27 June 2019
EMA/CHMP/425313/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tecentriq

International non-proprietary name: atezolizumab

Procedure No. EMEA/H/C/004143/X/0017

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

AE	adverse event
AESI	adverse event of special interest
ADA	anti-drug antibody
ADR	adverse drug reaction
ASCO-CAP	American Society of Oncology/College of American Pathologists
AST	aspartate aminotransferase
atezo+nP	atezolizumab plus nab-paclitaxel
BC	breast cancer
BRCA	BReast CAncer gene
CCOD	clinical cut-off date
Cmax	peak concentration
Cmin	trough concentration
CRF	case report form
CSR	clinical study report
CT	computed tomography
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC Quality-of-Life Questionnaire-Core 30
EORTC QLQ-BR23	EORTC Quality-of-Life Questionnaire-Breast Cancer Module
ER	estrogen receptor
GHS	global health status
HRQoL	health-related quality of life
IC	tumor-infiltrating immune cells
iDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IRC	Independent Review Committee
ISH	in-situ hybridization
IxRS	interactive voice or Web response system
mBC	metastatic breast cancer
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
PARPi	poly ADP ribose polymerase inhibitor
PAS	Prior Approval Supplement
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PD	progressive disease
PgR	progesterone receptor
pl+nP	placebo plus nab-paclitaxel
PopPK	population pharmacokinetic(s)
PgR	progesterone receptor
PRO	patient reported outcomes
PS	performance status
PT	preferred term
q2w	2-weekly / every 2 weeks
q3w	3-weekly / every 3 weeks
RRG	Roche Registration GmbH
SAE:	serious adverse event
SEER:	Surveillance, Epidemiology, and End Results
TC:	tumor cells
TIL:	tumor-infiltrating lymphocytes
TNBC:	triple-negative breast cancer
TTD:	time to deterioration

1. Background information on the procedure

1.1. Submission of the dossier

Roche Registration GmbH submitted on 13 September 2018 an extension of the marketing authorisation.

Extension application to add a new strength of 840 mg (60 mg/ml) for Tecentriq concentrate for solution for infusion in a vial and a new indication (metastatic triple-negative breast cancer (TNBC)). The new indication applies only to the 840mg strength.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(c)- Extensions of marketing authorisations.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0076/2015 and 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 MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Additional Data exclusivity/Marketing protection

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

Scientific advice

The MAH received Scientific advice from the CHMP on 26 May 2016 (EMEA/H/SA/2522/7/2016/II). The Scientific advice pertained to clinical aspects.

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

The application was received by the EMA on	13 September 2018
The procedure started on	4 October 2018
The Rapporteur's first Assessment Report was circulated to all CHMP	19 December 2018

members on	
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	19 December 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	02 January 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 January 2019
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	31 January 2019
The MAH submitted the responses to the CHMP consolidated List of Questions on	27 March 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	6 May 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2019
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	29 May 2019
The MAH submitted the responses to the CHMP List of Outstanding Issues on	04 June 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	12 June 2019
The outstanding issues were addressed by the MAH during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tecentriq on	27 June 2019
The CHMP adopted a report on the significant clinical benefit for Tecentriq in comparison with existing therapies	27 June 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

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

2.1.2. Epidemiology

Breast cancer is the most frequently diagnosed cancer among women and the leading cause of cancer-related deaths in women worldwide. In 2012, almost 1.7 million new breast cancer cases were diagnosed (25% of all cancers in women) and 521,900 deaths were estimated to have occurred (De Santis et al. 2015; Ferlay et al. 2015). In 2018, approximately 522,513 subjects were diagnosed with breast cancer and approximately 137,707 subjects died due to the disease in Europe (The Global Cancer Observatory, March, 2019). TNBC accounts for 12%–20% of newly diagnosed breast cancer (BC) cases (Chacón and Costanzo 2010; Foulkes et al. 2010).

2.1.3. Biologic features

TNBC, a distinct phenotypic subtype of breast cancer with the worst prognosis, is characterized immunohistologically by the lack of expression of hormonal receptors (estrogen receptor [ER] and progesterone receptor [PgR]), and lack of overexpression and/or amplification of the human epidermal growth factor receptor 2 (HER2)/NEU gene (Dent et al. 2007).

Programmed death ligand 1 (PD-L1) expression by tumour-infiltrating lymphocytes (TILs) and tumour cells has been reported in breast cancer. PD-L1 expression in breast cancer is more prevalent on Immune Cells (ICs) than tumour cells (TCs) (Cimino-Mathews et al. 2016). Breast cancer specimens who's TCs express PD-L1 usually also express PD-L1 on ICs (Li et al. 2018).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Compared to other breast cancer subtypes, TNBC tumours are generally larger in size, more poorly differentiated, have more extensive lymph node involvement at diagnosis, and exhibit an invasive phenotype. Patients with TNBC have a higher risk of both local and distant recurrence, and metastases are more likely to occur in visceral organs and the brain rather than bone compared to patients with other breast cancers (Carey et al. 2006). In the early disease setting, this is manifested in a shorter time to recurrence and shorter OS compared to patients with estrogen-driven cancer (Malorni et al. 2012; Press et al. 2017; Urru et al. 2018).

Consistent with the relatively poor prognosis of patients with early stage disease, patients with metastatic disease progress quickly on palliative chemotherapy. However, because few large randomized studies have been performed specifically in patients with metastatic TNBC, estimates of expected clinical outcomes are not as reliable as they are for other cancer populations. This challenge is exacerbated by the lack of a single consistent definition of triple-negative status across different studies. Meta-analyses, retrospective chart review, and subgroup analyses of metastatic breast cancer patients enrolled in Phase III studies can be used to set expectations. For example, Miles et al. (2013) observed a median PFS of 5.4 months and a median overall survival of 17.5 months among mTNBC patients in a pooled subgroup analysis of studies testing first-line bevacizumab in combination with chemotherapy for HER2-negative breast cancer. In a chart review of 111 patients with TNBC who received first-line chemotherapy at their institutions, Kassam et al. (2009) noted a median survival time of 13.3 months (range, 0.8–99.8 months). Other studies have reported divergent results, underscoring the need for large, well-conducted studies to set appropriate expectations for clinical trial design in patients with TNBC. Notwithstanding the relative lack of robust benchmarks in TNBC, an expected median PFS of approximately 6 months and OS of approximately 16 months in the study population are reasonably supported by the available evidence.

Despite optimal use of the best currently available systemic therapy, the vast majority of women with metastatic TNBC will ultimately die from their disease (Bonotto et al. 2014). As of 2014, the five-year survival rate for mTNBC is estimated at 9% (based on the most recent estimates from the Surveillance, Epidemiology, and End Results [SEER] database).

2.1.5. Management

With the exception of recent data demonstrating PFS (but not OS) benefit of the poly ADP ribose polymerase (PARP) inhibitor class of drugs in germline BReast CAncer (BRCA)-mutated metastatic breast cancer (Robson et al. 2017), there is no agent that effectively targets a defining vulnerability across TNBC. Per the latest European Society of Oncology-European Society for Medical Oncology (ESO-ESMO) guidelines (Cardoso et al. 2018a), cytotoxic chemotherapy remains the mainstay of treatment for both early-stage and non-BRCA–mutated advanced TNBC.

Current guidelines support the practice of TNBC being treated with conventional chemotherapy strategies as determined by the patient's characteristics and the toxicity profile of the treatment (NCCN 2018). For patients with metastatic disease, the ESO-ESMO (Cardoso et al. 2018a), ASCO (Partridge et al. 2014), and National Comprehensive Cancer Network (NCCN) guidelines recommend the use of sequential single-agent chemotherapy, except in patients with visceral crisis or rapidly progressing disease, but otherwise, these guidelines do not specifically address the management of TNBC. No single chemotherapy agent has demonstrated clear superiority and is considered the preferred agent in the first-line metastatic setting. There are several active agents considered appropriate for first-line chemotherapy, including taxanes, anthracyclines, capecitabine, gemcitabine, platinum-based compounds, vinorelbine, and ixabepilone.

Many combination chemotherapy regimens have been studied in an effort to improve outcomes for metastatic TNBC patients, and although combination regimens have resulted in improved response rates and longer time to progression compared to single agents, this advance has been made at the expense of increased toxicity, with no benefits in overall survival, and in many cases a decline in patients' quality of life (O'Shaughnessy et al. 2002; Sledge et al. 2003; Albain et al. 2004; Carrick et al. 2005; Cardoso et al. 2018b). Based on this evidence, the NCCN guideline panel found no compelling evidence that combination regimens are superior to sequential single agents (NCCN 2018). The ESO-ESMO and ASCO guidelines also recommend sequential monotherapy as the preferred option for metastatic breast cancer considering the reduced toxicity burden and potential for better quality of life (Partridge et al. 2014; Cardoso et al. 2018a).

Standard clinical practice is to continue palliative chemotherapy, as tolerated, until progression of disease because it improves progression-free survival while modestly extending overall survival (Muss HB 1991; Falkson et al.1998; Gennari et al. 2011). Due to the lack of consistent improvements in OS, the NCCN guidelines state that prolonged use of chemotherapy should be weighed against the detrimental effects of continuous chemotherapy on overall quality of life (NCCN 2018). The ESO-ESMO and ASCO guidelines (Partridge et al. 2014; Cardoso et al. 2018a) are largely consistent with the recommendation that each regimen (except anthracyclines) should be given until progression of disease or unacceptable toxicity and that the duration of each regimen and the number of regimens should be tailored to the individual patient.

Recently PARP inhibitors have been approved for the treatment of advanced TNBC with germline BRCA1/2 mutations in patients who have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting (EPAR Talzenna, EPAR Lynparza).

Although advanced TNBC may respond transiently to standard of care there is a pressing need for new clinically active agents to improve the long-term treatment outcomes and survival of patients with this diagnosis.

About the product

Atezolizumab is an Fc-engineered humanized immunoglobulin (IgG1) monoclonal antibody (MAb) targeting the programmed death-ligand 1 (PD-L1). Binding of atezolizumab to PD-L1 inhibits the

interaction of the PD-1 and B7.1 receptors. Both of these interactions are reported to provide inhibitory signals to T cells.

Tecentriq 1,200 mg concentrate for solution for infusion is currently indicated in the following indications:

- as monotherapy in the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy and locally advanced or metastatic urothelial carcinoma after treatment with chemotherapy or who are cisplatin-ineligible and have PD-L1 expression ≥ 5%.

- in combination with bevacizumab, paclitaxel and carboplatin, is also 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.

- as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK positive NSCLC should also have received targeted therapies before receiving Tecentriq (see SmPC section 5.1).

The recommended dose of Tecentriq is 1,200 mg administered intravenously every three weeks when administered in monotherapy. When given in combination with bevacizumab, paclitaxel, and carboplatin for the treatment of non-squamous NSCLC, 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 (induction phase). 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.

With this application the MAH sought the approval of a new strength, 840 mg concentrate for solution for infusion. In addition, the MAH applied for a new indication for Tecentriq 840 mg as follows:

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

The recommended dose of Tecentriq is 840 mg administered by intravenous infusion, followed by 100 mg/m^2 nab-paclitaxel. For each 28-day cycle, Tecentriq is administered on days 1 and 15, and nab-paclitaxel is administered on days 1, 8, and 15.

It is recommended that patients are treated with Tecentriq until disease progression or unmanageable toxicity (see SmPC sections 4.2 and 5.1).

Type of Application and aspects on development

In September and October 2015, the applicant sought National Scientific Advice Meetings to discuss the design of the pivotal study IMpassion130. Consequently, a confirmatory IRC review of PFS and retrospective confirmatory central testing of ER, PgR, and HER2 were established. To address critical comments on the choice of nab-paclitaxel as comparator in 1L metastatic TNBC, IMpassion131 was initiated to generate clinical evidence for atezolizumab in combination with paclitaxel.

In May 2016, due to a high number of unblinding requests, the applicant sought EMA Scientific advice (Procedure EMEA/H/SA/2522/7/2016/II). CHMP did not endorse the applicant's proposal to amend IMpassion130 to prevent unblinding individual patients' treatment assignment, except in the case of emergent safety events, until OS data from the study were available.

It is an application for a change to the existing marketing authorisation leading to an extension of the marketing authorisation; change or addition of a new strength intended for the extension of indication to

include the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors have PD-L1 expression ≥1% and who have not received prior chemotherapy for metastatic disease.

2.2. Quality aspects

2.2.1. Introduction

The currently authorised presentation of Tecentriq is a concentrate for solution for infusion. Each vial of concentrate contains 1,200 mg of atezolizumab (corresponding to 20 mL, 60 mg/mL). After dilution, one mL of solution contains approximately 4.4 mg of atezolizumab.

The applicant developed a new strength of 840 mg (same pharmaceutical form) in the context of the new therapeutic indication applied for. Each vial of concentrate contains 840 mg of atezolizumab (corresponding to 14 mL, 60 mg/mL). After dilution, one mL of solution contains approximately 3.2 mg of atezolizumab.

For both strengths atezolizumab finished product is provided as a sterile, single-use, colourless to slightly yellow solution for intravenous infusion and does not contain preservatives.

The finished product formulation and composition of the primary packaging materials remain unchanged.

2.2.2. Active Substance

Module 3.2.S is not affected by this application.

2.2.3. Finished Medicinal Product

Description and composition of the finished product

Reference is made to Table 1 for a comparison of the new atezolizumab finished product 840 mg presentation with the currently authorised 1200 mg presentation. The only differences are vial size, nominal fill volume and cap colour (mist grey for the 840 mg presentation, aqua for the 1200 mg presentation).

The primary packaging for atezolizumab finished product is a 15 mL colourless Ph. Eur. Type I glass vial sealed with a 20 mm rubber stopper and crimped with a 20 mm aluminium seal fitted with a plastic flip-off cap. All product-contacting materials are pharmaceutical-grade, are suitable for packaging sterile liquid products, and comply with relevant pharmacopoeial requirements.

Table 1: Atezolizumab finished product vial presentations comparison

Presentation	Vial 1200 mg	Vial 840 mg
Formulation	60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8	Unchanged
Dosage Form	Liquid concentrate for solution for infusion	Unchanged
Vial	20 mL, Type I glass	15 mL, Type I glass
Rubber Stopper	20 mm fluororesin-laminated rubber stopper (liquid-type D777-1)	Unchanged
Flip-Off Seal	Aluminum seal with plastic flip-off cap	Unchanged
Cap color	Aqua	Grey
Nominal Fill Volume	20 mL	14 mL

Note: "Unchanged" indicates no change in relation to the process described in the column to the left.

Manufacturing process development

The manufacturing process of the 840 mg and the 1200 mg vial is identical, except for the unit operation for filling which uses different process parameters due to the different vial and fill volumes. In order to support the finished product manufacturing process transfer to a new finished product facility, two technical batches were manufactured in the engineering run campaign: one of atezolizumab finished product vial 1200 mg and one of atezolizumab finished product vial 840 mg. Additionally, the manufacturing process for atezolizumab finished product 840 mg presentation was validated using three consecutive validation/registration batches;

The applicant performed an adequately designed comparability study in accordance with ICH Q5E guideline:

- Comparative batch release test assessment:

  Finished product release testing results for the three 840 mg validation batches (B0001, B0002 and B0003) met all release acceptance criteria. Finished product validation batch release test results for the assays met qualitative and quantitative predefined acceptance criteria. Quantitative criteria are based on the 95% confidence/99% probability tolerance interval (95/99 Tolerance Interval) of historical batch release results.

  Comparative extended characterisation assessment:

  The applicant adequately executed extended characterisation results for attributes considered relevant based on a gap assessment performed for the scope of the finished product transfer to a new finished product manufacturing facility Results from validation batches met predefined acceptance criteria based on historical data.

- Comparative stress stability comparability assessment:

  The adequately designed comparative stress study performed at 40°C/75% RH for up to 30 days shows a similar quality profile for the analysed parameters and therefore demonstrates evidence that the finished product manufactured at new finished product site (i.e. three 840 mg/14 mL validation batches) is sufficiently comparable to the finished product manufactured at the initial finished product manufacturing site (i.e. three 1200 mg/ 20 mL representative batches).

Comparability of atezolizumab finished product manufactured at different finished product manufacturing sites is considered demonstrated.

Manufacture of the product and process controls

Manufacture

Manufacture of finished product includes the following process steps:

- Thawing of frozen active substance; optional refreezing and storage of residual drug substance;

- Pooling of the active substance and mixing;

- Bioburden reduction filtration;

- Sterile filtration of the finished product, vial filling, and stoppering;

- Capping and crimping of vials;

- Inspection of vials;

- Labelling and secondary packaging.

Process validation

The manufacturing process for the atezolizumab finished product 840 mg presentation was prospectively validated using three consecutive validation batches; Critical steps and critical process parameters (CPPs) and corresponding in-process controls (IPCs) are adequately identified, i.e. bioburden, endotoxin, filter integrity and fill weight, and are based on the manufacturing process for the 1200 mg presentation but have been adapted for the process of the new 840 mg presentation. The defined action limits are in line with regulatory requirements. The results of the validation studies demonstrate consistent manufacturing of the 840 mg presentation, i.e. the pre-defined acceptance criteria for all quality attributes / parameters as well as for IPCs and release tests were adequately met. Furthermore, the proposed holding and processing times are justified based on the presented validation data.

Product specification, analytical procedures, batch analysis

Specifications

Release and shelf life specifications include control of identity, purity, potency and other general tests.

In comparison with the 1,200 mg presentation, the specifications and analytical methods remain unchanged.

The overall control strategy encompassing control by IPCs and specifications is considered justified to achieve and maintain the intended product quality.

Batch analysis

The batch genealogies of atezolizumab finished product registration/validation batches were provided. All batch analysis results meet the specifications that were in effect at the time of testing and release for each batch.

Stability of the product

The stability protocol is adequately designed and complies with relevant guidelines. The selected methods are considered suitable to detect changes in the stability-indicating critical quality attributes (CQAs). Stability data provided by the applicant include three consecutive validation batches at the recommended storage long-term condition (2°C-8°C) and additionally data at accelerated storage condition (25°C/60% relative humidity [RH]). Supportive long-term and accelerated stability data of the atezolizumab finished product engineering batch are also available. The real-time long-term (2°C-8°C) data show no critical trends and confirm the known stability profile.

Considering the totality of the stability data presented the following storage conditions, as approved for the currently authorised 1,200 mg presentation, are acceptable:

- Unopened vial: 3 years (2°C – 8°C)

- Diluted solution: Chemical and physical in use stability has been demonstrated for no more than 24 hours at 2°C to 8°C or 24 hours at ≤ 30°C from the time of preparation. From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C or 8 hours at ambient temperature (≤ 25 °C).

- The vial should be kept in the outer carton in order to protect from light.

In accordance with EU GMP guidelines (*6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union*), any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Adventitious agents

Module 3.2.A.2 is not affected by this application.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The applicant adequately addressed the two minor issues identified during the procedure.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided, CHMP considers that this line extension application is approvable from the quality point of view.

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

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

2.3.1. Ecotoxicity/environmental risk assessment

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

2.3.2. Discussion and conclusion on non-clinical aspects

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

2.3.3. Conclusion on the non-clinical aspects

No new nonclinical data has been provided for this extension. No further data is required.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

Table 2: Tabular overview of clinical studies

Pivotal study

Study No. (Phase)	Study Design	Population	No. of Patients	Dose, Route, and Regimen	Co-Primary Efficacy Endpoints	Secondary Efficacy Endpoints	Timing of Primary Analysis
WO29522 (III)	Multicenter, randomized, controlled, double-blind	Patients with locally advanced or metastatic TNBC who have not received prior chemotherapy for metastatic breast cancer (1L)	**Total:** ITT: n=902 PD-L1 positive: n=369 **atezo+nP:** ITT: n=451 PD-L1 positive: n=185 **pl+nP:** ITT: n=451 PD-L1 positive: n=184	**atezo or pl:** IV, 840 mg q2w until disease progression or unacceptable toxicity **nP:** IV, 100 mg/m^2 weeky for three consecutive weeks followed by a 1-week rest period	Investigator-assessed PFS per RECIST v1.1 and OS	Investigator assessed ORR and DOR per RECIST v1.1 TTD in GHS/HRQoL	After approximately both 600 PFS events and 352 OS events in the ITT population were observed

DOR=duration of response; GHS=global health status; HRQoL=health-related quality of life; ORR=objective response rate; OS=overall survival; Response Evaluation Criteria in Solid Tumors; TNBC=triple negative breast cancer; TTD=time to deterioration.

Supportive study

Protocol No.	Location of Synopsis and Location of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
GO27831 (PCD4989g)	**Interim CSR** Report No. 1064914 Synopsis and Interim CSR Data Cutoff: 2 December 2014	To evaluate safety, tolerability, and PK	Multicenter, first-inhuman, dose-escalation, open-label study	atezolizumab Phase I formulation: 0.01 mg/kg to 20 mg/kg IV q3w Phase III formulation: 1200 mg IV q3w	All solid tumor types n = 481 UC Cohort n = 92	Patients with locally advanced or metastatic solid tumors or hematologic malignancies, including UC (2L+ UC)	Up to 1 year or until loss of clinical benefit	Ongoing Interim CSR: Full report

1L=first-line treatment; 2L=second-line treatment; CSR=clinical study report; DOR=duration of response; IC=tumor-infiltrating immune cell; INV=investigator; IRF=independent review facility; IV=intravenous; PFS=progression-free survival; ORR=objective response rate; OS=overall survival; PD-L1=programmed death - ligand 1; PK=pharmacokinetics; q3w=every 3 weeks; RECIST=response Evaluation criteria in solid tumors; UC=urothelial carcinoma

Reference was also made to Study GP28328, an open-label, Phase Ib study that has six treatment arms and is designed to assess the safety, pharmacology and preliminary efficacy of atezolizumab administered with bevacizumab (Arm A) and with bevacizumab plus oxaliplatin, leucovorin, and 5-fluorouracil (5-FU) (FOLFOX) (Arm B), with carboplatin and paclitaxel (Arm C), with carboplatin and pemetrexed (Arm D), with carboplatin and nab-paclitaxel (Arm E), and with nab-paclitaxel (Arm F) in participants with locally advanced or metastatic solid tumours (NCT01633970) (Pohlmann et al. 2018).

2.4.2. Pharmacokinetics

The clinical pharmacology properties of atezolizumab were originally characterized using previous studies when atezolizumab was administered as 1200 mg IV every three weeks (q3w) as monotherapy in patients with predominantly mUC and NSCLC. Previous assessments have determined that Atezolizumab pharmacokinetics is linear over a dose range of 1 to 20 mg/kg. A target efficacy serum concentration of 6 µg/mL has been identified. In support of this application, the MAH submitted PK results from the pivotal IMPassion130 study.

Pharmacokinetics of atezolizumab and Nab Paclitaxel in IMPassion130

IMpassion130 is an ongoing Phase III, global, multicenter, double-blind, two-arm, 1:1 randomized, placebo-controlled study designed to evaluate the efficacy and safety of atezolizumab administered with nab-paclitaxel compared with placebo in combination with nab-paclitaxel in patients with locally advanced

or metastatic TNBC who have not received prior systemic therapy for mBC (see study methods under clinical efficacy).

Pharmacokinetics and immunogenicity were investigated in all 445 treated patients. The dosing regimen of atezolizumab was 840 mg IV Q2W. Nab-paclitaxel was administered 100 mg/m^2 IV (3 weeks on, 1 week of).

Table 3: Clinical study for PopPK Analysis

Study	Phase	N ITT	N Eval PK	Population	Dose and Schedule
IMpassion130 [4] (Study WO29522)	III	Atezo+nP Arm: 451 Placebo+nP Arm: 451[a]	Atezo+nP Arm: 443 NA	1L patients with metastatic TNBC	Atezolizumab 840 mg q2w Chemotherapy (3-weeks-on/1-week-off): • nab-paclitaxel 100 mg/m^2

Atezo+nP Arm=Atezolizumab + nab-paclitaxel; CnP Arm=Carboplatin + nab-paclitaxel; Eval.=evaluable; N=Number of patients; ITT=Intent to Treat; NA=not applicable; q2w=every 2 weeks; 1L=first-line (chemotherapy-naïve patients).
[a] data not used in this analysis.

