. C HR 0.76 p 0.0060 A vs. C HR 0.85 p 0.0983
*OS ITT-WT	Months	19.4	19.2	14.7	B vs. C HR 0.78 p 0.0164 A vs. C HR 0.88 p 0.2041
OS EGFR/ALK+	Months	21.2	NE	17.5	B vs. C HR 0.57 p 0.0930 A vs. C HR 0.86 p 0.5865
Unfavourable Effects					

Effect	Unit	Atezo+CP (arm A)	Atezo+Bev+CP (arm B)	Bev+CP (arm C)	Uncertainties / Strength of evidence
G3/4 AEs	%	57.5	63.6	58.4	• Safety of Atezo+Bev+CP compares less favourably with Bev+CP regarding numerical incidences of AEs • Atezo + CP has best tolerance and less treatment-related deaths
Serious AEs	%	39.3	44.3	34.3	
AESIs to Atezo	%	48.0	52.4	28.4	
G5 AEs	(n) %	(10) 2.5	(24) 6.1	(21) 5.3	
AEs leading to treatment withdrawal	%	13.3	33.8	24.9	
AEs leading to dose modification/ interruption	%	51.8	62.6	47.7	

* Primary efficacy endpoints

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

IMpower150 has met both its co-primary endpoints, demonstrating superiority of Atezo + Bev + CP (arm B) over Bev + CP (arm C) in terms of PFS in the ITT-WT (HR=0.59; 95% CI: 0.50, 0.70; p < 0.0001) and Teff-high WT populations (HR=0.50; 95% CI: 0.38, 0.66; p < 0.0001) and OS in the ITT-WT population (HR=0.78; 95% CI: 0.64, 0.96; p<0.0164).

PFS benefit from treatment in arms B or A, as compared to arm C, was much higher for patients with increasing PD-L1 IHC positivity (TC2/3 or IC2/3) and clinical benefit (PFS and OS) has also been observed in the PD-L1 negative subgroup (TC0/IC0) in arm B as compared to arm C, albeit with a late crossing of the OS curves after months 12. In patients with EGFR mutations and ALK translocations, despite limited numbers and the lack of mature OS data, a clinically meaningful benefit for the Atezo + Bev + CP can be concluded after failure of TKI therapies.

There was a high rate (30-40%) of ADA conversion (negative to positive) in both arms (A and B). The impact of ADA on the efficacy observed in both arms could be clinically meaningful and will be addressed post-approval.

Atezo + Bev + CP exhibited higher toxicity compared to the other treatment arms as observed with the higher incidence of any, G3/4, serious and G5 AEs. The risks of bevacizumab must be taken into account when considering treatment with Atezo + Bev + CP.

3.7.2. Balance of benefits and risks

The statistically significant and clinically relevant improvement in PFS of 1.6 month and 4.9 months increase in median survival for Atezo + Bev + CP compared to Bev + CP outweighs the worst safety profile observed with the addition of atezolizumab to Bev + CP.

The benefit-risk balance of Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC) is considered positive. 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.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Tecentriq in combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC is positive.

4. Recommendations

Outcome

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

Variations accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
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 bevacizumab, paclitaxel and carboplatin the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC), based on the interim results of study GO29436 (IMpower 150). As a consequence sections 4.1, 4.2, 4.4, 4.8, 5.1, 6.2 and 6.6 of the SmPC are updated. In addition update of section 4.8 of the SmPC in order to update the monotherapy safety data and reflect the largest pooled monotherapy population available (now including also data from IMvigor211 and PCD4989g studies). The Package Leaflet and the RMP (version 4.2) are updated in accordance. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to make small corrections and formatting changes throughout the SmPC.

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