The PK objectives for this study were: characterization the pharmacokinetics of atezolizumab when administered with nab-paclitaxel, and characterization of the pharmacokinetics of nab-paclitaxel when administered with atezolizumab.

The incidence of ADA against atezolizumab and the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy were also evaluated.

PK samples were collected in all patients who received at least one dose of atezolizumab. Serum samples for PK analysis were obtained at baseline (before dosing), at post-dose (Cmax or 30 minutes after the end of the atezolizumab infusion at Cycle 1), and at the following timepoints: pre-dose at Cycles 2, 3, 4, 8, 16, at termination, and at follow-up after termination; in addition, starting from study protocol v3, samples were collected every 8 cycles after Cycle 16.

A quantitative sandwich ELISA assay was used to determine the concentration of atezolizumab and paclitaxel concentrations were determined with a liquid chromatography tandem mass spectrometry (LC-MS/MS) method. Anti-atezolizumab antibodies (ADAs) were detected with an ELISA assay.

PK results

All 445 patients in the atezolizumab-treated arm (100%) had evaluable atezolizumab pharmacokinetics. A total of 2232 atezolizumab serum concentrations from 443 patients (5.0/patients) out of 452 ITT patients (98%) were used for the popPK analysis. Of note, PK samples taken at unscheduled visits were also included in the analysis. Concentrations below the limit of quantification (LOQ) (439 out of 2700, 16%), a moderate fraction of the dataset, were ignored for the analysis and treated as a missing dependent variable.

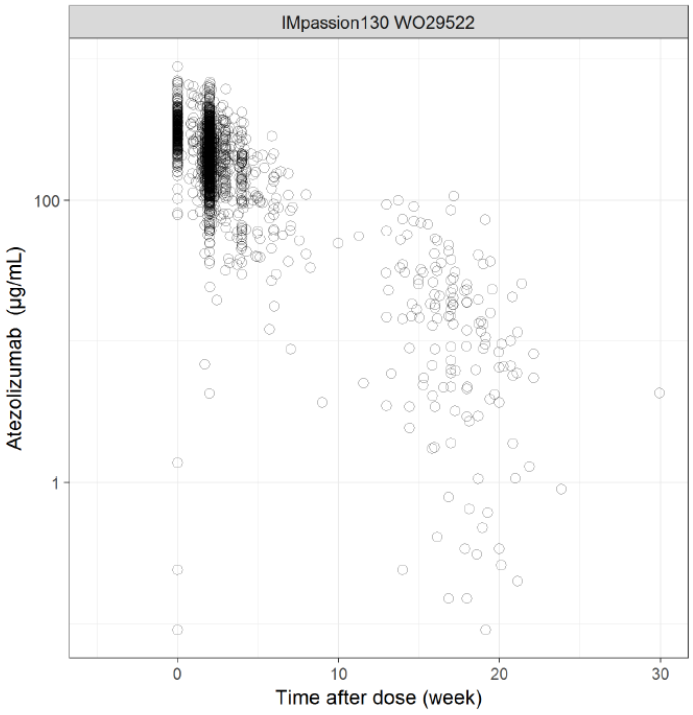


Figure 1: Graphical data exploration of atezolizumab concentration data in Impassion130

Pharmacokinetic data analysis

The descriptive statistics of the maximum serum concentration (Cmax; 30 minutes following the end of the infusion in Cycle 1) and minimum serum concentration (Cmin; pre-dose) of atezolizumab for the atezo+nP arm following 840 mg q2w IV administration of atezolizumab were summarized.

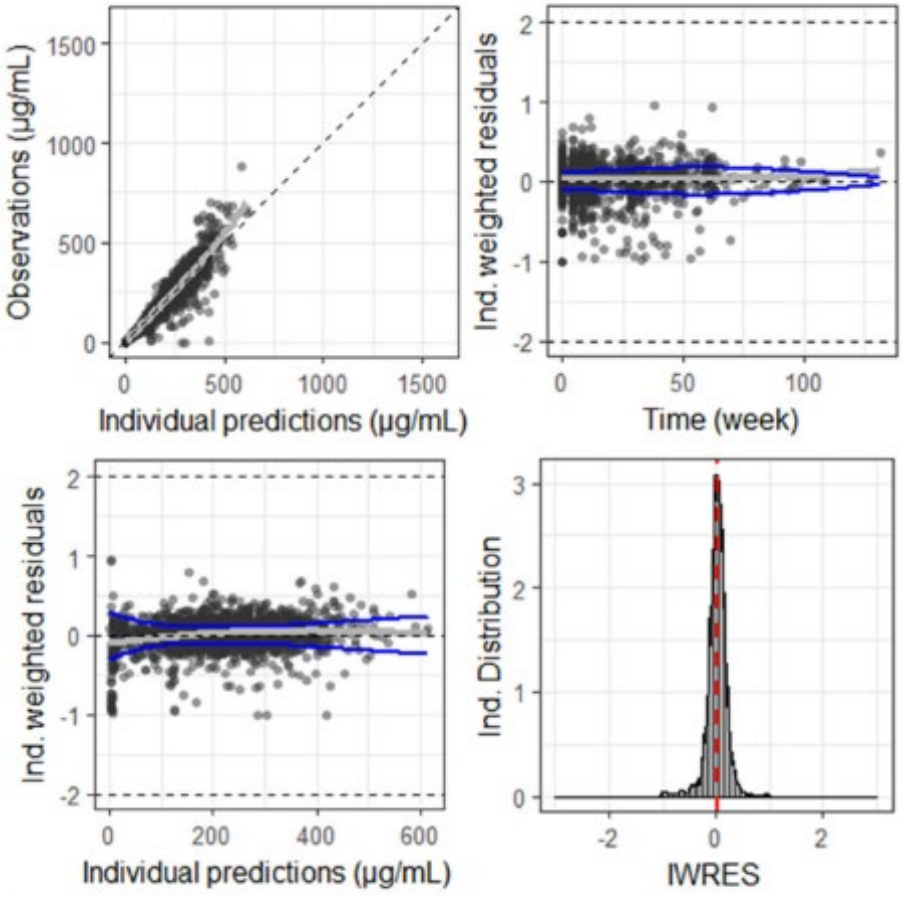
A total of 19 patients in the atezo+nP arm had measurable pre-dose Cycle 1, Day 1 concentrations, which were deemed to be artifacts and excluded from the descriptive statistics. Another three Cmax values close to the limit of detection were also deemed not physiologically possible and excluded from the descriptive statistics.

In addition, the MAH conducted external validation of the previously established population PK model using PK data resulting from Study Impassion 130. The Phase I popPK model was used to derive the individual PK estimates based on atezolizumab observed concentration-time profiles in IMpassion130. A total 443 out of the 445 treated patients (99.6%) contributed to the popPK analysis. A nonlinear mixed effects modeling approach was used with the Bayesian post-hoc estimation (MAXEVAL = 0) in NONMEM 7, Version 7.3 (ICON, Maryland).

A prediction-corrected visual predictive check (pcVPC) was performed based on the Phase I popPK model and observed peak (Cmax) and trough (Cmin) concentrations in IMpassion130 compared to corresponding predictive distributions. Summary statistics of model-derived atezolizumab exposure metrics for IMpassion130 were compared to those simulated from the Phase I model.

- **Evaluation and Qualification of Models**

Figure 3 Goodness-of-Fit for the Phase I popPK Model from IMpassion130 at Individual Level



Ind.=Individual; IWRES=individual weighted residuals.
Grey lines are LOESS (locally weighted scatterplot smoothing);
Blue lines are LOESS in positive or negative residuals.

Figure 2: Goodness-of-Fit for the phase I popPK model from Impassion130 at individual level.

Pharmacokinetics in target population

The descriptive statistics of Cmax in Cycle 1 and Cmin are presented in **Table 6**.

Table 4 Summary Statistics for Atezolizumab C_{max} and C_{min} Following 840 mg IV Infusion of Atezolizumab Every 2 Weeks in Combination with nab-Paclitaxel (Weekly 100 mg/m^2 IV Infusion, 3 Weeks On and 1 Week Off)

Visit *	Nominal Time from First Dose (day)	N	AM (μg/mL)	AM SD (μg/mL)	AM (%CV)	GM (μg/mL)	GM (%CV)	Min (μg/mL)	Median (μg/mL)	Max (μg/mL)
C1D1 (C_{max})	0.0625	407	329	98.9	30.1	316	28.9	78.6	316	1110
C1D27 (C_{min})	28	420	145	52.6	36.2	133	62.9	0.03	147	457
C2D27 (C_{min})	56	373	215	78.3	36.5	198	49.8	4.24	210	686
C3D27 (C_{min})	84	343	245	90.3	36.8	221	68.5	0.41	240	624
C7D27 (C_{min})	196	188	274	111	40.5	249	53.2	12.1	260	691

N=number used to calculate statistics; AM=Arithmetic Mean; SD=standard deviation; CV=coefficient of variation; GM=Geometric Mean.
Note: Data with one or more of following conditions are excluded from the PK summary table:
a) Measurable PK concentration at baseline before dosing
b) Incomplete or missing PK sample date/time
c) Duplicates either by visit/time point or date/time
d) Implausible concentrations
e) Unscheduled PK sample collection
* Visit is denoted by cycle (abbreviated as "C") and day (abbreviated as "D"). For example, C1D1 corresponds to Cycle 1, Day 1. Pre-dose Cycle 1 is C1D1, 0 days. C_{max} is C1D1, 30 minutes post end of infusion. Pre-dose Cycle 2 is C1D27, pre-dose Cycle 3 is C2D27, etc.
Source: t_pkc1 (IMpassion130 CSR, Table 29).

Table 5: Summary statistics (geometric mean [90% PI or %CV]) of atezolizumab exposure metrics at dose 1 and steady-state predicted using PopPK Model

	Geometric Mean (Geometric Mean [CV% or 90%PI])		
Study (N)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC (µg.day/mL)
Phase I popPK Model Simulation (N=500)***	281 [187, 420]	74 [48, 116]	1720 [1234, 2474]***
IMpassion130, Atezo+nP Arm (N=444)	311 [16.5]**	71.3 [23.3]**	1880 [15.5]**

	Geometric Mean (Geometric Mean [CV% or 90% PI])		
Study (N)	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)	$AUC_{,ss}$ (µg.day/mL)
Phase I popPK Model Simulation (N=500)	517 [334, 801]	226 [118, 426]	4376 [2672, 7466]
IMpassion130, Atezo+nP Arm (N=444)	547 [22.6]**	232 [39.4]**	4521 [29.3]**

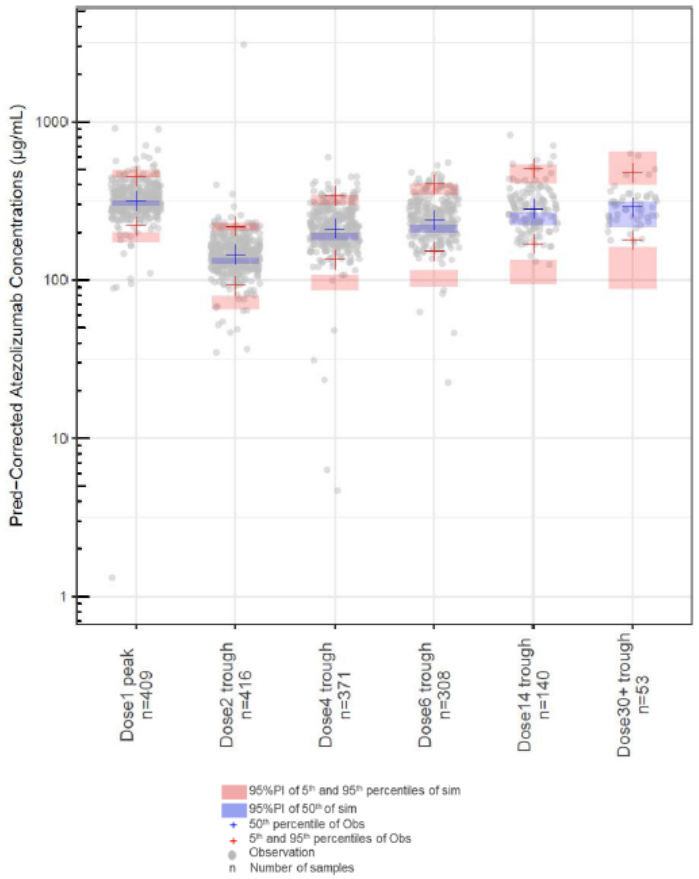
	Geometric Mean (Geometric Mean [CV%])				
Study (N)	CL (L/day)	V1 (L)	V2 (L)	$t_{1/2}$beta* (day)	Accumulation Ratio*
Phase I popPK Model (N=472)***	0.2 [29]	3.28 [18]	3.63 [34]	27	3.3
IMpassion130, Atezo+nP Arm (N=444)	0.18 [7.16]**	2.68 [46.5]**	2.64 [23.0]**	21.3 [4.64]**	2.81 [17.2]**

N=number of patients; C_{max}=C_{max} at dose 1; C_{min}=C_{min} at dose 1; AUC=$AUC_{(0-14)}$ at dose 1; CV=coefficient of variation; PI=predicted interval; $C_{max,ss}$=C_{max} at steady-state; $C_{min,ss}$=C_{min} at steady-state; $AUC_{,ss}$=AUC at steady-state.

*Accumulation ratio is derived using t1/2 beta. t1/2 beta is the terminal half-life based on post-hoc parameter estimates for this parameter harmonic mean and pseudo-standard deviation are reported; Accumulation ratio is calculated based on $t_{1/2}$ beta;
Atezo +nP Arm=Atezolizumab +nab-paclitaxel;

**For IMpassion130, individual PK parameters used for the predictions of exposures, were estimated on dose 1 PK data only with 840 mg q2w dosing while for the Phase 1 study, the individual PK parameters were estimated on all PK data with 1200 mg q3w dosing.

***Phase1 popPK Model Simulation for AUC was derived as twice the weekly AUC from 840 mg q2w dosing. Phase 1 popPK Model PK parameters are based on typical values and inter-individual variability (%) (see report No. 1066935).
Source: Appendix 13 of popPK Report No. 1089809.



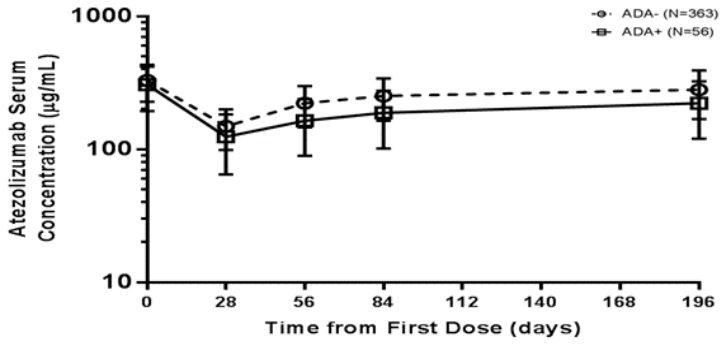
CI = confidence interval; popPK = population pharmacokinetics; VPC = visual predictive check.
Source: TNBC external-validation popPK Report, Figure A.

Figure 3: Prediction-corrected VPC of atezolizumab data in Impassion130 using the popPK Model

Subgroup analyses of PK by ADA status

The incidence rate of treatment-emergent ADA was 13.1% in the ITT population. On average, C_{min} estimates for Cycle 3, Day 27 (or pre-dose Cycle 4 or approximate steady state) in the atezo+nP arm were 252 µg/mL for the ADA-negative group and 188 µg/mL for the ADA-positive group (a difference of 25.4%) but their distributions largely overlapped. Regardless of the ADA status, the average C_{min} at Cycle 4 were 31 to 42-fold above the target serum concentration of 6 µg/mL.

Atezolizumab concentrations by ADA status are plotted in Figure 4.



Source: g_pkc1_mean_log_ata (IMpassion130 CSR, Figure 13).

Figure 4: Mean (±SD) Plot of Atezolizumab Concentrations versus Time Following 840 mg of Atezolizumab Given as IV infusion Every 2 Weeks in Combination with Weekly 100 mg/m^2 IV Infusion of nab-Paclitaxel (3 Weeks On and 1 Week Off) by Treatment-Emergent ADA Status

Interactions

PK of Nab-Paclitaxel

Following 100 mg/m^2 IV administration of nab-paclitaxel (3 weeks on, 1 week off), plasma paclitaxel concentrations were measured with or without atezolizumab co-administration. The descriptive statistics of paclitaxel concentrations during infusion (5-10 minutes prior to the end of induction [EOI]) and Cmax (1 hour post EOI) at Cycle 3 are summarized in Table 8.

A total of 781/890 patients treated with nab-paclitaxel (87.8%) had evaluable paclitaxel pharmacokinetics; 449 from the atezo+nP arm and 332 from the nab-paclitaxel arm. A total of 6 patients had measurable pre-treatment concentrations, 3 in each arm. These values were deemed artifacts and were excluded from the summary statistics. A total of 72 paclitaxel concentrations at 1-hour post EOI were higher than their concentration during infusion and 148 data points were greater than 4 times the median. These samples were deemed not physiologically possible and were excluded from the summary statistics. The mean plasma paclitaxel concentrations over time are presented in Figure 6. The overall Cmax variability of nab-paclitaxel exposure was high (%CV of geometric mean >100%). On average, the nab-paclitaxel Cmax and concentration collected during infusion were comparable with or without atezolizumab co-administration, showing a minimal percent difference of 7.5 and 3.6, respectively.

Table 6: Summary statistics for paclitaxel Cmax and Cmin following weekly 100 mg/m2 IV infusion of nab-paclitaxel (3 weeks on and 1 week off) with or without 1200 mg IV infusion of atezolizumab q3w

Treatment	Visit1	Nominal Time From First Dose (day)	N	AM (ng/mL)	AM SD (ng/mL)	GM (ng/mL)	GM (%CV)	Min (ng/mL)	Median (ng/mL)	Max (ng/mL)
atezo+nP (N=449)	C3D1	56 (during infusion)	298	3080	2050	2090	200	2.26	2730	10600
	C3D1	56 (Cmax)	280	400	275	323	76.8	5.40	319	1340
pl+nP (N=332)	C3D1	56 (during infusion)	255	2970	2300	1870	210	2.33	2515	10800
	C3D1	56 (Cmax)	221	370	244	310	64.4	43.9	303	1310

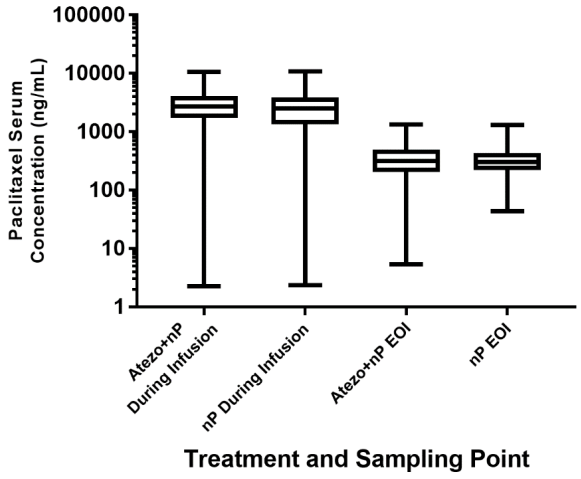
N=number used to calculate statistics, AM=arithmetic mean, SD=standard deviation, CV=coefficient of variation, GM=geometric mean, atezo+nP = atezolizumab and nab-paclitaxel, pl+nP = placebo and nab-paclitaxel

Note: Implausible concentrations due to dosing/sampling/assay errors were not included in the summary statistics.

[1] Visit is denoted by cycle (abbreviated as "C") and day (abbreviated as "D"). For example, C3D1 corresponds to Cycle 3, Day 1. During infusion was taken approximately 10 min prior to the end of infusion.

Source: adapted from t_pkc2 (IMpassion130 CSR, Table 31).

Figure 5: Box Plot of Paclitaxel Concentrations by Sampling Point and Treatment on Cycle 3, Day 1 Following Weekly 100 mg/m^2 IV Infusion of nab-Paclitaxel (3 Weeks On and 1 Week Off) with or without 1200 mg IV Infusion of Atezolizumab q3w

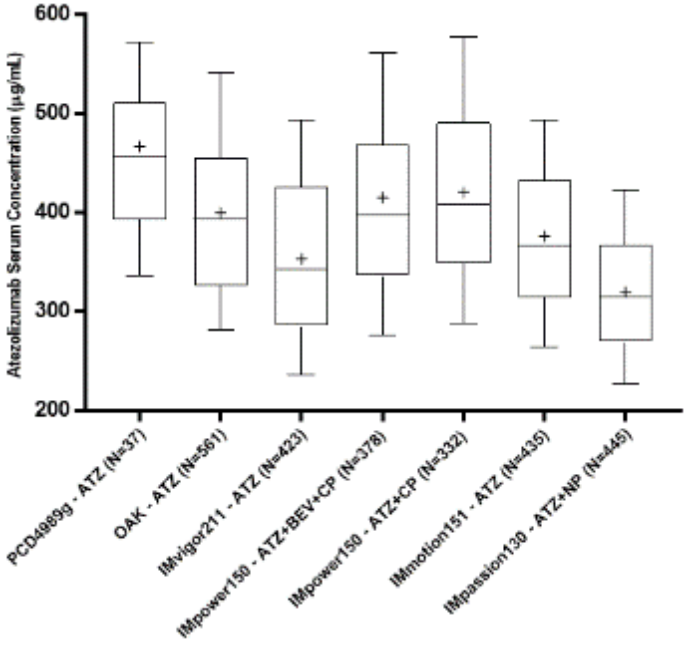


Atezo=atezolizumab; EOI=end of induction; nP=nab-paclitaxel.
Source: adapted from g_pkc2_meansd_linear (IMpassion130 CSR, Figure 13).

Comparison and analyses of atezolizumab PK across studies

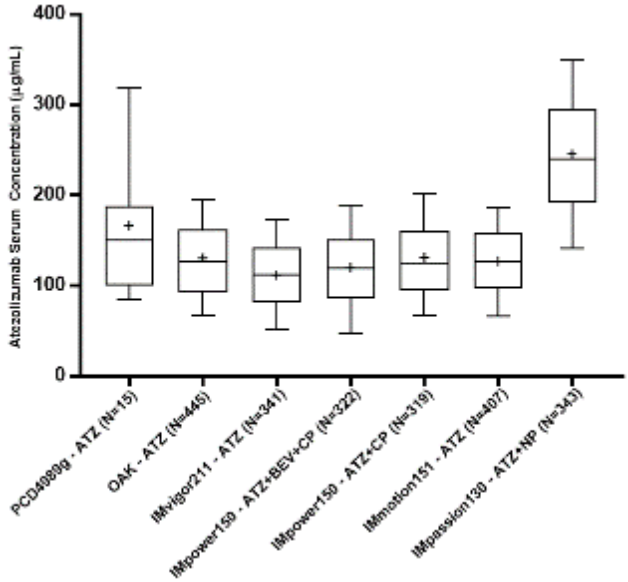
Exposure measures of atezolizumab in the Phase I trial and multiple Phase III pivotal trials, including IMpassion130, is presented in the Figures below.

Figure 6 : Atezolizumab C_{max} (30 min Dose on Day 1, Cycle 1) by Study and Treatment Group Following 1200 mg or 840 mg Intravenous Infusion as Monotherapy or in Combination



1200 mg atezolizumab q3w was administered for Study PCD4989g, OAK, IMvigor211, IMpower150, and IMmotion151
840 mg atezolizumab q2w was administered for IMpassion130
ATZ = atezolizumab; BEV = bevacizumab; CP=cisplatin; NP=nab-paclitaxel.
The box plot shows the median, 25th and 75th percentiles of the population distribution. The plus symbol represents the mean. The bars are 5th and 95th percentiles of the population distribution.
Source: Study PCD4989g Interim CSR, OAK Primary CSR, IMvigor211 CSR, IMpower150 Primary CSR, IMmotion151 Primary CSR, and IMpassion130 CSR.

Figure 7: Atezolizumab C_{min} at Steady State (Pre-Dose on Day 42 for q3w and Pre-Dose on Day 56 for q2w) by Study Following 1200 mg q3w or 840 q2w Intravenous Infusion as Monotherapy or in Combination



1200 mg atezolizumab q3w was administered for Study PCD4989g, OAK, IMvigor211, IMpower150, and IMmotion151.
840 mg atezolizumab q2w was administered for IMpassion130.
ATZ=atezolizumab; BEV = bevacizumab; CP=cisplatin; NP=nab-paclitaxel.
The box plot shows the median, 25th and 75th percentiles of the population distribution. The plus symbol represents the mean. The bars are 5th and 95th percentiles of the population distribution.
Source: Study PCD4989g Interim CSR, OAK Primary CSR, IMvigor211 CSR, IMpower150 Primary CSR, IMmotion151 Primary CSR, and IMpassion130 CSR.

Special populations

Covariate effects (such as body weight, gender, ADA status, albumin levels, and tumor burden) in the IMpassion130 data were consistent with those identified in the popPK model.

Pharmacokinetic interaction studies

No pharmacokinetic interaction studies were submitted as part of this application (see discussion on clinical pharmacology).

2.4.3. Pharmacodynamics

Immunogenicity results

At baseline, 1.6% of the ADA-evaluable patients in the atezo+nP arm had an ADA-positive sample. After the first atezolizumab dose (post-baseline), 13.1% (57 patients) and 11.8% (21 of 178) of the ADA-evaluable patients in the ITT and PD-L1-positive populations, respectively, were treatment-emergent ADA positive; all cases were treatment induced.

The presence of atezolizumab in ADA serum samples can interfere with ADA detection. In validation experiments, the ADA assay was able to detect 500 ng/mL of surrogate positive control anti-atezolizumab antibodies in the presence of 200 µg/mL atezolizumab. Of all post-baseline ADA samples tested, the majority (52.9% in the atezo+nP arm) had atezolizumab concentrations that were at or below 200 µg/mL. The high proportion of samples that had drug levels within the assay drug tolerance minimized the likelihood of false negatives in the ADA assay.

The impact of ADAs on PK, efficacy and safety in Impassion 130 has been investigated.

The median PFS for ADA-negative and ADA-positive patients in the ITT population was 7.36 months and 5.52 months, respectively. The median PFS for ADA-negative and ADA-positive patients in the PD-L1-positive population was 8.11 months and 8.25 months, respectively. Both populations had overlapping 95% CIs for PFS. The median OS could not be estimated for the ADA-positive subgroup.

Table 7: PFS by atezolizumab ADA status in atezolizumab-treated patients in Impassion130

	ADA–negative N=377		ADA–positive N=57	
	Subjects with Events/Evaluated (%)	Time to Event (Months) Median (95%CI)	Subjects with Events/Evaluated (%)	Time to Event (Months) Median (95%CI)
Overall survival (ITT)	147/377 (39.0%)	21.88 (17.54,25.03)	20/57 (35.1%)	NE (14.59,NE)
PFS (Investigator) (ITT)	299/377 (79.3%)	7.36 (6.44,8.28)	44/57 (77.2%)	5.52 (4.11,8.25)
Overall Survival (PD-L1 IC1/2/3)	54/157 (34.4%)	25.03 (22.60,NE)	5/21 (23.8%)	NE (14.59,NE)
PFS (Investigator) (PD-L1 IC1/2/3)	116/157 (73.9%)	8.11 (7.20,9.30)	16/21 (76.2%)	8.25 (5.49,11.24)

ADA=anti-drug antibodies; ADA–=without TX enhanced/induced; ADA+=with TX enhanced/induced; CI=confidence interval; IIT=intent-to-treat population; TX=treatment.

Source: Modified from t_ef_all_ada_P_ADA_17APR2018_29522 (IMpassion130, Table 70).

A total of 28.1% of ADA-positive patients versus 21.5% of ADA-negative patients had serious adverse events (SAEs). The SAEs were those commonly reported in cancer patients and the rate difference was not driven by any single preferred term.

Table 8: Safety summary profile by atezolizumab treatment-emergent ADA status (ADA-evaluable atezolizumab patients in pooled safety-evaluable population)

	ADA– N=377	ADA+ N=57
Total number of patients with at least one AE	374 (99.2%)	57 (100%)
Total number of AEs	6494	829
Total number of deaths	147 (39.0%)	20 (35.1%)
Total number of patients with at least one		
AE with fatal outcome	4 (1.1%)	1 (1.8%)
Related AE with fatal outcome	2 (0.5%)	0
Grade 3-4 AE	184 (48.8%)	28 (49.1%)
Related Grade 3-4 AE	153 (40.6%)	23 (40.4%)
Serious AE	81 (21.5%)	16 (28.1%)
Related Serious AE	45 (11.9%)	9 (15.8%)
Related AE	369 (97.9%)	53 (93.0%)
AE leading to any study treatment discontinuation	60 (15.9%)	10 (17.5%)
AE leading to Atezolizumab/Placebo discontinuation	22 (5.8%)	6 (10.5%)
AE leading to Nab-paclitaxel discontinuation	60 (15.9%)	10 (17.5%)
AE leading to any dose reduction or study treatment interruption	179 (47.5%)	29 (50.9%)
AE leading to dose interruption of Atezolizumab/Placebo	115 (30.5%)	22 (38.6%)
AE leading to dose reduction or interruption of Nab-paclitaxel	163 (43.2%)	28 (49.1%)

ADA=anti-drug antibodies; ADA–=without TX enhanced/induced; ADA+=with TX enhanced/induced; TX=treatment.

Note: Investigator text for AEs is coded using MedDRA version 21.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately. Includes AEs with onset from first dose of study drug through the clinical cutoff.

Source: t_saf_sum_ada_ADA_17APR2018_29522 (IMpassion130 CSR, Table 71).

A similar proportion of ADA-negative patients (58.6%) compared with ADA-positive patients (52.6%) had an AESI of any grade. Across other key AESI parameters, including Grade 3-4 AESIs, AESIs reported as serious and all medical concepts, both ADA subgroups were generally balanced.

2.4.4. Discussion on clinical pharmacology

The purpose of this application is to provide data supporting the line extension for atezolizumab to add an 840-mg vial with 2-weekly (q2w) administration in triple-negative breast cancer (TNBC). In addition to the currently licensed atezolizumab drug product 1200-mg vial, the atezolizumab 840-mg vial was developed to facilitate a q2w administration of atezolizumab together with weekly nab-paclitaxel on a 3-weeks on/1-week off schedule in locally advanced or metastatic TNBC.

The ADME characteristics of atezolizumab have been characterized in previous submission where atezolizumab was administered as monotherapy 1200 mg Q3W. In the clinical study Impassion130 in

patients with TNBC, atezolizumab was administered 840 mg Q2W in combination with 100 mg/m^2 IV administration of nab paclitaxel (3 weeks on, 1 week off).

Atezolizumab pharmacokinetics is linear over a dose range of 1 to 20 mg/kg of atezolizumab, including the fixed 840 mg and 1200 mg dose of atezolizumab.

The analytical methods used are considered acceptable. However, 19 patients had measurable atezolizumab prior to treatment, probably due to operational errors, e.g. sample mixed up, contamination during sampling handling etc.). A fully validated ELISA method was used to detect, confirm and determine titers of ADAs. Although no information was provided in this submission about neutralising antibodies, Nabs were also measured and are being analysed. The applicant is recommended to submit an assessment of the effect of atezolizumab ADAs and neutralizing antibodies on PK and efficacy endpoints including the results of study IMpassion130.

The Phase I pop PK model has been assessed within previous procedures and has been deemed fit for purpose. Model diagnostics (external pcVPC, goodness-of-fit plots) indicate that the Phase I popPK model was adequate to predict atezolizumab pharmacokinetics in IMpassion130 patients and to estimate individual exposure parameters. In relation to the comparison and analyses of atezolizumab PK across studies, Cmax in cycle 1 is as expected lower for the 840 mg first dose compared to the 1200 mg first dose, and Cmin at steady state is higher for the 840 mg Q2W dosing regimen compared to the 1200 Q3W dosing regimen. An increase in Ctrough_ss is expected due to the greater accumulation factor. Population PK suggests an increase in Ctrough_ss of 16%, data presented however indicate a greater rise in Ctrough levels following Q2W dosing.

Overall, atezolizumab PK measures obtained in IMpassion130 are consistent with the popPK model estimates derived from previous studies which indicates consistent PK of atezolizumab across indications, also when co-administered with nab-paclitaxel in patients with TNBC. The pcVPC indicates an under-estimation of the median and 5th percentile of exposure (ctrough) at steady state could be the result of time-dependent decrease in clearance caused by improvement in patient's general health status during treatment. This has been observed for other check point inhibitors.

A Q2W dosing regimen has been proposed and was used in the clinical study Impassion130 to support the Application. The Q2W dosing is more convenient since nab-paclitaxel is dosed 3 weeks on, 1 week of. The effort to align the dosing regimen of atezolizumab with the dosing regimen of nab-paclitaxel is acknowledged, and the observed PK data and model-predicted exposure parameters confirm that Cmin is maintained well above the expected target concentration of 6 µg/ml, previously identified. Both C_{max} and C_{min} from IMpassion130 are within the 95% CI of exposure predicted from a popPK model developed using the 1,200 mg Q3W dose regimen.

No apparent PK drug-drug interaction (DDI) was observed when atezolizumab was administered in combination with nab-paclitaxel. Atezolizumab exposure was in concordance with historical data based on popPK analyses.When atezolizumab is administered in combination with nab-paclitaxel, the pharmacokinetics of atezolizumab can be described using the popPK model developed from monotherapy data. The popPK model supports the finding that nab-paclitaxel does not impact atezolizumab pharmacokinetics when administered in combination. Furthermore, paclitaxel concentrations were comparable with or without atezolizumab co administration (Figure 6).

The q3w dose of nab-paclitaxel administered at 260 mg/m^2 was established from the Phase III study comparing paclitaxel with nab-paclitaxel. However, this dose regimen is not generally used in current clinical practice. At the time of study initiation, the 100 mg/m^2 of nab-paclitaxel weekly on a 3-weeks-on/1-week-off schedule was the best-studied and tolerated dose, with suggestions of improved efficacy and decreased toxicities in mBC compared with both higher weekly doses and the every 3-week

dosing (see discussion on clinical efficacy). The covariate effects investigated in Impassion130 were overall consistent with previous findings and no unexpected covariates were identified.

The post-baseline incidence of treatment-emergent atezolizumab ADA was 13.1% in the ITT population and 11.8% in the PD–L1–positive population. However, no data regarding neutralizing antibodies have yet been submitted. It is agreed that ADAs do not overall appear to have a major impact on atezolizumab PK, but the number of patients with treatment ADAs is small. A general trend seems to indicate lower Cmin for all cycles for ADA positive patients, which is in line with the POP PK results where ADA positive patients have a 16 % higher clearance compared to ADA negative patients. Further exploration across indications of the impact of ADAs and NAbs on atezolizumab PK and clinical outcomes is expected in the post-approval commitment agreed previously with CHMP.

No clear clinically meaningful ER relationships have previously been identified for atezolizumab when patient prognostic factors (i.e., albumin, baseline sum of lesion diameter, gender, etc.) were considered in the analysis. A target serum concentration of 6µg/mL has been agreed in approved indications and is also expected to be relevant for TNBC.

The impact of ADAs on efficacy and safety in Impassion 130 has been investigated. The overall efficacy and safety profile was generally concordant between the ADA-positive and ADA-negative patients, but inconclusive due to small numbers (n=21). The impact of atezolizumab NAbs on efficacy is still unknown but likely comparable across indications. To further clarify if the presence of ADAs and/or NAbs could have an impact on PK, efficacy or safety, the CHMP recommended for the applicant to conduct an assessment of the effect of atezolizumab ADAs and Nabs across studies and indications as a post-approval measure. The IMpassion130 study will be included in this assessment and the MAH will also provide updated ADA analyses for Impassion 130 as part of the final Clinical Study Report submission.

Overall, the proposed 840 mg Q2W atezolizumab dosing regimen is supported based on the analyses of PK measures in study Impassion130 and Pop PK analyses confirming an appropriate exposure and previously identified covariates.

2.4.5. Conclusions on clinical pharmacology

The PK data and analysis submitted are adequate to support the proposed 840 mg IV Q2W dosing regimen of atezolizumab.

2.5. Clinical efficacy

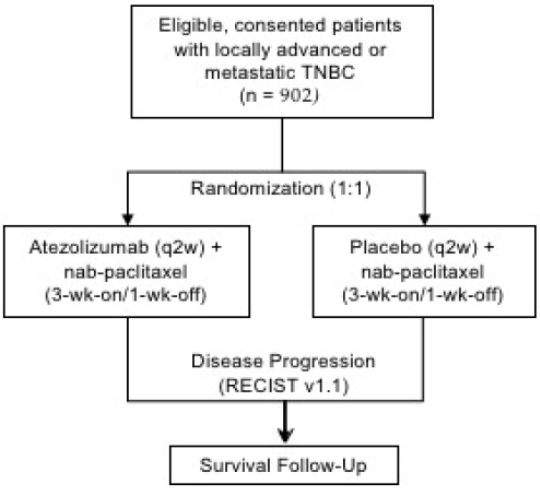
This application is supported by one pivotal study which was a single, pivotal, international, multicenter, randomized, placebo-controlled, double-blinded, two-arm phase III Study WO29522 (hereinafter referred to as IMpassion130), evaluating the efficacy and safety of atezolizumab + nP compared with placebo plus nab-paclitaxel (hereinafter referred to as pl+nP) in patients with locally advanced or metastatic TNBC, who have not received prior chemotherapy for metastatic breast cancer.

2.5.1. Dose response study

No dose response study was submitted.

2.5.2. Main study – Impassion130

Methods



q2w=every 2 weeks; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, version 1.1; TNBC=triple-negative breast cancer; wk=week.

Figure 8: Study design – Impassion130

Study Participants

Main inclusion criteria

- Women or men aged ≥ 18 years
- Metastatic or locally advanced, histologically documented TNBC (absence of HER2, ER, PR expression) as per American Society of Clinical Oncology-American College of Pathologists (ASCO-CAP) criteria
- No prior chemotherapy or targeted systemic therapy for inoperable locally advanced or metastatic TNBC (patients could have received prior chemotherapy in the neoadjuvant/adjuvant setting if treatment was completed ≥ 12 months prior to randomization)
- Eligible for taxane monotherapy (i.e., absence of rapid clinical progression, life-threatening visceral metastases, or the need for rapid symptom and/or disease control)
- Tissue evaluable for tumor PD-L1 expression by an external central laboratory prior to study randomization
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Measurable disease, as defined by RECIST v1.1
- Adequate hematologic and end-organ function
- For women of childbearing potential: agreement to remain abstinent or use contraceptive methods during the treatment period and for at least 5 months after the last dose of atezolizumab/placebo or 1 month after the last dose of nab-paclitaxel, whichever is later
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm
- For Women who are not postmenopausal or surgically sterile: negative serum pregnancy test result within 14 days prior to initiation of study drug.

Main exclusion criteria

- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥ 2 weeks prior to randomization
- Known CNS disease, except for treated asymptomatic CNS metastases (only supratentorial and cerebellar metastases allowed; 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)
- Leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites
- Uncontrolled tumor-related pain
- Uncontrolled hypercalcemia
- Malignancies other than TNBC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome
- Pregnancy or lactation
- Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver disease
- Significant cardiovascular disease
- Severe infection within 4 weeks prior to randomization
- Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1
- Major surgical procedure within 28 days prior to randomization or anticipation of the need for a major surgical procedure during the course of the study other than for diagnosis
- Known hypersensitivity to nab-paclitaxel or to any of the excipients
- 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
- Prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest CT scan (history of radiation pneumonitis in the radiation field (fibrosis) permitted)
- Positive test for HIV
- Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C
- Active tuberculosis
- Receipt of a live, attenuated vaccine within 4 weeks prior to randomization or anticipation that such a live, attenuated vaccine will be required during the study
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-cytotoxic T lymphocyte (CTLA)-4, anti- programmed death-1 (PD-1), or anti-PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including but not limited to interferons or IL-2) within 4 weeks or five half-lives of the drug (whichever is shorter) prior to randomization
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications within 2 weeks prior to randomization, or anticipated requirement for systemic immunosuppressive medications during the study.

Treatments

Atezolizumab or Placebo

Atezolizumab 840 mg or placebo is administered by IV infusion Q2W. Dose reduction of atezolizumab/placebo is not permitted.

Nab-Paclitaxel

Nab-Paclitaxel is administered according to the local prescribing information. The starting dose level of nab-paclitaxel is 100 mg/m^2 administered intravenously over 30 minutes on Days 1, 8, and 15 of each 28-day cycle (3 weeks on/1 week off schedule). Doses of nab-paclitaxel cannot be administered more frequently than every 7 days. Dose modifications are permitted. Sites were instructed to follow their institutional standard of care for determining the nab-paclitaxel dose for patients who are obese and for dose adjustments in the event of patient weight changes. In the absence of disease progression or unacceptable toxicity, nab-paclitaxel can be administered for a target of at least 6 cycles, with no maximum.

Objectives

Co-primary efficacy objectives

- To evaluate the efficacy of atezo+nP compared with pl+nP as measured by PFS (per investigator assessment using Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1])
- To evaluate the efficacy of atezo+nP compared with pl+nP as measured by OS

Secondary efficacy objectives

- To evaluate the efficacy of atezo+nP compared with pl+nP as measured by objective response rate (ORR; per investigator assessment using RECIST v1.1)
- To evaluate the efficacy of atezo+nP compared with pl+nP as measured by duration of objective response (DOR; per investigator using RECIST v1.1) among patients with an objective response
- To evaluate patient-reported outcomes (PROs) of global health status (GHS)/health-related quality of life (HRQoL) associated with atezo+nP compared with pl+nP, as measured by the time to deterioration (TTD) in Items 29 and 30 of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30)

Safety objectives

The safety objectives for this study were as follows:

- To evaluate the safety and tolerability of atezo+nP compared with pl+nP
- To evaluate the incidence 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, pharmacodynamics, safety, and efficacy

Exploratory objectives

The exploratory objectives for this study were as follows:

- To evaluate PROs of function and disease/treatment-related symptoms associated with atezo+nP compared with pl+nP, as measured by the EORTC QLQ-C30 and its breast cancer module (QLQ-BR23)

- To evaluate health utility as measured by the European Quality of Life 5 Dimension 5 Level (EQ-5D-5L) questionnaire for health economic modeling of atezo+nP compared with pl+nP
- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status and/or response to study treatment

Outcomes/endpoints

The co-primary efficacy outcome measures to be assessed in the ITT population and in the PD-L1 selected subpopulation are as follows:

- PFS, defined as the time from randomization to the time of radiographic progression or death from any cause during the study, whichever occurs first. Progression will be assessed by the investigator using RECIST v1.1
- OS, defined as the time from the date of randomization to the date of death from any cause

The secondary efficacy outcome measures to be assessed in the ITT population and in the PD-L1 selected subpopulation are as follows:

- ORR, defined as the proportion of patients with an objective tumour response (either partial response [PR] or complete response [CR] per investigator using RECIST v1.1)
- DOR, defined as the time from the first occurrence of a documented objective tumour response to the time of radiographic progression (per investigator using RECIST v1.1) or death from any cause on study, whichever occurs first
- TTD in global health status/HRQoL, defined by a minimally important decrease of 10 points on the global health status/HRQoL scale of the EORTC QLQ-C30

Biomarker Assessment

PD-L1 expression in IMpassion130 was assessed in both fresh and archival TNBC tumour samples by an external central laboratory using the Ventana PD-L1 (SP142) IHC Assay. Patients were stratified by PD-L1-positive status and a patient was considered PD-L1 positive when his/her tumour specimen contained discernible staining of any intensity on ICs covering $\geq$ 1% of the tumour area (IC1/2/3). Expression on IC was assessed as the proportion of tumour area occupied by PDL1–positive IC of any intensity.

Table 9: Criteria for PD-L1 Expression Assessment – Impassion130

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

IC=tumor-infiltrating immune cell; PD-L1=programmed death-ligand 1.

Randomisation

Patients were randomized 1:1 to the pl+nP arm or the atezo+nP arm. The following stratification factors were used:

- Presence of liver metastases (yes vs. no).
- Prior taxane treatment (yes vs. no).
- Tumour PD-L1 status (tumour-infiltrating immune cell score [IC] 0 vs. IC 1/2/3).

Blinding (masking)

This study was designed as double blind. Patients treated in the placebo+nP arm receive an injection consisting of the vehicle without the antibody instead of atezolizumab. The following individuals were blinded to treatment assignment and PD-L1 status: the patient; the study site personnel, including the investigator; and the Sponsor and its agents, except iDMC members, who were aware of treatment assignment and PD-L1 status. In addition, the PD-L1 assay provider was blinded to treatment assignment and PK laboratory personnel were blinded to PD-L1 status. The blind for a patient could be broken in the case of emergency and unblinding did not result in the withdrawal of the patient from the study.

Statistical methods

Co-Primary endpoint - Progression free survival

Progression-free survival (PFS) was defined as the time from randomization to the occurrence of disease progression, as determined by investigators from tumour assessments, per RECIST v1.1, or death from any cause, whichever occurs first.

Treatment comparisons were based on the stratified (liver metastases, PD-L1 status, and prior taxane treatment) log-rank test. The HR with the 95% CI was estimated using a stratified Cox regression model with the same stratification variables used for the stratified log-rank test. Kaplan-Meier methodology was used to estimate median PFS for each treatment arm and to construct survival curves for each treatment arm. The Brookmeyer-Crowley methodology was used to construct the 95% CI for the median PFS for each treatment arm. For all cases, results from an un-stratified analysis were provided.

Censoring rules

Patients who have not experienced disease progression or death at the time of analysis were to be censored at the time of the last tumour assessment. Patients with no post-baseline tumour assessment were to be censored on the date of randomization.

Sensitivity analyses

- Censoring for non-protocol therapy: Non-protocol therapy was defined as any anti-cancer therapy other than study treatment that typically is the subsequent line of therapy. A sensitivity analysis was to be performed in which data for patients who received NPT were to be censored at the last tumour assessment date before the patient received NPT.
- PFS by IRC: An analysis of PFS on the basis of the IRC assessments was to be performed using the same methodology as specified for PFS on the basis of investigator assessment.

Co-Primary endpoint overall survival

Overall survival was defined as the time from the date of randomization to the date of death due to any cause. Patients who were not reported as having died at the time of analysis were to be censored at the date when they were last known to be alive. Patients who did not have post-baseline information were to be censored at the date of randomization. The analysis of OS was performed analogously to PFS.

Sensitivity analyses

Several sensitivity analyses were planned to take into account the effect of subsequent cancer therapies in overall survival.

Censoring for treatment switching: Treatment switching was defined as any checkpoint inhibitor therapy other than study treatment as subsequent line of therapy. Censoring for treatment switching were to be applied to OS, analogue to censoring for NPT for PFS.

Rank-preserving structural failure time (RPSFT) method provided an estimate of the overall survival time for the placebo arm had treatment switching not occurred. It estimated overall survival measured from the time of treatment switching by applying an estimate of the benefit of the atezolizumab treatment. The adjusted OS time (sum of time to switching and the estimated survival time after switching) was then to be analysed together with the OS times of the patients who did not switch by using the same methodology as for the primary analysis of OS.

Inverse Probability of Censoring Weighting method: The idea of this method was to create a pseudo population that would have been observed if censoring at treatment switching had not occurred by giving increased weight to non-censored patients with similar characteristics to censored patients. These time varying weights were then included into the analysis (e.g., in a Cox model or log-rank test) so that the final analysis was corrected for the effect of treatment switching. This method was not implemented because the number of switching patients was too low (29 patients, 3.2%) for this method to be applicable.

Secondary Efficacy Endpoints

The secondary efficacy endpoints were objective response rate, duration of response and time to deterioration in the Global Heath Status [GHS]/Health-Related Quality of Life [HRQoL].

Objective response rate was defined as the proportion of patients with measurable disease at baseline who have an objective response. Patients not meeting this criterion, including patients without any post-baseline tumour assessment, will be considered as non-responders. Objective response rate will be compared between treatment arms using the stratified Cochran-Mantel-Haenszel test. The stratification factors will be the same as those described for the analysis of the primary endpoint of PFS. The difference

in ORR between treatment arms will be calculated, and its 95% CI will be calculated using the normal approximation to the binomial distribution. An estimate of ORR will be calculated for each treatment arm, and its 95% CI will be calculated using the Clopper-Pearson method. ORR is simultaneously assessed in the ITT and PD-L1-selected subgroup with measurable disease at baseline.

The remaining secondary endpoints (duration of objective response and time to deterioration in GHS/HRQoL) were not to be adjusted for multiple testing and are based on a non-randomized subset of patients.

Sensitivity analyses

For ORR and DOR the analysis were to be performed using the IRC assessment.

Type I error control

The type I error for this study was 0.05 (two-sided). Type I error was to be controlled for PFS and OS both evaluated in the ITT and in the PD-L1-selected populations. Type I error was to be controlled by comparing these endpoints between treatment arms according to the following testing procedure (Figure 10).

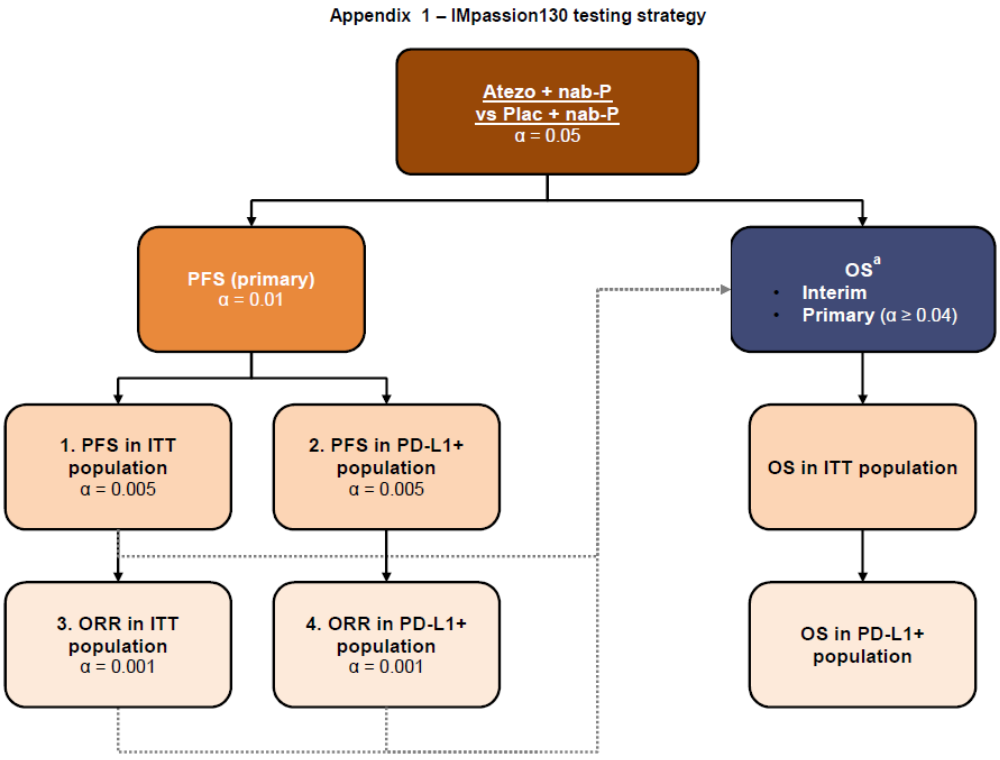


Figure 9: Impassion130 testing strategy – Impassion130

At the time of the analysis of PFS, the co-primary endpoints of PFS and OS and the secondary endpoint of ORR were to be tested in the ITT population and in the PD-L1-selected subpopulation, as follows:

1. Alpha (0.05) was to be allocated between PFS (0.01) and OS (0.04). The allocated type I error for PFS was further allocated to PFS in the ITT (0.005) and PFS in the PD-L1-selected subgroup (0.005).

Testing of PFS and ORR

2. Test the null hypothesis of no difference in PFS between the two arms in the ITT population and the PD-L1-selected subgroup with the allocated type I error

3. If one or both of the null hypotheses from the step above was rejected, ORR was to be subsequently compared between the two arms in the corresponding populations (one or both) using a Type I error of 0.001 for each correspondingly.

Testing of OS

4. At the time of the analysis of PFS, an interim analysis of OS in the ITT (OS [ITT]) was tobe performed. The interim analysis of OS (ITT) was to be performed regardless of the results of the analyses of PFS and ORR. Allocation of the alpha level to the comparison of OS (ITT) depended on the outcome of the testing of PFS and ORR outlined in the Steps 1-3 above. Details for the different alpha level allocations to the OS (ITT) testing dependent on the PFS and ORR results are provided in Table 12 (see column 'Alpha Level' for the total alpha level allocated to the OS[ITT] analysis). The interim analyses boundaries for statistical significance were determined based on the Lan-DeMets implementation of the O'Brien-Fleming function according to the Type I error allocated to the comparison of OS (ITT) (see Table 12, column 'Stopping Boundary in p-value').

5. If hypothesis of no difference in OS in the ITT population can be rejected, OS in the PD-L1-selected subgroup was to be compared by subsequently using the same type I error used for OS (ITT) testing.

Table 10: Interim and final analyses for overall survival – Impassion130

Different Scenarios of PFS and ORR Testing	Alpha Level	Analysis Timing	Time from 1st Patient Enrolled (months)	Information Fraction	No. of Events	Stopping Boundary in HR	Stopping Boundary in p-value
Both PFS and ORR are statistically significant in both IC1/2/3 and ITT	0.05	First interim	30	53%	IC1/2/3: 133 AC: 347	IC1/2/3: HR ≤ 0.608 AC: HR ≤ 0.735	p-value ≤ 0.0041
		Second interim	41	80%	IC1/2/3: 201 AC: 524	IC1/2/3: HR ≤ 0.726 AC: HR ≤ 0.820	p-value ≤ 0.0231
		Final	56	100%	IC1/2/3: 251 AC: 655	IC1/2/3: HR ≤ 0.774 AC: HR ≤ 0.853	p-value ≤ 0.0425
PFS is statistically significant in both IC1/2/3 and ITT; ORR is statistically significant in either IC1/2/3 or ITT, but not both	0.049	First interim	30	53%	IC1/2/3: 134 AC: 349	IC1/2/3: HR ≤ 0.608 AC: HR ≤ 0.735	p-value ≤ 0.004
		Second interim	41	80%	IC1/2/3: 202 AC: 526	IC1/2/3: HR ≤ 0.725 AC: HR ≤ 0.820	p-value ≤ 0.0225
		Final	56	100%	IC1/2/3: 253 AC: 658	IC1/2/3: HR ≤ 0.774 AC: HR ≤ 0.853	p-value ≤ 0.0417
PFS is statistically significant in both IC1/2/3 and ITT; ORR is not statistically significant in either IC1/2/3 or ITT	0.048	First interim	30	53%	IC1/2/3: 135 AC: 351	IC1/2/3: HR ≤ 0.609 AC: HR ≤ 0.735	p-value ≤ 0.0039
		Second interim	42	80%	IC1/2/3: 203 AC: 530	IC1/2/3: HR ≤ 0.725 AC: HR ≤ 0.820	p-value ≤ 0.0210
		Final	57	100%	IC1/2/3: 254 AC: 662	IC1/2/3: HR ≤ 0.774 AC: HR ≤ 0.853	p-value ≤ 0.0408
PFS is statistically significant in either IC1/2/3 or ITT, but not both, and the subsequent ORR is statistically significant	0.045	First interim	30	52%	IC1/2/3: 135 AC: 350	IC1/2/3: HR ≤ 0.602 AC: HR ≤ 0.729	p-value ≤ 0.0031
		Second interim	42	80%	IC1/2/3: 207 AC: 538	IC1/2/3: HR ≤ 0.724 AC: HR ≤ 0.819	p-value ≤ 0.0204
		Final	59	100%	IC1/2/3: 259 AC: 673	IC1/2/3: HR ≤ 0.773 AC: HR ≤ 0.852	p-value ≤ 0.0384

Different Scenarios of PFS and ORR Testing	Alpha Level	Analysis Timing	Time from 1st Patient Enrolled (months)	Information Fraction	No. of Events	Stopping Boundary in HR	Stopping Boundary in p-value
PFS is statistically significant in either IC1/2/3 or ITT, but not both ; ORR is not statistically significant	0.044	First interim	30	52%	IC1/2/3: 136 AC: 352	IC1/2/3: HR ≤ 0.601 AC: HR ≤ 0.729	p-value ≤ 0.003
		Second interim	43	80%	IC1/2/3: 209 AC: 542	IC1/2/3: HR ≤ 0.725 AC: HR ≤ 0.819	p-value ≤ 0.0200
		Final	59	100%	IC1/2/3: 261 AC: 677	IC1/2/3: HR ≤ 0.773 AC: HR ≤ 0.852	p-value ≤ 0.0376
PFS is not statistically significant in either IC1/2/3 or ITT	0.04	First interim	30	50%	IC1/2/3: 134 AC: 347	IC1/2/3: HR ≤ 0.586 AC: HR ≤ 0.718	p-value ≤ 0.002
		Second interim	44	80%	IC1/2/3: 214 AC: 554	IC1/2/3: HR ≤ 0.723 AC: HR ≤ 0.818	p-value ≤ 0.0179
		Final	62	100%	IC1/2/3:268 AC: 693	IC1/2/3: HR ≤ 0.772 AC: HR ≤ 0.851	p-value ≤ 0.0344

AC=all-comer; HR=Hazard Ratio; IC=tumor-infiltrating immune cell; ITT=intent-to-treat; ORR=objective response rate; PFS=progression-free survival.

Analysis population

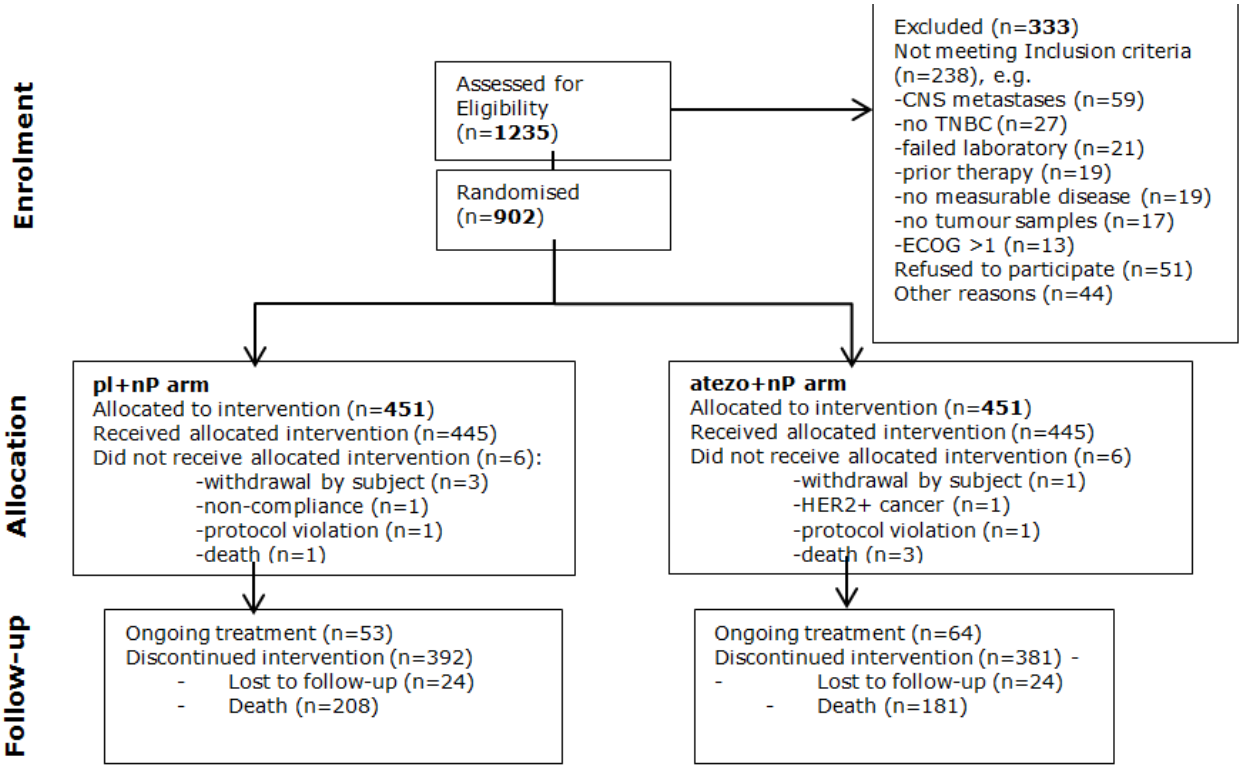
The analysis populations were defined as follows:

- The ITT population was defined as all randomized patients, whether or not the assigned study treatment was received.
- The PD-L1-selected subpopulation was defined as patients in the ITT population whose PD-L1 status is IC1/2/3 at the time of randomization.
- The ORR-evaluable population was defined as patients in the ITT population with measurable disease at baseline.
- The PD-L1-ORR-evaluable population was defined as patients in the PD-L1-selected subpopulation with measurable disease at baseline.
- The duration of response (DOR)-evaluable population was defined as patients with an objective response.
- The patient-reported outcome (PRO)-evaluable population was defined as patients in the ITT population with a baseline and ≥1 post-baseline PRO assessment.
- The safety-evaluable population was defined as patients who received any amount of any study drug.
- The pharmacokinetic (PK)-evaluable population was defined as all patients who received any dose of study medication and who have at least one post-baseline PK sample available.

For all efficacy analyses, patients were to be grouped according to the treatment assigned at randomization. Demographics, baseline disease characteristics and breast cancer history were to be compared between both treatment arms for the ITT population. Descriptive baseline summaries of continuous data were to present the group mean, standard deviation, median, ranges and inter-quartile ranges. Descriptive baseline summaries of discrete data were to present the category counts as frequencies and percentages.

Results

Participant flow



Baseline data

Table 11: Demographics and baseline characteristics (ITT population) – Impassion130

	Placebo + nab-Paclitaxel (N=451)	Atezolizumab + nab-Paclitaxel (N=451)	Total (N=902)
Age (yr)			
n	451	451	902
Mean (SD)	55.4 (12.1)	54.3 (12.3)	54.9 (12.2)
Median	56.0	55.0	55.0
25% and 75%-ile	47.0 - 65.0	46.0 - 64.0	46.0 - 64.0
Min - Max	26 - 86	20 - 82	20 - 86
Age Group (yr)			
n	451	451	902
18 - 40	51 (11.3%)	63 (14.0%)	114 (12.6%)
41 - 64	285 (63.2%)	284 (63.0%)	569 (63.1%)
>=65	115 (25.5%)	104 (23.1%)	219 (24.3%)
Sex			
n	451	451	902
Male	1 (0.2%)	3 (0.7%)	4 (0.4%)
Female	450 (99.8%)	448 (99.3%)	898 (99.6%)
Race			
n	451	451	902
White	301 (66.7%)	308 (68.3%)	609 (67.5%)
Asian	76 (16.9%)	85 (18.8%)	161 (17.8%)
Black or African American	33 (7.3%)	26 (5.8%)	59 (6.5%)
American Indian or Alaska Native	23 (5.1%)	17 (3.8%)	40 (4.4%)
Unknown	15 (3.3%)	12 (2.7%)	27 (3.0%)
Multiple	3 (0.7%)	2 (0.4%)	5 (0.6%)
Native Hawaiian or other Pacific Islander	0	1 (0.2%)	1 (0.1%)
Baseline Weight (kg)			
n	442	444	886
Mean (SD)	70.14 (17.79)	70.85 (17.21)	70.50 (17.50)
Median	67.25	68.05	67.85
25% and 75%-ile	58.00 - 78.80	59.00 - 79.00	58.60 - 79.00
Min - Max	38.4 - 189.6	37.9 - 162.0	37.9 - 189.6
Baseline Height (cm)			
n	429	425	854
Mean (SD)	161.27 (7.56)	161.37 (7.90)	161.32 (7.73)
Median	161.00	162.00	161.50
25% and 75%-ile	156.00 - 166.00	157.00 - 166.00	156.00 - 166.00
Min - Max	141.9 - 180.3	103.0 - 183.5	103.0 - 183.5
Baseline ECOG Performance Status			
n	450	450	900
0	270 (60.0%)	256 (56.9%)	526 (58.4%)
1	179 (39.8%)	193 (42.9%)	372 (41.3%)
2	1 (0.2%)	1 (0.2%)	2 (0.2%)

Table 12: Breast cancer history and disease characteristics (ITT population) – Impassion130

	Placebo + nab-Paclitaxel (N=451)	Atezolizumab + nab-Paclitaxel (N=451)	Total (N=902)
Prior Taxane Treatment (CRF)			
n	451	451	902
Yes	230 (51.0%)	231 (51.2%)	461 (51.1%)
No	221 (49.0%)	220 (48.8%)	441 (48.9%)
Presence of Liver Metastases (CRF)			
n	451	451	902
Yes	118 (26.2%)	126 (27.9%)	244 (27.1%)
No	333 (73.8%)	325 (72.1%)	658 (72.9%)
PD-L1 Status (lab)			
n	451	451	902
IC 0	267 (59.2%)	266 (59.0%)	533 (59.1%)
IC 1/2/3	184 (40.8%)	185 (41.0%)	369 (40.9%)
Brain Metastases			
n	451	451	902
Yes	31 (6.9%)	30 (6.7%)	61 (6.8%)
Unknown	420 (93.1%)	421 (93.3%)	841 (93.2%)
Nodal Only Disease			
n	449	450	899
Yes	23 (5.1%)	33 (7.3%)	56 (6.2%)
No	426 (94.9%)	417 (92.7%)	843 (93.8%)
Lung Metastases			
n	451	451	902
Yes	242 (53.7%)	226 (50.1%)	468 (51.9%)
No	209 (46.3%)	225 (49.9%)	434 (48.1%)
Bone Metastases			
n	451	451	902
Yes	141 (31.3%)	145 (32.2%)	286 (31.7%)
No	310 (68.7%)	306 (67.8%)	616 (68.3%)
Baseline Disease Status			
n	450	450	900
Locally Advanced Unresectable	42 (9.3%)	46 (10.2%)	88 (9.8%)
Metastatic	408 (90.7%)	404 (89.8%)	812 (90.2%)
Number of Sites			
n	449	450	899
0-3	341 (75.9%)	332 (73.8%)	673 (74.9%)
>3	108 (24.1%)	118 (26.2%)	226 (25.1%)
Prior Anthracycline Treatment			
n	451	451	902
Yes	242 (53.7%)	243 (53.9%)	485 (53.8%)
No	209 (46.3%)	208 (46.1%)	417 (46.2%)
Prior (neo)Adjuvant Chemotherapy			
n	451	451	902
Yes	286 (63.4%)	284 (63.0%)	570 (63.2%)
No	165 (36.6%)	167 (37.0%)	332 (36.8%)
Time from Initial Diagnosis Until Local Recurrence or Metastatic Disease (Years)			
n	448	447	895
Mean (SD)	2.75 (3.63)	2.38 (3.09)	2.57 (3.37)
Median	1.84	1.78	1.81
25% and 75%-ile	0.09 - 3.44	0.06 - 2.99	0.07 - 3.18
Min - Max	0.0 - 22.9	0.0 - 21.7	0.0 - 22.9

RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Table 13: Most commonly reported (≥10% in either treatment arm) concurrent medical conditions at baseline (ITT population) – Impassion130

	pl+nP N=451 n (%)	atezo+nP N=451 n (%)
Hypertension	139 (30.8%)	139 (30.8%)
Anxiety	54 (12.0%)	78 (17.3%)
Insomnia	63 (14.0%)	67 (14.9%)
Depression	51 (11.3%)	63 (14.0%)
Fatigue	51 (11.3%)	59 (13.1%)
Back pain	44 (9.8%)	56 (12.4%)
Cough	50 (11.1%)	55 (12.2%)
Hypothyroidism	60 (13.3%)	49 (10.9%)

Source: t_mh_CNCR_IT_17APR2018_29522.

Numbers analysed

A total of 902 patients (ITT) were randomised and of these 369 patients were PD-L1-positive and reflective of the target population (185 patients randomised to the atezo-arm).

Outcomes and estimation

Efficacy results were provided with clinical cut-off (17 April 2018) for the analyses which represents the protocol-defined final analysis of PFS and 1st interim analysis of OS. At the time of the primary analysis the median observation time was 12.9 months in both arms (80% events in the PD-L1 positive population).

Updated efficacy data were submitted with data cut-off 2 January 2019 which represent the second interim analysis for OS (55% events in the PD-L1-positive population).

Co-Primary endpoint – PFS by investigator

Final investigator-assessed PFS analysis (cut-off 17 April 2018)

Table 14: Summary of Investigator-Assessed PFS (ITT Population) - Impassion130 (cut-off 17 April 2018)

	Placebo + nab-Paclitaxel (N=451)		Atezolizumab + nab-Paclitaxel (N=451)
Patients with event (%)	378 (83.8%)		358 (79.4%)
Earliest contributing event			
Death	28		26
Disease Progression	350		332
Patients without event (%)	73 (16.2%)		93 (20.6%)
Time to event (months)			
Median	5.49		7.16
95% CI	(5.32, 5.59)		(5.59, 7.46)
25% and 75%-ile	2.46, 10.41		3.65, 11.27
Range	0.0* to 25.0*		0.0* to 29.7*
Stratified Analysis			
p-value (log-rank)		0.0025	
Hazard Ratio		0.80	
95% CI		(0.69, 0.92)	
Unstratified Analysis			
p-value (log-rank)		0.0036	
Hazard Ratio		0.81	
95% CI		(0.70, 0.93)	
One year duration			
Patients remaining at risk	57		77
Event Free Rate (%)	17.68		23.73
95% CI	(13.96, 21.40)		(19.55, 27.92)
Difference in Event Free Rate		-6.05	
95% CI		(-11.66, -0.45)	
p-value (Z-test)		0.0341	

* Censored value. ^ Censored and event.
Summaries of Progression-Free Survival (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: presence of liver metastases, prior taxane treatment and tumor PD-L1 status. Hazard ratios were estimated by Cox regression.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Table 15: Summary of Investigator-Assessed PFS (PD-L1-Positive Population) - Impassion130 (cut-off 17 April 2018)

	Placebo + nab-Paclitaxel (N=184)		Atezolizumab + nab-Paclitaxel (N=185)
Patients with event (%)	157 (85.3%)		138 (74.6%)
Earliest contributing event			
Death	13		7
Disease Progression	144		131
Patients without event (%)	27 (14.7%)		47 (25.4%)
Time to event (months)			
Median	4.96		7.46
95% CI	(3.81, 5.55)		(6.70, 9.23)
25% and 75%-ile	1.94, 9.03		3.58, 13.67
Range	0.0* to 25.0*		0.0* to 29.7*
Stratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.62	
95% CI		(0.49, 0.78)	
Unstratified Analysis			
p-value (log-rank)		0.0001	
Hazard Ratio		0.64	
95% CI		(0.51, 0.80)	
One year duration			
Patients remaining at risk	22		38
Event Free Rate (%)	16.37		29.14
95% CI	(10.78, 21.97)		(22.19, 36.10)
Difference in Event Free Rate		-12.77	
95% CI		(-21.70, -3.85)	
p-value (Z-test)		0.0050	

* Censored value. ^ Censored and event.
Summaries of Progression-Free Survival (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: presence of liver metastases and prior taxane treatment. Hazard ratios were estimated by Cox regression.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Table 16: Event-Free Rates for PFS - Impassion130 (cut-off 17 April 2018)

	ITT population		PD-L1 positive population	
	pl + nP	atezo + nP	pl + nP	atezo + nP
Month 6	42.7 (38.1, 47.4)	52.7 (48.0, 57.3)	36.0 (28.9, 43.1)	58.4 (51.2, 65.6)
Month 9	31.4 (27.0, 35.8)	40.0 (35.4, 44.6)	25.6 (19.1, 32.1)	44.0 (36.7, 51.3)
Month12	17.7 (14.0, 21.4)	23.7 (19.6, 27.9)	16.4 (10.8, 22.0)	29.1 (22.2, 36.1)

atezo = atezolizumab; ITT = intent-to-treat; nP = nab-paclitaxel; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; pl = placebo
Sources: t_ef_km_PFS_INV_IT_17APR2018; t_ef_km_PFS_INV_PDL1POS_IT_17APR2018_29522

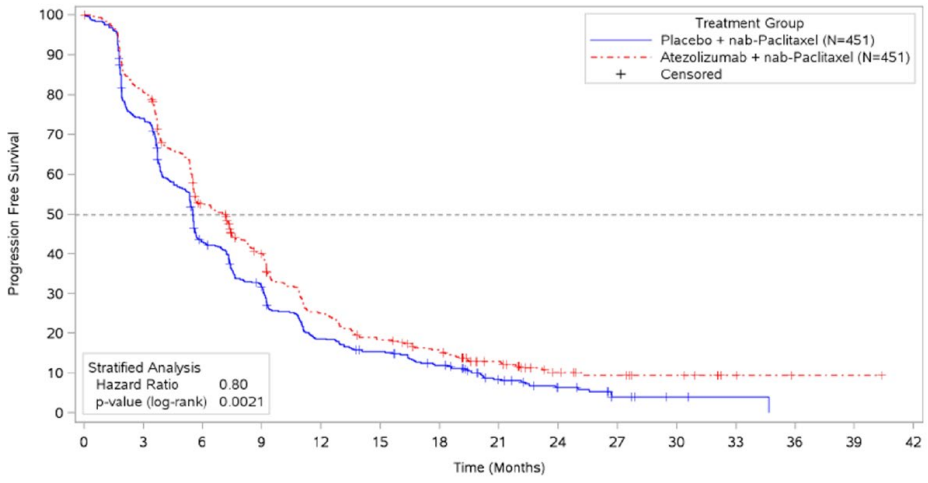
Updated investigator-assessed PFS analysis (cut-off 2 January 2019)

Table 17: Summary of investigator-assessed PFS (ITT population) – Impassion130 (cut-off 2 January 2019)

	Placebo + nab-Paclitaxel (N=451)		Atezolizumab + nab-Paclitaxel (N=451)
Patients with event (%)	404 (89.6%)		379 (84.0%)
Earliest contributing event			
Death	34		27
Disease Progression	370		352
Patients without event (%)	47 (10.4%)		72 (16.0%)
Time to event (months)			
Median	5.49		7.16
95% CI	(5.32, 5.62)		(5.55, 7.43)
25% and 75%-ile	2.46, 10.64		3.65, 11.86
Range	0.0* to 34.7		0.0* to 40.4*
Stratified Analysis			
p-value (log-rank)		0.0021	
Hazard Ratio		0.80	
95% CI		(0.69, 0.92)	
Unstratified Analysis			
p-value (log-rank)		0.0031	
Hazard Ratio		0.81	
95% CI		(0.70, 0.93)	
One year duration			
Patients remaining at risk	78		100
Event Free Rate (%)	18.67		24.73
95% CI	(14.97, 22.37)		(20.60, 28.86)
Difference in Event Free Rate		-6.06	
95% CI		(-11.61, -0.52)	
p-value (Z-test)		0.0321	

* Censored value. ^ Censored and event.
Summaries of Progression-Free Survival (median, percentiles) are Kaplan-Meier estimates.
95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: presence of liver metastases, prior taxane treatment and tumor PD-L1 status. Hazard ratios were estimated by Cox regression.
RAVE Data Snapshot Date: 13FEB2019. Data Cutoff Date: 02JAN2019.

Program: /opt/BIOSTAT/prod/cdpt3864/s29522a/t_ef_tte.sas
Output: /opt/BIOSTAT/prod/cdt3864a/129522a/reports/t ef tte PFS INV IT 02JAN2019 29522.out



Patients remaining at risk

Placebo	451	329	186	134	78	62	46	24	13	5	2	1	NE	NE	NE
Atezolizumab	451	361	227	165	100	73	58	37	17	11	8	3	1	1	NE

RAVE Data Snapshot Date: 13FEB2019. Data Cutoff Date: 02JAN2019.

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Figure 10: Kaplan-Meier plot of investigator assessed PFS (ITT population) – Impassion130 (cut-off 2 January 2019)

Table 18: Summary of investigator assessed PFS (PD-L1-positive population) – Impassion130 (cut-off 2 January 2019)

	Placebo + nab-Paclitaxel (N=184)		Atezolizumab + nab-Paclitaxel (N=185)
Patients with event (%)	163 (88.6%)		149 (80.5%)
Earliest contributing event			
Death	14		8
Disease Progression	149		141
Patients without event (%)	21 (11.4%)		36 (19.5%)
Time to event (months)			
Median	5.29		7.46
95% CI	(3.81, 5.55)		(6.70, 9.23)
25% and 75%-ile	1.94, 9.13		3.58, 13.93
Range	0.0* to 34.7		0.0* to 40.4*
Stratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.63	
95% CI		(0.50, 0.80)	
Unstratified Analysis			
p-value (log-rank)		0.0002	
Hazard Ratio		0.66	
95% CI		(0.53, 0.82)	
One year duration			
Patients remaining at risk	30		51
Event Free Rate (%)	17.32		30.31
95% CI	(11.71, 22.93)		(23.47, 37.15)
Difference in Event Free Rate		-12.99	
95% CI		(-21.84, -4.14)	
p-value (Z-test)		0.0040	

* Censored value. ^ Censored and event.
Summaries of Progression-Free Survival (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: presence of liver metastases and prior taxane treatment. Hazard ratios were estimated by Cox regression.
RAVE Data Snapshot Date: 13FEB2019. Data Cutoff Date: 02JAN2019.

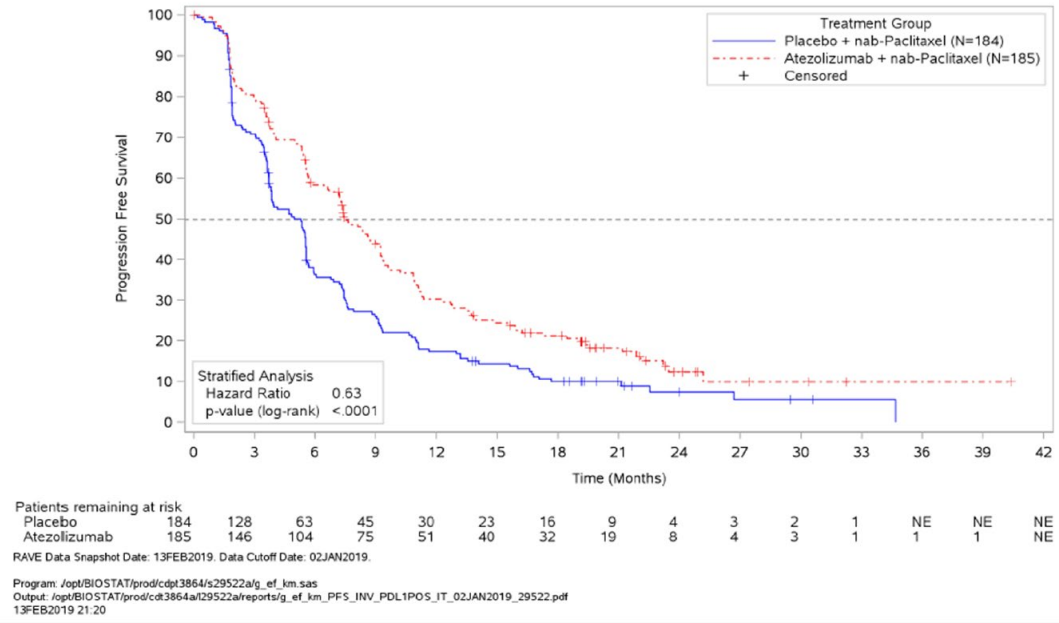


Figure 11: Kaplan-Meier Plot of investigator-assessed PFS (PD-L1–positive Population) - Impassion130 (cut-off 2 January 2019)

Co-Primary endpoint – OS

1st interim analysis of OS (cut-off 17 April 2018)

Table 19: Summary of overall survival (ITT population) - Impassion130 (cut-off 17 April 2018)

	Placebo + nab-Paclitaxel (N=451)		Atezolizumab + nab-Paclitaxel (N=451)
Patients with event (%)	208 (46.1%)		181 (40.1%)
Earliest contributing event			
Death	208		181
Patients without event (%)	243 (53.9%)		270 (59.9%)
Time to event (months)			
Median	17.58		21.26
95% CI	(15.93, 20.01)		(17.25, 23.43)
25% and 75%-ile	9.59, 30.26		10.94, 31.08
Range	0.0* to 33.2*		0.0* to 32.3*
Stratified Analysis			
p-value (log-rank)		0.0840	
Hazard Ratio		0.84	
95% CI		(0.69, 1.02)	
Unstratified Analysis			
p-value (log-rank)		0.0984	
Hazard Ratio		0.85	
95% CI		(0.69, 1.03)	
Two years duration			
Patients remaining at risk	27		26
Event Free Rate (%)	39.72		42.11
95% CI	(33.17, 46.27)		(34.29, 49.93)
Difference in Event Free Rate		-2.39	
95% CI		(-12.59, 7.81)	
p-value (Z-test)		0.6464	

* Censored value. ^ Censored and event.
Summaries of OS (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: presence of liver metastases, prior taxane treatment and tumor PD-L1 status. Hazard ratios were estimated by Cox regression.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Table 20: Summary of Overall Survival (PD-L1-Positive Population) - Impassion130 (cut-off 17 April 2018)

	Placebo + nab-Paclitaxel (N=184)		Atezolizumab + nab-Paclitaxel (N=185)
Patients with event (%)	88 (47.8%)		64 (34.6%)
Earliest contributing event			
Death	88		64
Patients without event (%)	96 (52.2%)		121 (65.4%)
Time to event (months)			
Median	15.47		25.03
95% CI	(13.14, 19.35)		(22.60, NE)
25% and 75%-ile	8.90, 28.65		12.09, 31.08
Range	0.1* to 29.5*		0.0* to 32.3*
Stratified Analysis			
p-value (log-rank)		0.0035	
Hazard Ratio		0.62	
95% CI		(0.45, 0.86)	
Unstratified Analysis			
p-value (log-rank)		0.0041	
Hazard Ratio		0.62	
95% CI		(0.45, 0.86)	
Two years duration			
Patients remaining at risk	13		15
Event Free Rate (%)	36.60		53.46
95% CI	(26.45, 46.75)		(42.29, 64.62)
Difference in Event Free Rate		-16.85	
95% CI		(-31.94, -1.77)	
p-value (Z-test)		0.0285	

* Censored value. ^ Censored and event.
Summaries of Overall Survival (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: presence of liver metastases and prior taxane treatment. Hazard ratios were estimated by Cox regression.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Table 21: Event-Free Rates for OS - Impassion130 (cut-off 17 April 2018)

	ITT population		PD-L1 positive population	
	pl + nP	atezo + nP	pl + nP	atezo + nP
Month 6	86.4 (83.3, 89.6)	89.0 (86.0, 91.9)	84.0 (78.7, 89.4)	89.0 (84.5, 93.6)
Month 12	67.7 (63.2, 72.1)	71.9 (67.7, 76.2)	64.0 (56.8, 71.3)	75.4 (69.0, 81.7)
Month 18	48.6 (43.0, 54.2)	54.0 (48.4, 59.8)	43.9 (34.7, 53.2)	59.4 (50.5, 68.2)
Month 24	39.7 (33.2, 46.3)	42.1 (34.3, 49.9)	36.6 (26.4, 46.8)	53.5 (42.3, 64.6)

atezo = atezolizumab; nP = nab-paclitaxel; OS = overall survival; PD-L1 = programmed death-ligand 1; ITT = intent-to-treat; pl = placebo
Sources: t_ef_km_OS_IT_17APR2018_29522; t_ef_km_OS_PDL1POS_IT_17APR2018_29522

Updated OS analysis (cut-off 2 January 2019)

Table 22: Summary of overall survival (ITT population) - Impassion130 (cut-off 2 January 2019)

	Placebo + nab-Paclitaxel (N=451)		Atezolizumab + nab-Paclitaxel (N=451)
Patients with event (%)	279 (61.9%)		255 (56.5%)
Earliest contributing event			
Death	279		255
Patients without event (%)	172 (38.1%)		196 (43.5%)
Time to event (months)			
Median	18.73		20.99
95% CI	(16.85, 20.30)		(19.02, 22.60)
25% and 75%-ile	9.59, 33.68		10.97, 33.48
Range	0.0* to 41.3*		0.0* to 40.8*
Stratified Analysis			
p-value (log-rank)		0.0777	
Hazard Ratio		0.86	
95% CI		(0.72, 1.02)	
Unstratified Analysis			
p-value (log-rank)		0.0823	
Hazard Ratio		0.86	
95% CI		(0.73, 1.02)	
Two years duration			
Patients remaining at risk	87		88
Event Free Rate (%)	38.67		42.35
95% CI	(33.74, 43.60)		(37.29, 47.42)
Difference in Event Free Rate		-3.69	
95% CI		(-10.75, 3.38)	
p-value (Z-test)		0.3068	

* Censored value. ^ Censored and event.
Summaries of OS (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: presence of liver metastases, prior taxane treatment and tumor PD-L1 status. Hazard ratios were estimated by Cox regression.
RAVE Data Snapshot Date: 13FEB2019. Data Cutoff Date: 02JAN2019.

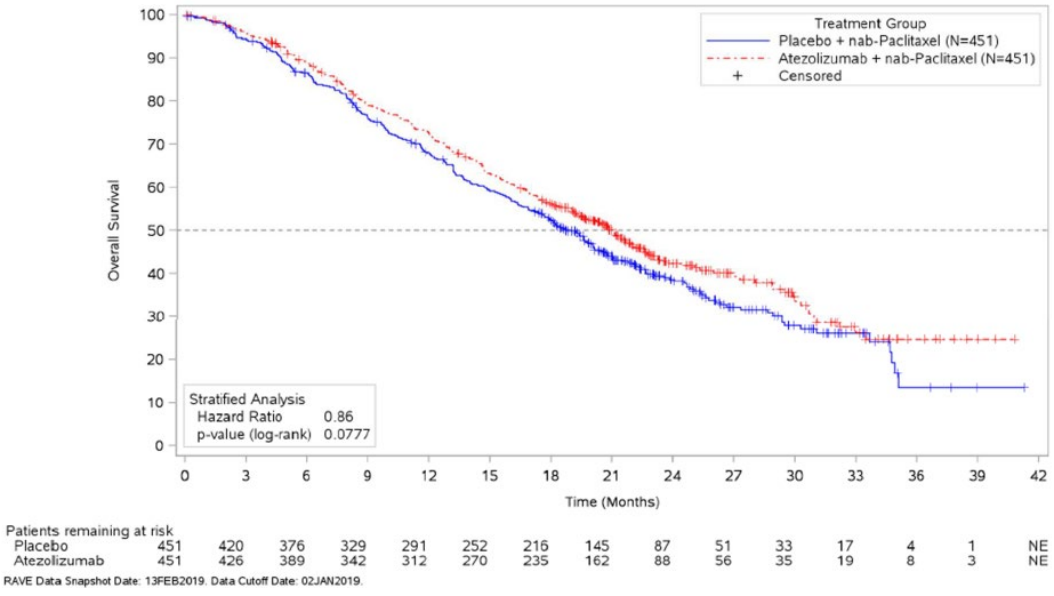


Figure 12: Kaplan-Meier plot of overall survival (ITT population) - Impassion130 (cut-off 2 January 2019)

Table 23: Summary of overall survival (PD-L1-positive population) - Impassion130 (cut-off 2 January 2019)

	Placebo + nab-Paclitaxel (N=184)		Atezolizumab + nab-Paclitaxel (N=185)
Patients with event (%)	110 (59.8%)		94 (50.8%)
Earliest contributing event			
Death	110		94
Patients without event (%)	74 (40.2%)		91 (49.2%)
Time to event (months)			
Median	17.97		25.03
95% CI	(13.63, 20.07)		(19.55, 30.65)
25% and 75%-ile	8.90, 34.76		12.16, NE
Range	0.1* to 37.7*		0.0* to 40.8*
Stratified Analysis			
p-value (log-rank)		0.0133	
Hazard Ratio		0.71	
95% CI		(0.54, 0.93)	
Unstratified Analysis			
p-value (log-rank)		0.0154	
Hazard Ratio		0.71	
95% CI		(0.54, 0.94)	
Two years duration			
Patients remaining at risk	26		43
Event Free Rate (%)	36.90		50.70
95% CI	(28.96, 44.85)		(42.89, 58.52)
Difference in Event Free Rate		-13.80	
95% CI		(-24.94, -2.66)	
p-value (Z-test)		0.0152	

* Censored value. ^ Censored and event.
Summaries of Overall Survival (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: presence of liver metastases and prior taxane treatment. Hazard ratios were estimated by Cox regression.
RAVE Data Snapshot Date: 13FEB2019. Data Cutoff Date: 02JAN2019.

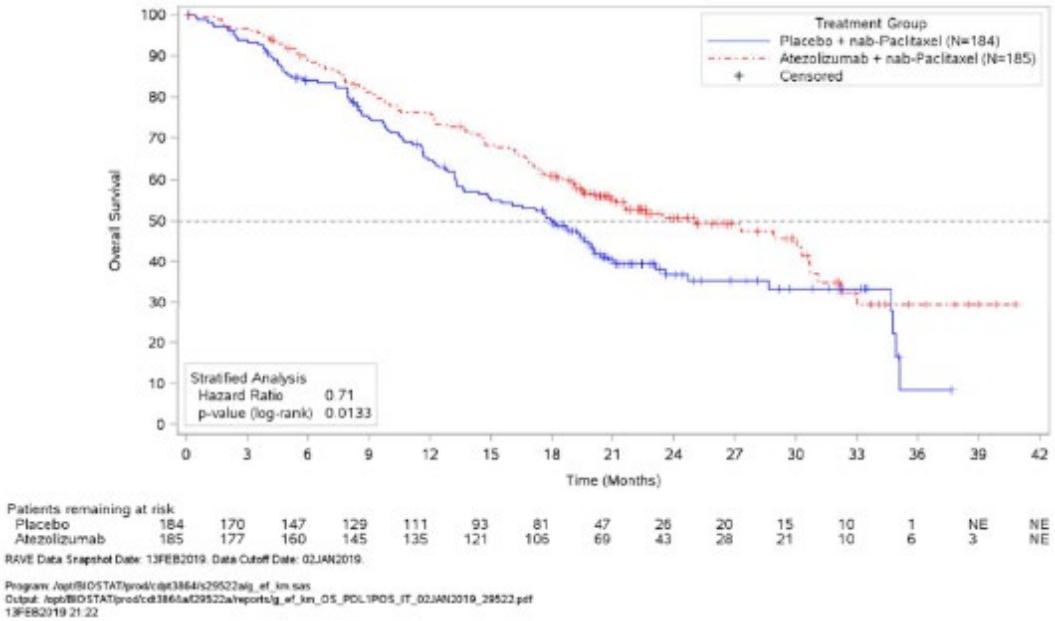


Figure 13: Kaplan-Meier plot of overall survival (PD-L1-positive population) - Impassion130 (cut-off 2 January 2019)

<u>Secondary endpoint – ORR</u>

Table 24: Summary of investigator-assessed ORR (PD-L1-positive response evaluable population) -Impassion130 (cut-off 17 April 2018)

	Placebo + nab-Paclitaxel (N=183)		Atezolizumab + nab-Paclitaxel (N=185)
Responders	78 (42.6%)		109 (58.9%)
95% CI	(35.36, 50.13)		(51.46, 66.08)
Stratified Analysis			
Difference in Overall Response Rates (95% CI)		16.30 (5.67, 26.92)	
p-value (Cochran-Mantel-Haenszel)		0.0016	
Odds Ratio for Overall Response (95% CI)		1.96 (1.29, 2.98)	
Complete Response (CR)	2 (1.1%)		19 (10.3%)
95% CI	(0.13, 3.89)		(6.30, 15.57)
Partial Response (PR)	76 (41.5%)		90 (48.6%)
95% CI	(34.31, 49.03)		(41.25, 56.09)
Stable Disease (SD)	49 (26.8%)		38 (20.5%)
95% CI	(20.51, 33.81)		(14.96, 27.09)
Progressive Disease (PD)	46 (25.1%)		31 (16.8%)
95% CI	(19.03, 32.07)		(11.68, 22.93)
Not Evaluable	2 (1.1%)		0
Missing	8 (4.4%)		7 (3.8%)

95% CI for rates were constructed using Clopper-Pearson method. 95% CI for difference in rates were constructed using normal approximation to the binomial distribution. 95% CI for odds ratio was constructed using the Wald method. Patients were classified as "Stable Disease" if assessment was at least 7 weeks from baseline. Patients were classified as missing or unevaluable if no post-baseline response assessments were available or all post-baseline response baseline assessments were unevaluable.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Table 25: Clinical benefit rates (investigator), PD-L1-selected patients, Response-evaluable population (investigator) -Impassion130 (cut-off 17 April 2018)

	Placebo + nab-Paclitaxel (N=183)		Atezolizumab + nab-Paclitaxel (N=185)
Responders	70 (38.3%)		109 (58.9%)
95% CI	(31.18, 45.71)		(51.46, 66.08)
Stratified Analysis			
Difference in Overall Response Rates (95% CI)		20.67 (10.13, 31.20)	
p-value (Cochran-Mantel-Haenszel)		<.0001	
Odds Ratio for Overall Response (95% CI)		2.35 (1.54, 3.59)	

95% CI for rates were constructed using Clopper-Pearson method. 95% CI for difference in rates were constructed using normal approximation to the binomial distribution. 95% CI for odds ratio was constructed using the Wald method. Clinical benefit rate (CBR) is defined using confirmed rates of CR+PR+SD>6 months.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Secondary endpoint – DOR

Table 26: Investigator-assessed duration of response (PD-L1-positive population) - Impassion130 (cut-off 17 April 2019)

	Placebo + nab-Paclitaxel (N=78)	Atezolizumab + nab-Paclitaxel (N=109)
Responders with subsequent event (%)	59 (75.6%)	70 (64.2%)
Earliest contributing event		
Death	2	0
Disease Progression	57	70
Responders without subsequent event (%)	19 (24.4%)	39 (35.8%)
Duration of response (months)		
Median	5.49	8.48
95% CI	(3.71, 7.13)	(7.33, 9.66)
25% and 75%-ile	3.12, 12.19	5.13, 16.46
Range	0.0* to 20.8*	1.7 to 28.1*
Unstratified Analysis		
p-value (log-rank)	0.0047	
Hazard Ratio	0.60	
95% CI	(0.43, 0.86)	

* Censored value. ^ Censored and event.
Summaries of DOR (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios was estimated by Cox regression.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Table 27: Investigator-assessed duration of response (PD-L1-positive population) - Impassion130 (cut-off 2 January 2019)

	Placebo + nab-Paclitaxel (N=77)	Atezolizumab + nab-Paclitaxel (N=109)
Responders with subsequent event (%)	63 (81.8%)	79 (72.5%)
Earliest contributing event		
Death	2	0
Disease Progression	61	79
Responders without subsequent event (%)	14 (18.2%)	30 (27.5%)
Duration of response (months)		
Median	5.52	8.48
95% CI	(3.75, 7.13)	(7.33, 10.22)
25% and 75%-ile	3.12, 12.91	5.13, 19.94
Range	0.0* to 29.0*	1.7 to 38.8*
Unstratified Analysis		
p-value (log-rank)	0.0044	
Hazard Ratio	0.62	
95% CI	(0.44, 0.86)	

* Censored value. ^ Censored and event.
Summaries of DOR (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios was estimated by Cox regression.
RAVE Data Snapshot Date: 13FEB2019. Data Cutoff Date: 02JAN2019.

Secondary endpoint – time to deterioration of HR-QOL

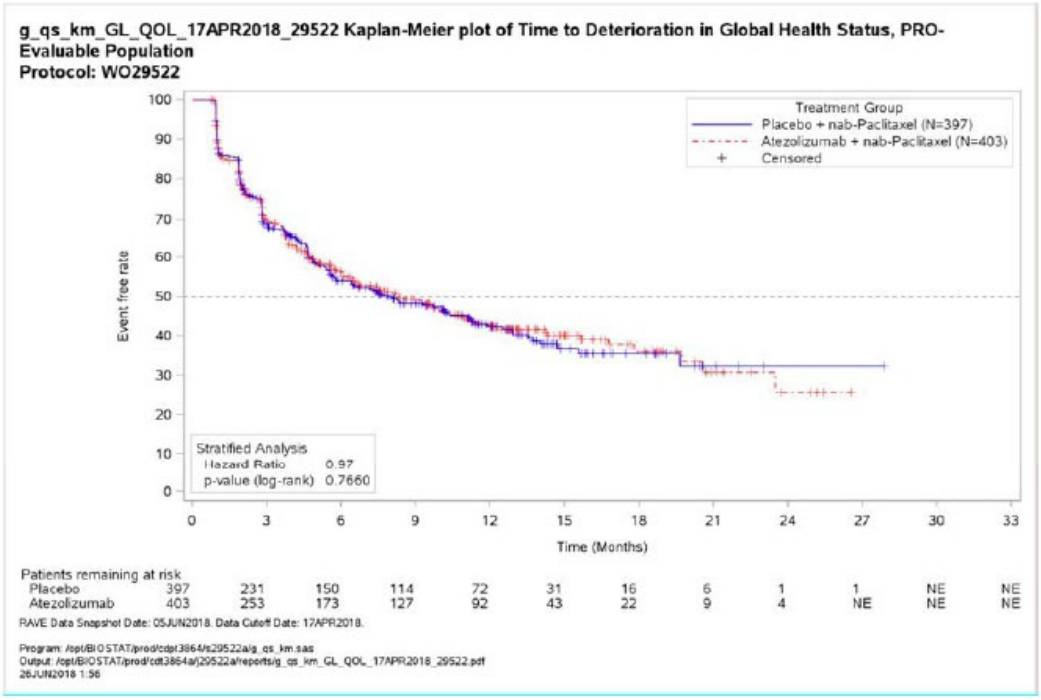


Figure 14: Kaplan-Meier plot of time to deterioration in Global Health status (PRO-evaluable population) - Impassion130 (cut-off 17 April 2018)

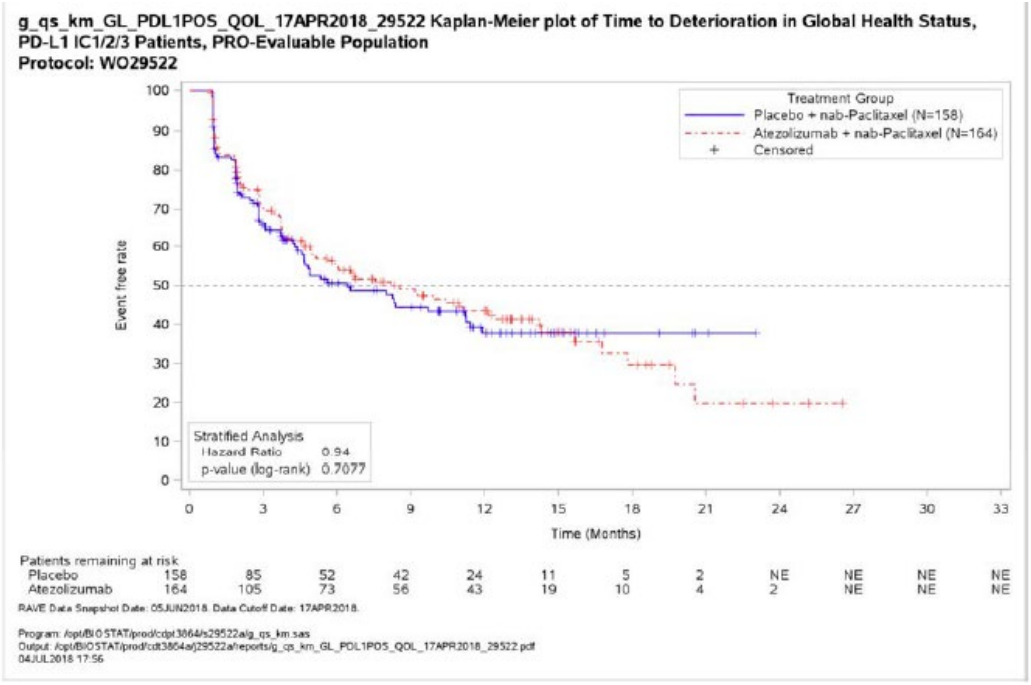


Figure 15: Kaplan-Meier plot of TTD in Global Health status (PRO-evaluable population PD-L1-population) - Impassion130 (cut-off 17 April 2018)

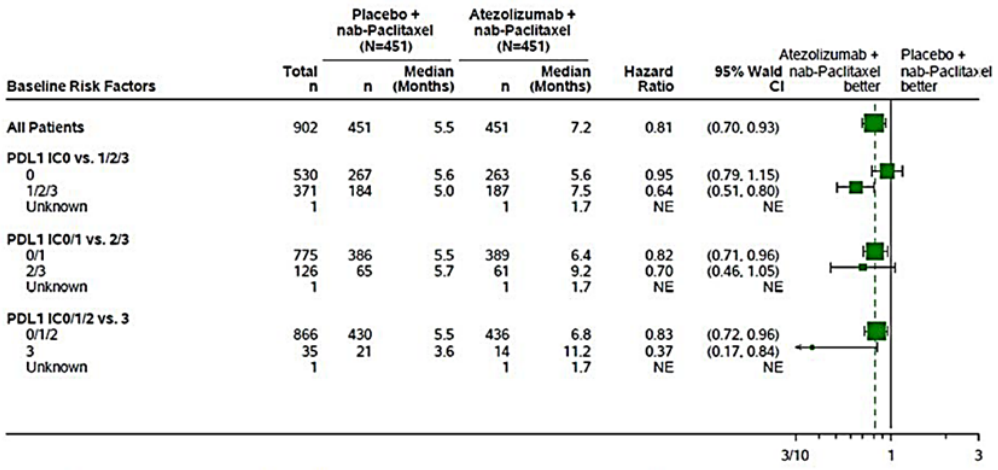
Ancillary analyses

Subgroup analyses

PD-L1 subgroups

PFS

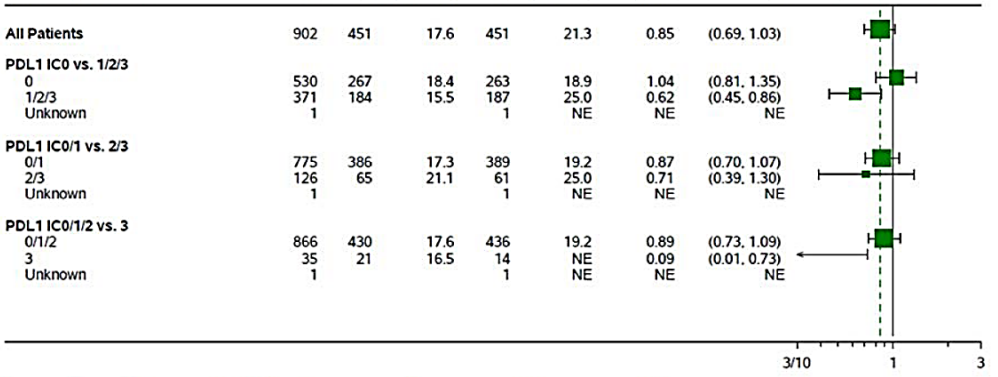
Baseline Risk Factors	Total n	Placebo + nab-Paclitaxel (N=451) n	Median (Months)	Atezolizumab + nab-Paclitaxel (N=451) n	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	902	451	5.5	451	7.2	0.81	(0.70, 0.93)
PDL1 IC0 vs. 1/2/3							
0	530	267	5.6	263	5.6	0.95	(0.79, 1.15)
1/2/3	371	184	5.0	187	7.5	0.64	(0.51, 0.80)
Unknown	1			1	1.7	NE	NE
PDL1 IC0/1 vs. 2/3							
0/1	775	386	5.5	389	6.4	0.82	(0.71, 0.96)
2/3	126	65	5.7	61	9.2	0.70	(0.46, 1.05)
Unknown	1			1	1.7	NE	NE
PDL1 IC0/1/2 vs. 3							
0/1/2	866	430	5.5	436	6.8	0.83	(0.72, 0.96)
3	35	21	3.6	14	11.2	0.37	(0.17, 0.84)
Unknown	1			1	1.7	NE	NE



Hazard ratios and the associated Wald confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.
Program: /opt/BIOSTAT/prod/cdpt3864/s29522a/g_ef_fp_biom.sas
Output: /opt/BIOSTAT/prod/cdt3864a/j29522a/reports/g_ef_fp_biom_PFS_INV_IT_17APR2018_29522.pdf 24AUG2018 9:48

OS

Baseline Risk Factors	Total n	Placebo + nab-Paclitaxel (N=451) n	Median (Months)	Atezolizumab + nab-Paclitaxel (N=451) n	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	902	451	17.6	451	21.3	0.85	(0.69, 1.03)
PDL1 IC0 vs. 1/2/3							
0	530	267	18.4	263	18.9	1.04	(0.81, 1.35)
1/2/3	371	184	15.5	187	25.0	0.62	(0.45, 0.86)
Unknown	1			1	NE	NE	NE
PDL1 IC0/1 vs. 2/3							
0/1	775	386	17.3	389	19.2	0.87	(0.70, 1.07)
2/3	126	65	21.1	61	25.0	0.71	(0.39, 1.30)
Unknown	1			1	NE	NE	NE
PDL1 IC0/1/2 vs. 3							
0/1/2	866	430	17.6	436	19.2	0.89	(0.73, 1.09)
3	35	21	16.5	14	NE	0.09	(0.01, 0.73)
Unknown	1			1	NE	NE	NE



Hazard ratios and the associated Wald confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.
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Figure 16: Forest plot of PFS (investigator assessed) and OS by PD-L1 subgroups - Impassion130 (cut-off 17 April 2018)

KM curves for PD-L1 subgroup IC0 for PFS and OS

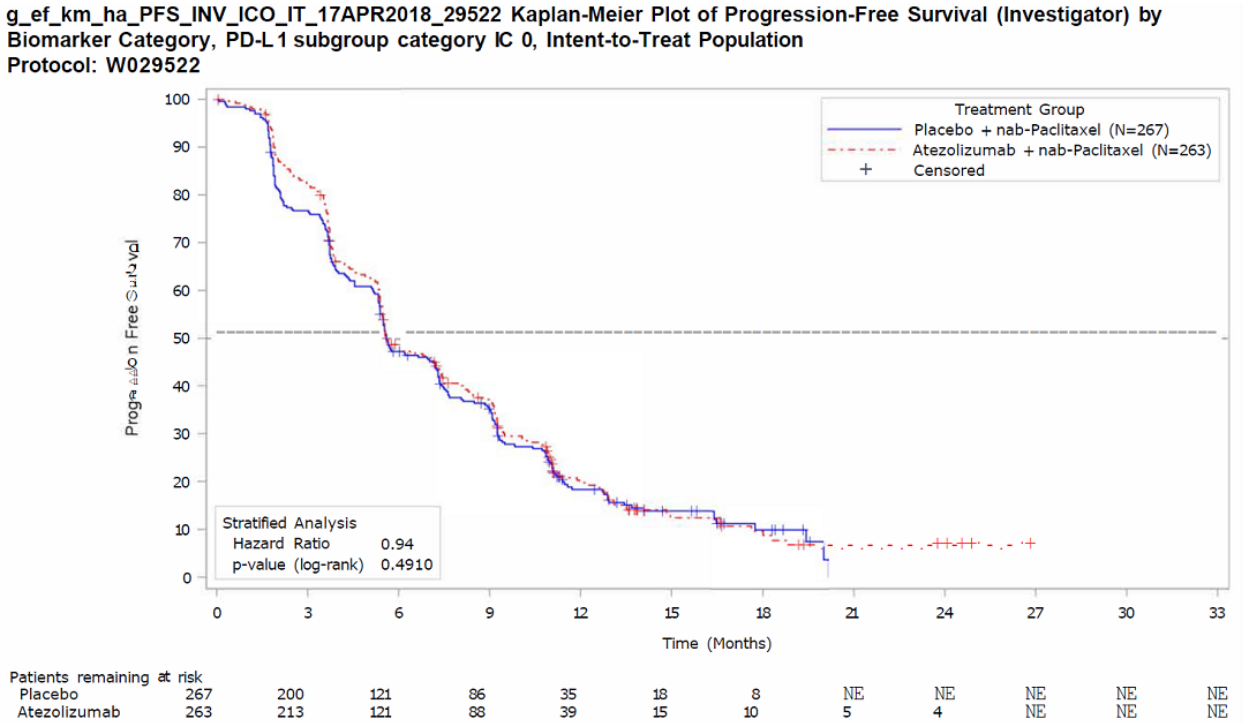


Figure 17: Kaplan-Meier plot of PFS (investigator) by biomarker category, PD-L1 subgroup category IC0, ITT population - Impassion130 (cut-off 17 April 2018)

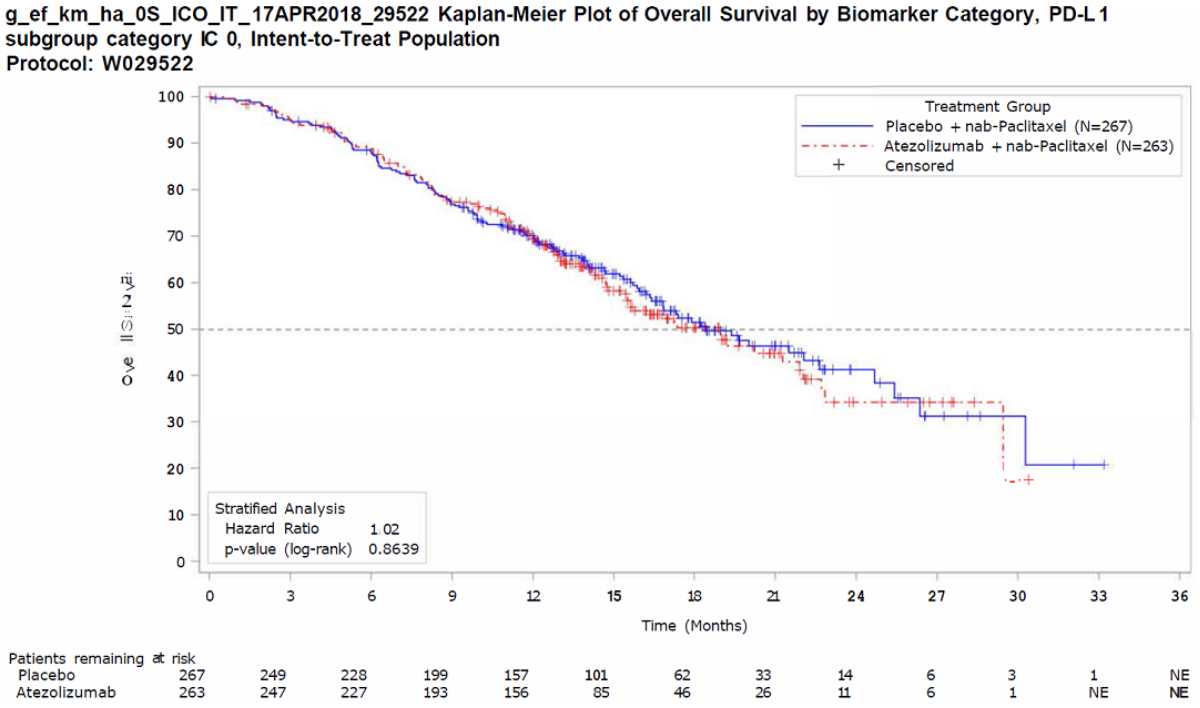


Figure 18: Kaplan-Meier plot of OS by biomarker category, PD-L1 subgroup category IC0, ITT population - Impassion130 (cut-off 17 April 2018)

Table 28: Prevalence of PD-L1 IC Subgroups - Impassion130

PD-L1 Expression Level	Prevalence
IC<1% (IC0)	59% (533/902)

IC≥1% and <5% (IC1)	27% (243/902) [a]		41% (369/902)
IC≥5 and <10% (IC2)	10% (91/902)	14% (126/902) [b]	
IC ≥10% (IC3)	4% (35/902)		

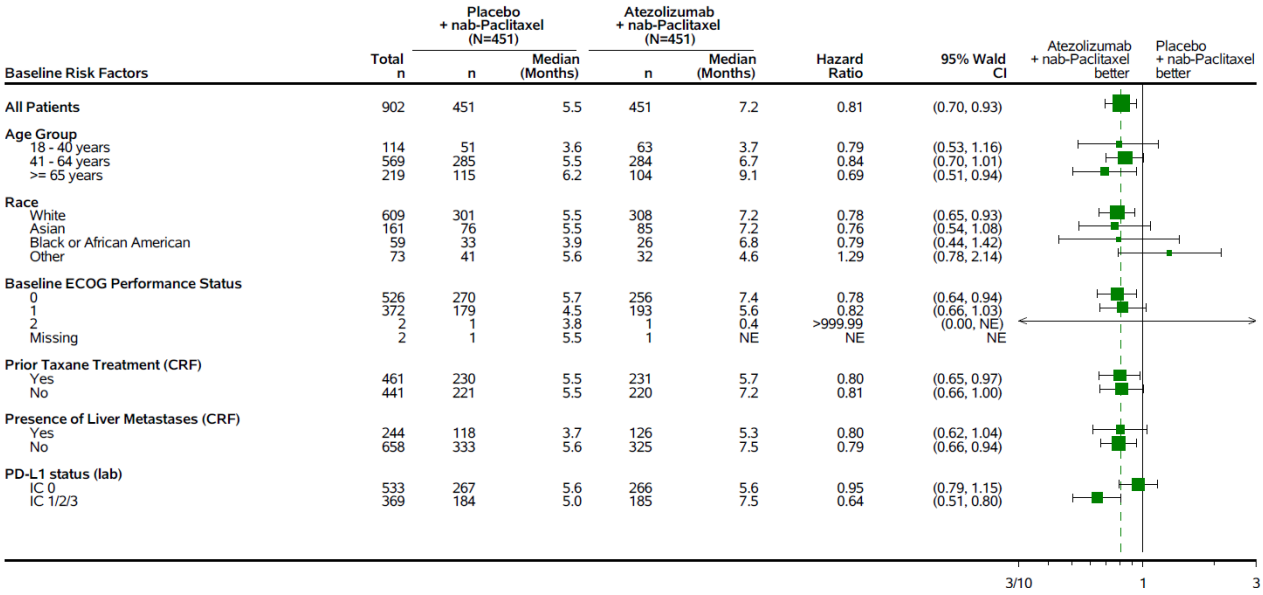
IC = immune cells; PD-L1 = programmed death-ligand 1

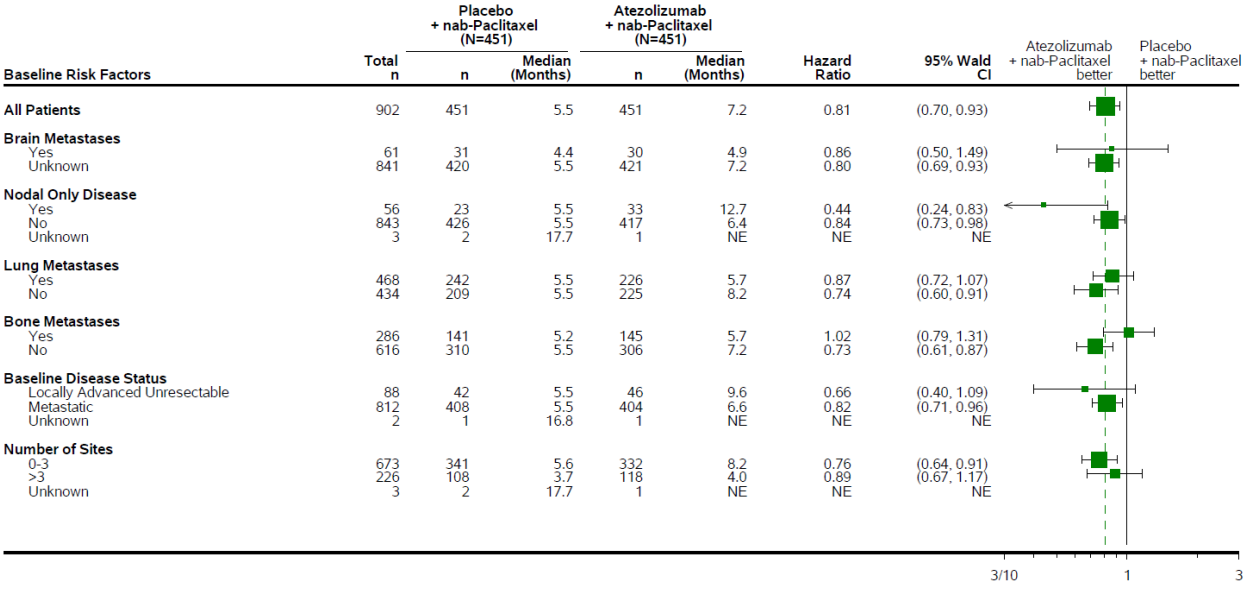
[a] "PD-L1 positive low"

[b] "PD-L1 positive high"

Baseline demographic and disease characteristics

Subgroup analyses of efficacy (PFS and OS) across subgroups defined by baseline demographic and disease characteristics are shown below (cut off 17 April 2018).





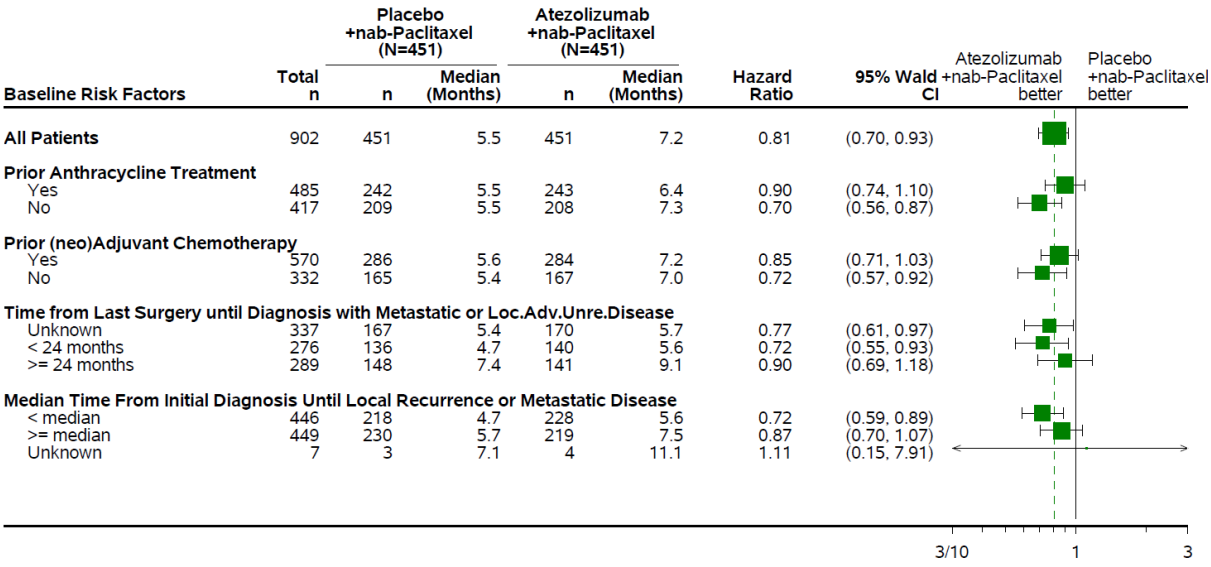
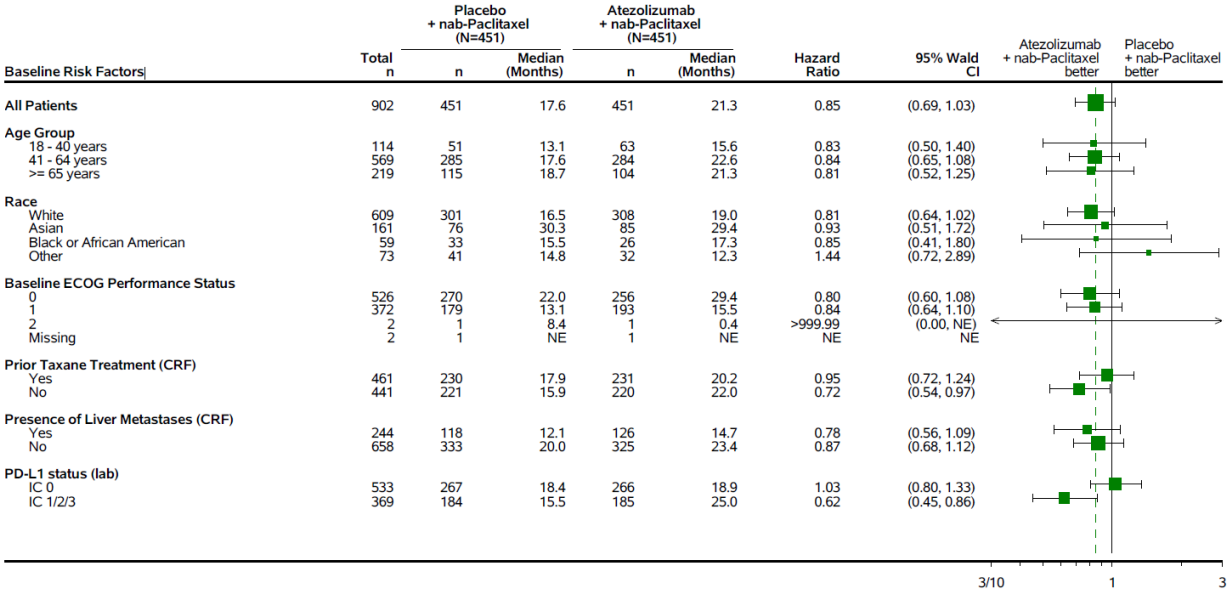
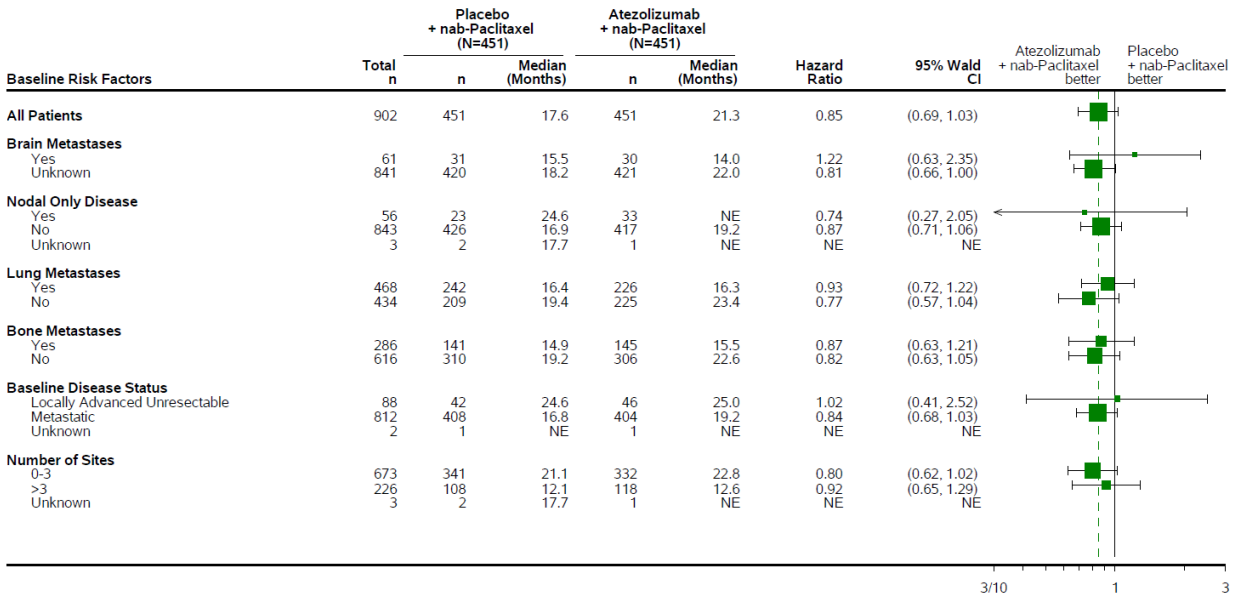


Figure 19: Forest Plot of Hazard Ratio for Progression-Free Survival (Investigator) by Subgroup, ITT - Impassion130 (cut off 17 April 2018)





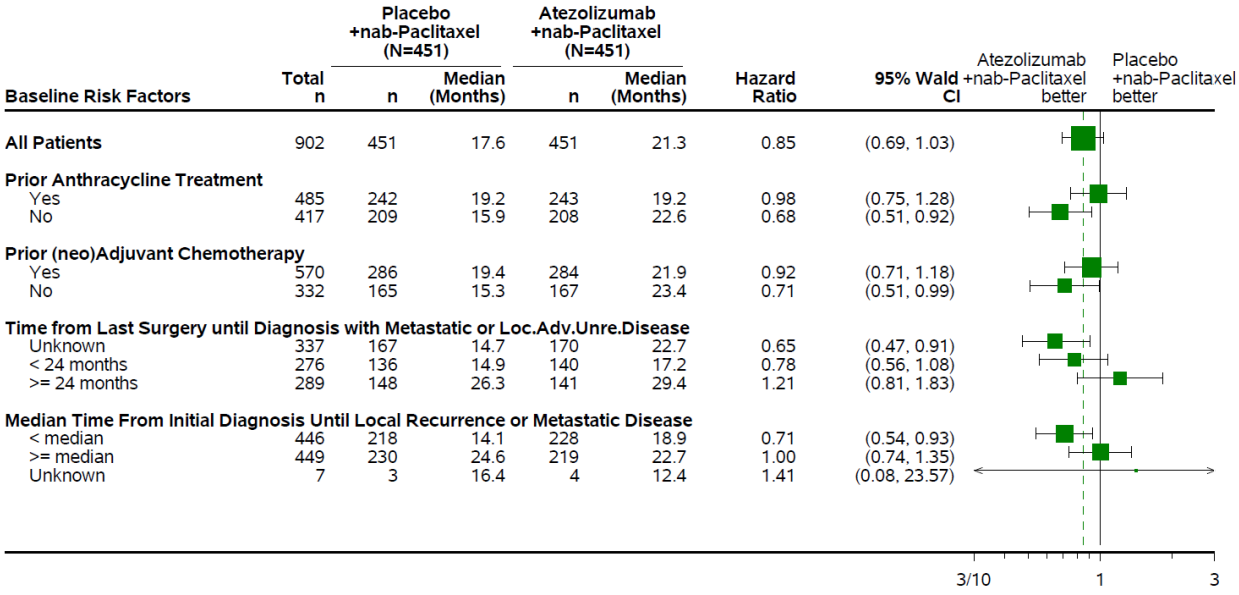


Figure 20: Forest Plot of Hazard Ratio for Overall Survival by Subgroup, Intent-to-Treat Population - Impassion130 (cut off 17 April 2018)

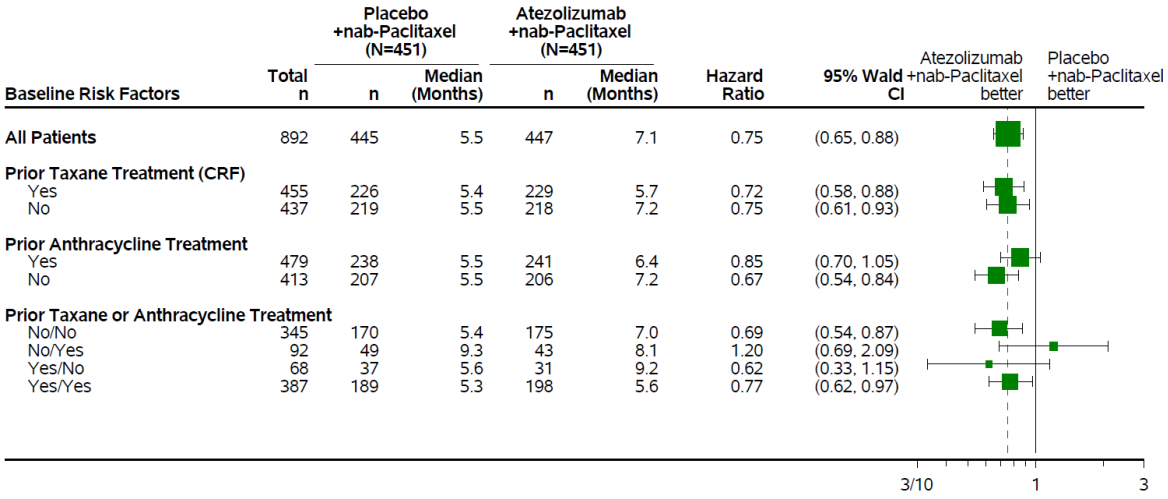
Table 29: Efficacy in subjects with prior (neo) adjuvant chemotherapy and brain metastasis - Impassion130 (cut off 17 April 2018)

Subgroups	n	**PFS** HR (95% CI)	**OS** HR (95% CI)

Prior taxane			
ITT	461	0.80 (0.65, 0.97)	0.95 (0.72, 1.24)
PD-L1+-pop.	190	0.74 (0.54, 1.01)	0.89 (0.58, 1.37)
Prior anthracycline			
ITT	485	0.90 (0.74, 1.10)	0.98 (0.75, 1.28)
PD-L1+-pop	210	0.82 (0.60, 1.11)	0.85 (0.56, 1.29)
Prior (neo)adj. therapy			
ITT	570	0.85 (0.71; 1.03)	0.92 (0.71; 1.18)
PD-L1+-pop.	242	0.76 (0.57; 1.01)	0.74 (0.5; 1.10)
Brain metastases			
ITT	61	0.86 (0.50, 1.49)	1.22 (0.63, 2.35)
PD-L1+-pop	26	1.4 (0.57, 3.44)	2.0 (0.63, 6.39)

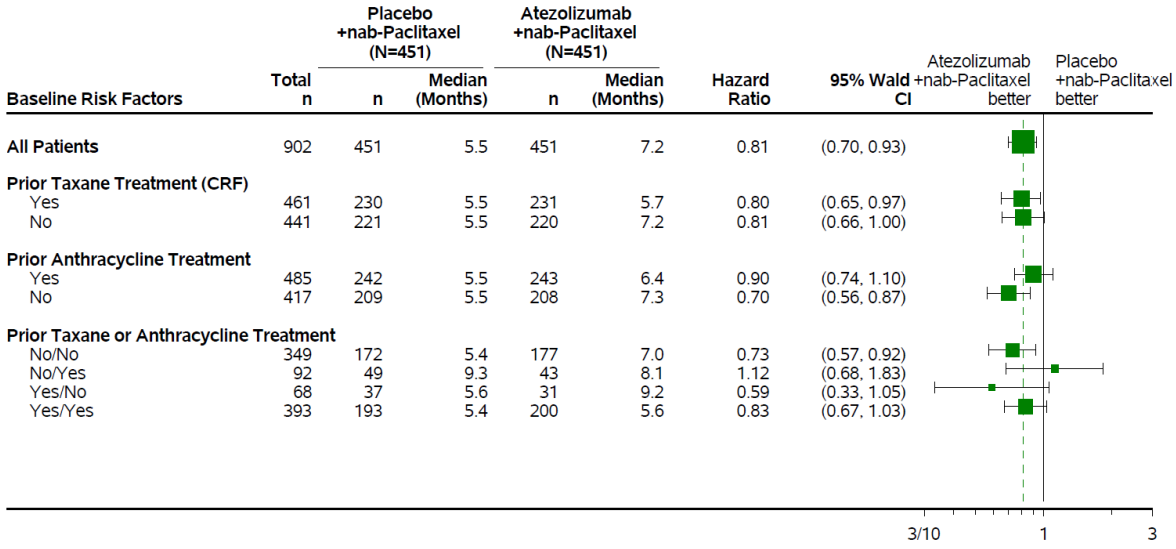
Adjusted Analyses

ITT Population (all)



Hazard ratios and the associated Wald confidence intervals were estimated using unstratified Cox regression adjusted for log sum of diameters at baseline, presence of liver metastases, age, ECOG performance status, race group, number of sites and time from initial diagnosis to Metast/LA diagnosis (years).
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

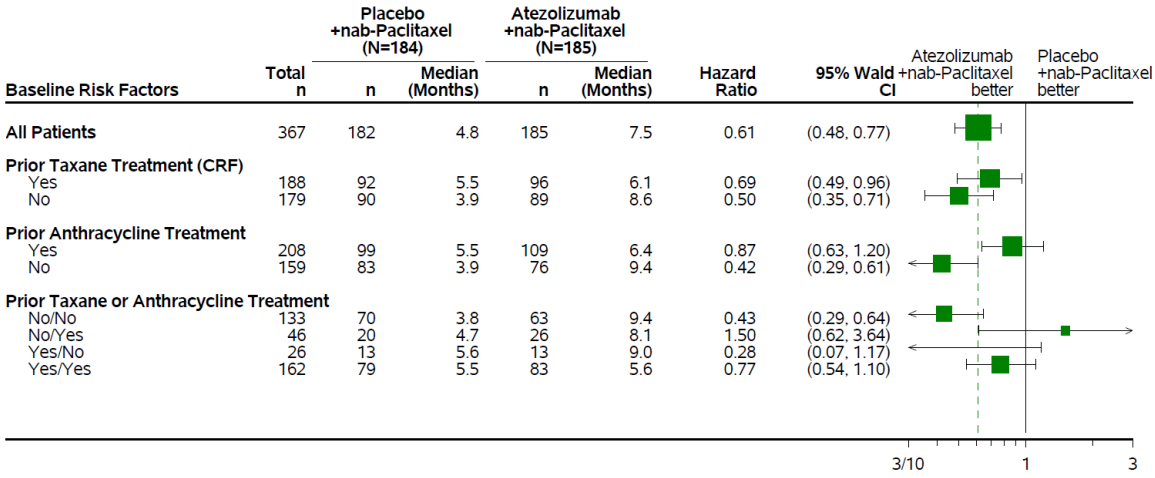
Figure 21: Forest Plot of HR for PFS (Investigator) by Taxane and Anthracycline Subgroup, ITT Population - Impassion130 (cut off 17 April 2018)



Hazard ratios and the associated Wald confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

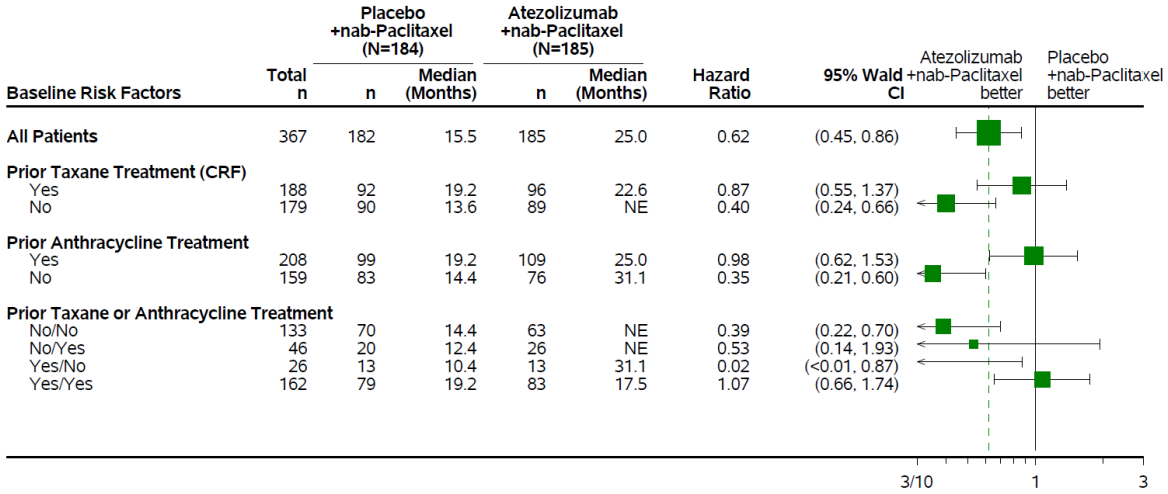
Figure 22: Forest Plot of HR for OS by Taxane and Anthracycline Subgroup, ITT Population - Impassion130 (cut off 17 April 2018)

PD-L1 positive population



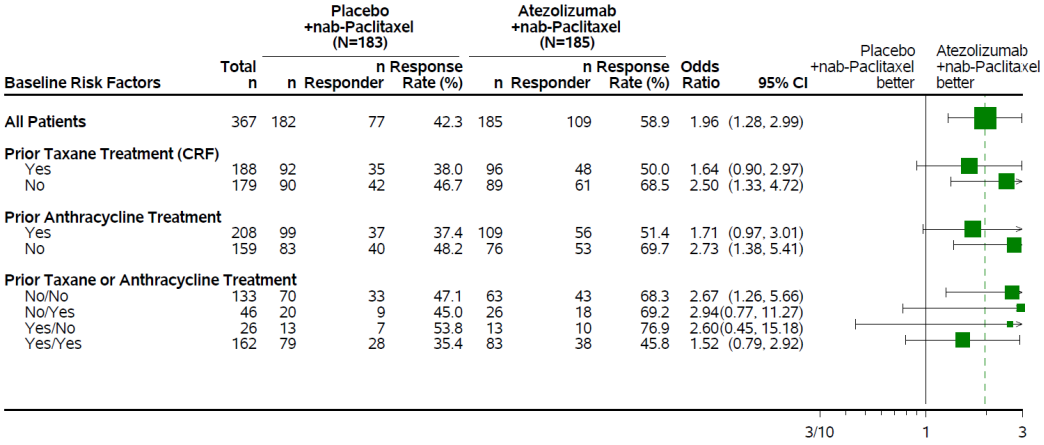
Hazard ratios and the associated Wald confidence intervals were estimated using unstratified Cox regression adjusted for log sum of diameters at baseline, presence of liver metastases, age, ECOG performance status, race group, number of sites and time from initial diagnosis to Metast/LA diagnosis (years).
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Figure 23: Forest Plot of HR for PFS (Investigator) by Taxane and Anthracycline Subgroup, PD-L1 pos. patients - Impassion130 (cut off 17 April 2018)



Hazard ratios and the associated Wald confidence intervals were estimated using unstratified Cox regression adjusted for log sum of diameters at baseline, presence of liver metastases, age, ECOG performance status, race group, number of sites and time from initial diagnosis to Metast/LA diagnosis (years).
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Figure 24: Forest Plot of HR for OS by Taxane and Anthracycline Subgroup, PD-L1 positive patients - Impassion130 (cut off 17 April 2018)



Odds ratios and the associated Wald confidence intervals were estimated using unstratified logistic regression adjusted for log sum of diameters at baseline, presence of liver metastases and time from initial diagnosis to Metast/LA diagnosis (years).
The vertical dashed line indicates the odds ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Figure 25: Forest Plot of Odds Ratio for Best ORR (Investigator) by Taxane and Anthracycline Subgroup, PD-L1 positive patients, Response-Evaluable Population (Investigator) - Impassion130 (cut off 17 April 2018)

KM curves for PD-L1 positive patients

- **Prior taxane**

PFS (prior taxane vs. no prior taxane)

g_ef_km_PFS_INV_PRTAX_PDL1POS_IT_17APR2018_29522 Kaplan-Meier Plot of Progression-Free Survival (Investigator), Prior Taxane Patients, PD-L1 IC1/2/3 Patients, Intent-to-Treat Population
Protocol: WO29522

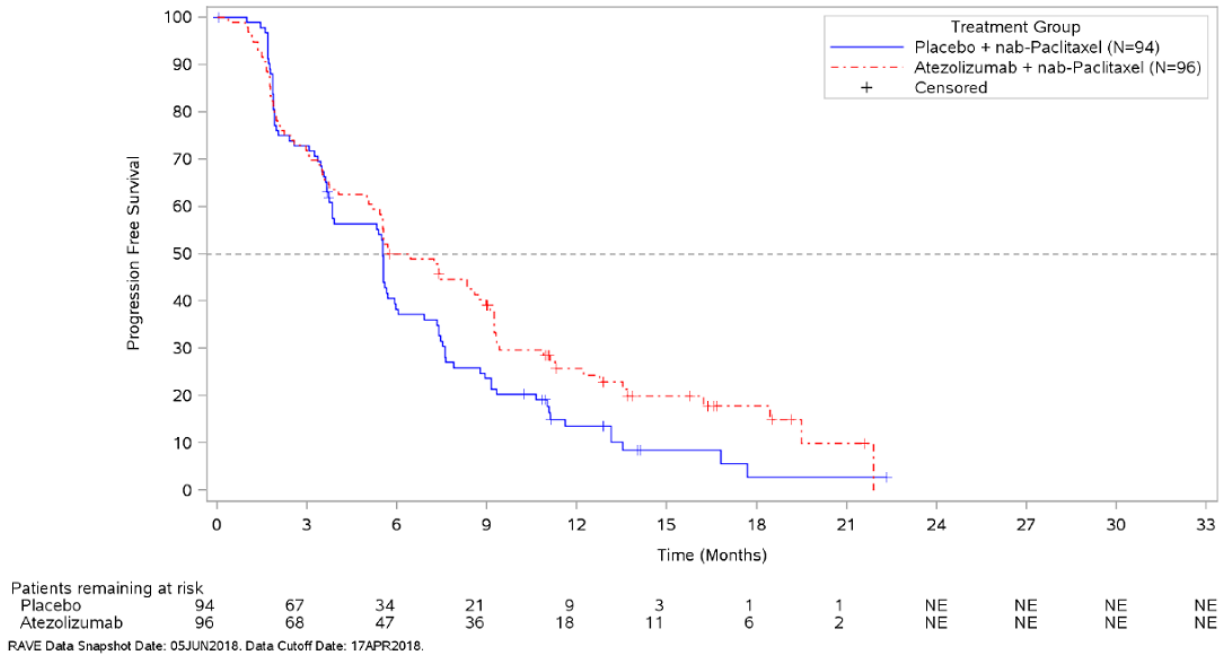


Figure 26: Kaplan-Meier Plot of PFS (investigator), Prior taxane patients, PD-L1 IC1/2/3 patients, ITT - Impassion130 (cut off 17 April 2018)

g_ef_km_PFS_INV_NPRTAX_PDL1POS_IT_17APR2018_29522 Kaplan-Meier Plot of Progression-Free Survival (Investigator), No Prior Taxane Patients, PD-L1 IC1/2/3 Patients, Intent-to-Treat Population
Protocol: WO29522

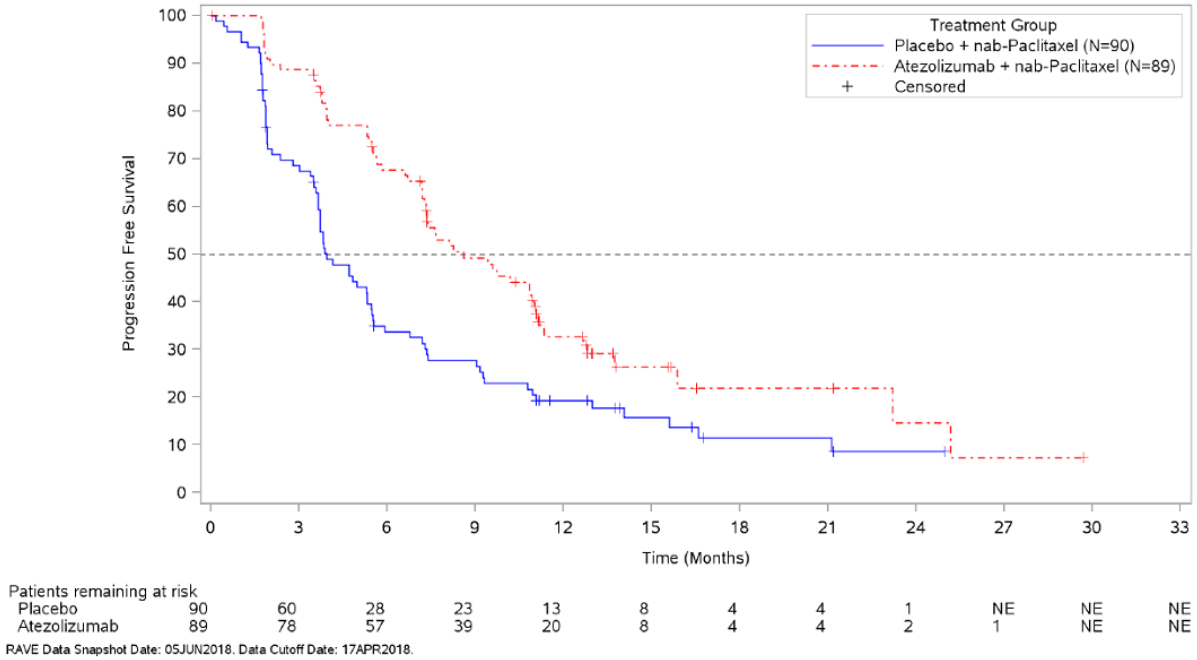


Figure 27: Kaplan-Meier Plot of PFS, No prior taxane patients, PD-L1 IC1/2/3 patients, ITT - Impassion130 (cut off 17 April 2018)

OS (prior taxane vs. no prior taxane)

g_ef_km_OS_PRTAX_PDL1POS_IT_17APR2018_29522 Kaplan-Meier Plot of Overall Survival (Investigator), Prior Taxane Patients, PD-L1 IC1/2/3 Patients, Intent-to-Treat Population
Protocol: WO29522

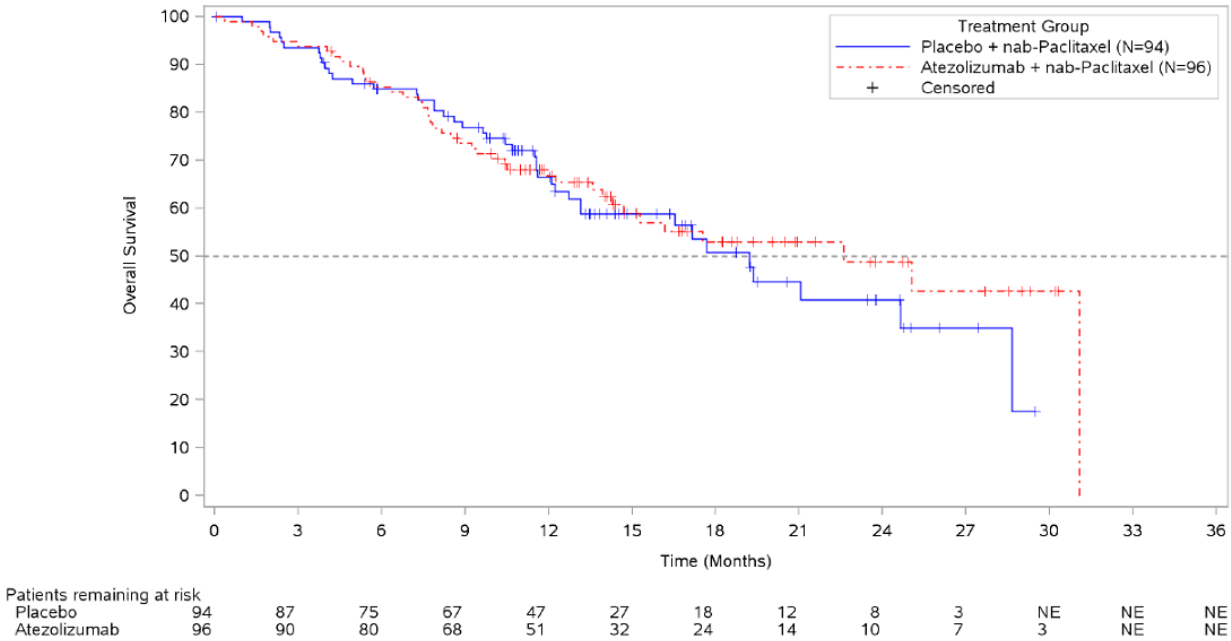


Figure 28: Kaplan-Meier Plot of OS, Prior taxane patients, PD-L1 IC1/2/3 patients, ITT - Impassion130 (cut off 17 April 2018)

g_ef_km_OS_NPRTAX_PDL1POS_IT_17APR2018_29522 Kaplan-Meier Plot of Overall Survival (Investigator), No Prior Taxane Patients, PD-L1 IC1/2/3 Patients, Intent-to-Treat Population
Protocol: WO29522

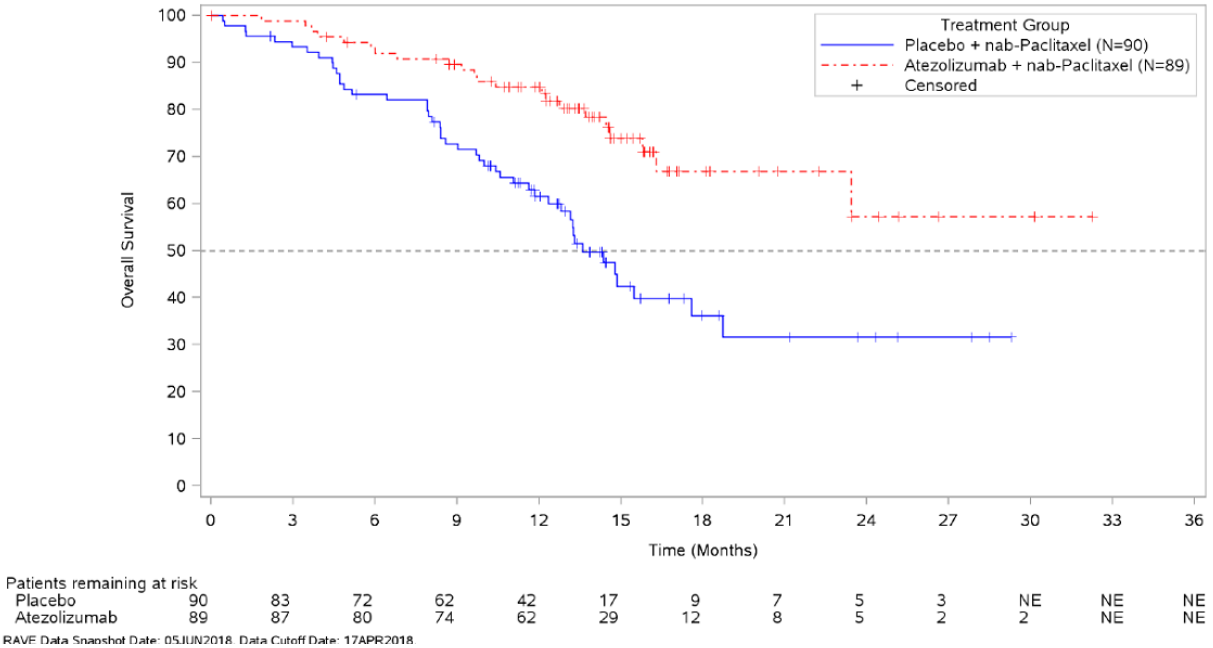


Figure 29: Kaplan-Meier Plot of OS, No prior taxane patients, PD-L1 IC1/2/3 patients, ITT - Impassion130 (cut off 17 April 2018)

- **Prior anthracycline**

PFS (prior anthracycline vs. no prior anthracycline)

g_ef_km_PFS_INV_PRANTH_PDL1POS_IT_17APR2018_29522 Kaplan-Meier Plot of Progression-Free Survival (Investigator), Prior Anthracycline Patients, PD-L1 IC1/2/3 Patients, Intent-to-Treat Population
Protocol: WO29522

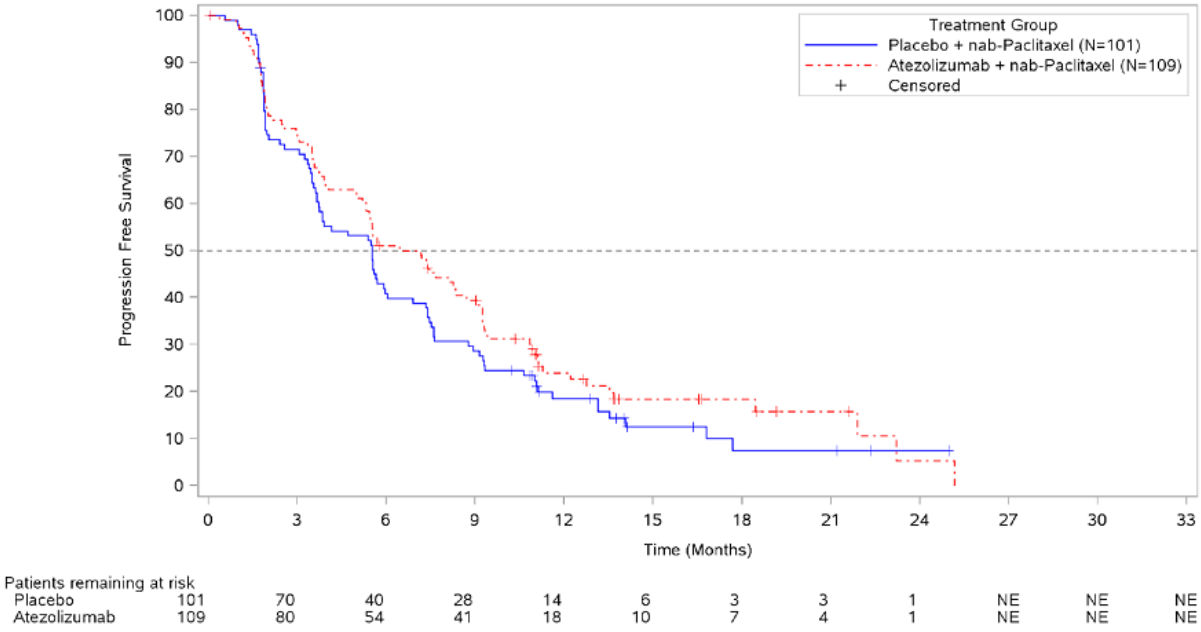


Figure 30: Kaplan-Meier Plot of PFS (investigator), Prior Anthracycline patients, PD-L1 IC1/2/3 patients, ITT - Impassion130 (cut off 17 April 2018)

g_ef_km_PFS_INV_NPRANTH_PDL1POS_IT_17APR2018_29522 Kaplan-Meier Plot of Progression-Free Survival (Investigator), No Prior Anthracycline Patients, PD-L1 IC1/2/3 Patients, Intent-to-Treat Population
Protocol: WO29522

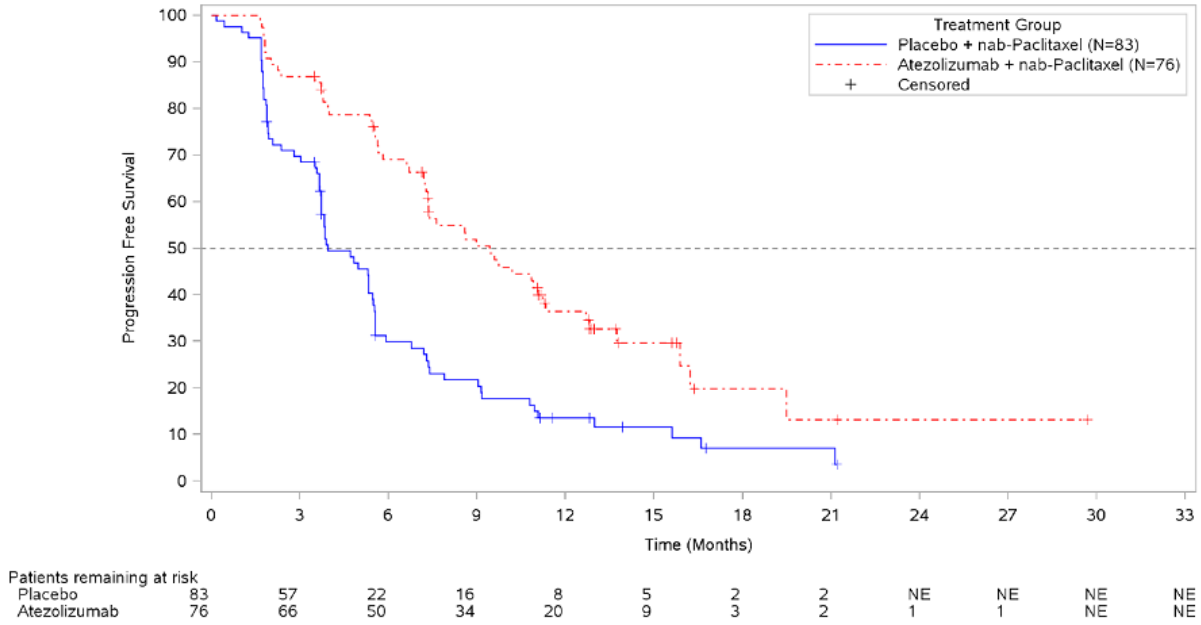


Figure 31: Kaplan-Meier Plot of PFS (investigator), No prior Anthracycline patients, PD-L1 IC1/2/3 patients, ITT - Impassion130 (cut off 17 April 2018)

<u>OS (prior anthracycline vs. no prior anthracycline)</u>

g_ef_km_OS_PRANTH_PDL1POS_IT_17APR2018_29522 Kaplan-Meier Plot of Overall Survival (Investigator), Prior Anthracycline Patients, PD-L1 IC1/2/3 Patients, Intent-to-Treat Population
Protocol: WO29522

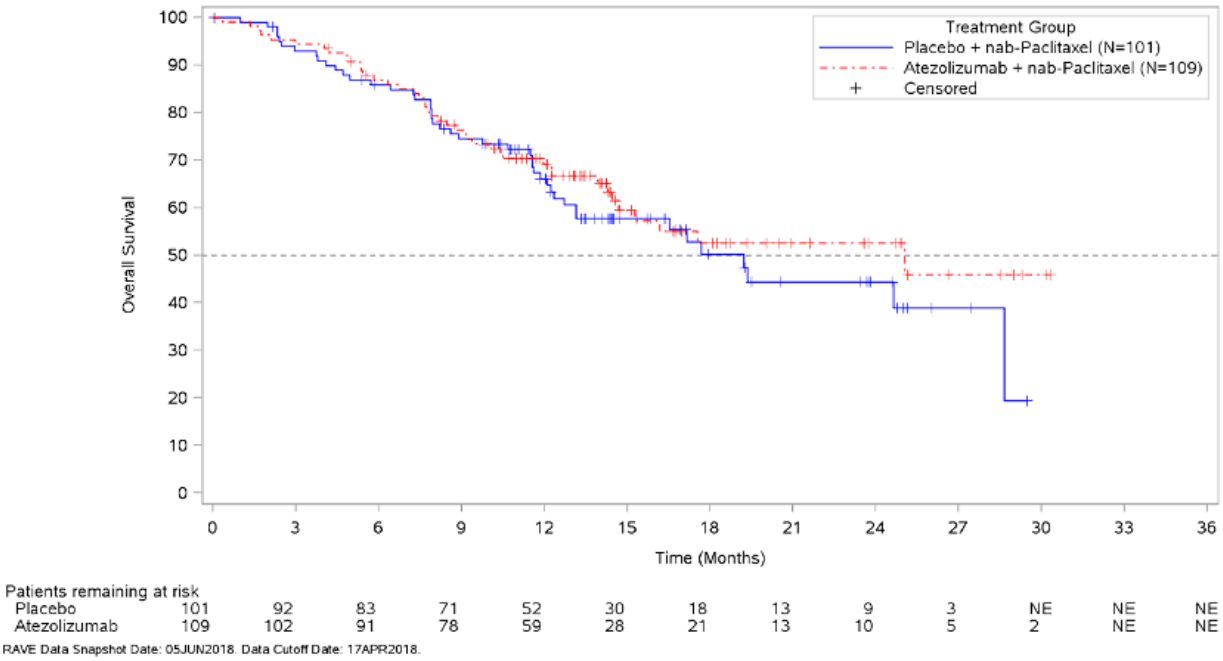


Figure 32: Kaplan-Meier Plot of OS, Prior Anthracycline patients, PD-L1 IC1/2/3 patients, ITT - Impassion130 (cut off 17 April 2018)

g_ef_km_OS_NPRANTH_PDL1POS_IT_17APR2018_29522 Kaplan-Meier Plot of Overall Survival (Investigator), No Prior Anthracycline Patients, PD-L1 IC1/2/3 Patients, Intent-to-Treat Population
Protocol: WO29522

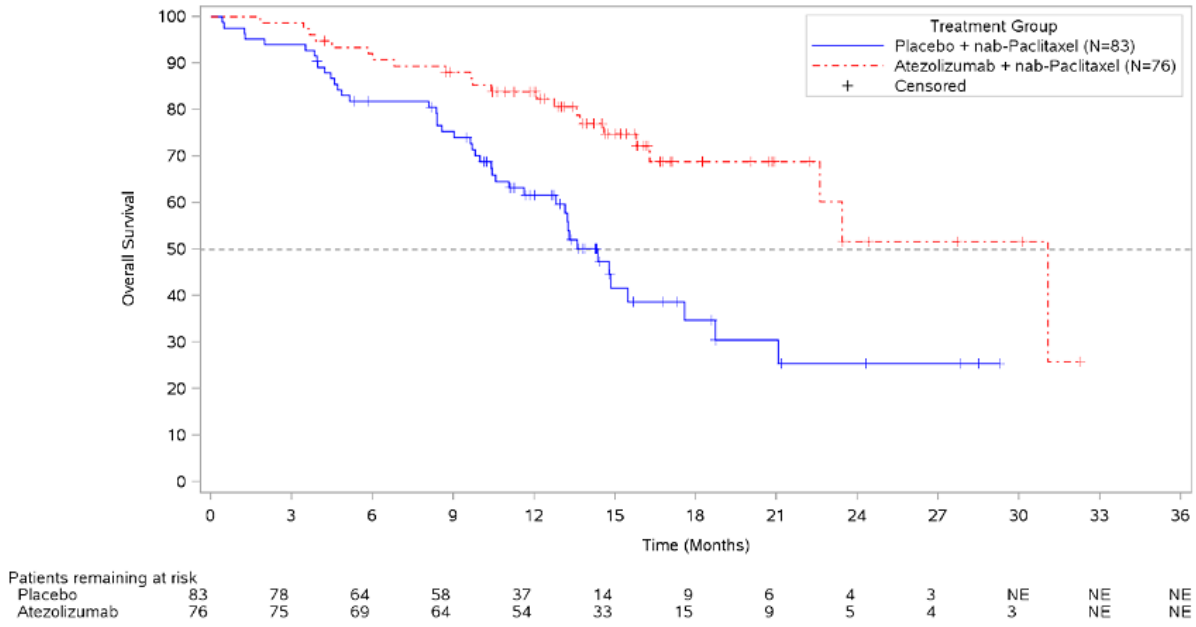


Figure 33: Kaplan-Meier Plot of OS, No prior Anthracycline patients, PD-L1 IC1/2/3 patients, ITT - Impassion130 (cut off 17 April 2018)

Sensitivity analyses

Table 30: Summary of sensitivity analyses on PFS (ITT population) - Impassion130 (cut-off 17 April 2018)

	PI+nP N=451	Atezo+nP N=451	Hazard Ratio (95% CI)	Log-Rank p-value
Investigator-assessed PFS (stratified) – primary analysis				
N (%) events	378 (83.8%)	358 (79.4%)	0.80	0.0025
Median, months	**5.5**	**7.2**	0.69–0.92	
IRC-assessed PFS (stratified)				
N (%) events	346 (76.7%)	328 (72.7%)	0.78	0.0014
Median, months	5.5	7.2	0.67–0.91	
Investigator-assessed PFS with censoring for non-protocol therapy (stratified)				
N (%) events	365 (80.9%)	346 (76.7%)	0.79	0.0016
Median, months	5.5	7.2	0.68–0.91	
Investigator-assessed PFS stratification based on eCRF data (stratified)				
N (%) events	378 (83.8%)	358 (79.4%)	0.80	0.0028
Median, months	5.5	7.2	0.69–0.93	

Sources: t_ef_tte_PFS_INV_IT_17APR2018_29522, t_ef_tte_PFS_IRC_IT_17APR2018_29522, t_ef_tte_PFSNPT_INV_IT_17APR2018_29522, t_ef_tte_ecrf_PFS_INV_IT_17APR2018_29522

Table 31: Summary of investigator-assessed PFS with censoring for missing tumour assessments (FDA definition) (ITT population) - Impassion130 (cut-off 17 April 2018)

	Placebo + nab-Paclitaxel (N=451)		Atezolizumab + nab-Paclitaxel (N=451)
Patients with event (%)	366 (81.2%)		350 (77.6%)
Earliest contributing event			
Death	20		23
Disease Progression	346		327
Patients without event (%)	85 (18.8%)		101 (22.4%)
Time to event (months)			
Median	5.49		7.00
95% CI	(5.29, 5.59)		(5.55, 7.43)
25% and 75%-ile	2.40, 9.33		3.65, 11.24
Range	0.0* to 25.0*		0.0* to 29.7*
Stratified Analysis			
p-value (log-rank)		0.0018	
Hazard Ratio		0.79	
95% CI		(0.68, 0.92)	
Unstratified Analysis			
p-value (log-rank)		0.0026	
Hazard Ratio		0.80	
95% CI		(0.69, 0.92)	
One year duration			
Patients remaining at risk	52		74
Event Free Rate (%)	17.39		23.76
95% CI	(13.62, 21.16)		(19.53, 27.99)
Difference in Event Free Rate		-6.37	
95% CI		(-12.04, -0.71)	
p-value (Z-test)		0.0275	

* Censored value. ^ Censored and event.
Summaries of PFS (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: presence of liver metastases, prior taxane treatment and tumor PD-L1 status. Hazard ratios were estimated by Cox regression.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Program: /opt/BIOSTAT/prod/cdpt3864/s29522a/t_ef_tte.sas
Output: /opt/BIOSTAT/prod/cdt3864a/j29522a/reports/t_ef_tte_PFSUS_INV_IT_17APR2018_29522.out
26JUN2018 1:16

Summary of main efficacy results

Table 32: Overview of efficacy (ITT and PD-L1-positive populations) - Impassion130

	First Interim OS Analysis				Second Interim OS Analysis			
	ITT		PD-L1–Positive		ITT		PD-L1–Positive	
	pl+nP N = 451	atezo+nP N = 451	pl+nP N = 184	atezo+nP N = 185	pl+nP N = 451	atezo+nP N = 451	pl+nP N = 184	atezo+nP N = 185
Co-Primary Endpoint: Overall Survival								
No. (%) of patients with events	208 (46.1%)	181 (40.1%)	88 (47.8%)	64 (34.6%)	279 (61.9%)	255 (56.5%)	110 (59.8%)	94 (50.8%)
Median, months	17.6	21.3	15.5	25.0	18.7	21.0	18.0	25.0
Stratified hazard ratio (95% CI) p-value (log-rank)	0.84 (0.69-1.02) 0.0840		0.62 (0.45-0.86) 0.0035*		0.86 (0.72-1.02) 0.0777		0.71 (0.54-0.93) 0.0133*	
Co-Primary Endpoint: Investigator-Assessed Progression-Free Survival								
No. (%) of patients with events	378 (83.8%)	358 (79.4%)	157 (85.3%)	138 (74.6%)	404 (89.6%)	379 (84.0%)	163 (88.6%)	149 (80.5%)
Median, months	5.5	7.2	5.0	7.5	5.5	7.2	5.3	7.5
Stratified hazard ratio (95% CI) p-value (log-rank)	0.80 (0.69-0.92) 0.0025		0.62 (0.49-0.78) < 0.0001		0.80 (0.69-0.92) 0.0021		0.63 (0.50-0.80) < 0.0001	
Co-Primary Endpoint: Investigator-Assessed Progression-Free Survival with Censoring (FDA Definition)								
No. (%) of patients with events	366 (81.2%)	350 (77.6%)	151 (82.1%)	136 (73.5%)	388 (86.0%)	370 (82.0%)	156 (84.8%)	147 (79.5%)
Median, months	5.5	7.0	4.8	7.4	5.5	6.8	4.8	7.4
Stratified hazard ratio (95% CI) p-value (log-rank)	0.79 (0.68-0.92) 0.0018		0.60 (0.48-0.77) < 0.0001		0.78 (0.67-0.90) 0.0008		0.61 (0.48-0.77) < 0.0001	

CI: confidence interval;

* not formally tested

Sources: t_ef_all_P_IT_17APR2018_29522; t_ef_all_P_IT_02JAN2019_29522.

The following tables summarise 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 33: Summary of efficacy for trial Impassion 130

Title: A phase III, multicenter, randomized, placebo-controlled study of atezolizumab (anti-PD-L1-antibody) in combination with nab-paclitaxel compared with placebo with nab-paclitaxel for patients with previously untreated metastatic triple-negative breast cancer.		
Study identifier	WO29522	
Design	Phase III, multicenter, double-blind, two-arm, randomized, placebo-controlled. Randomization was stratified by the presence of liver metastases at baseline (yes vs. no), prior taxane treatment (yes vs. no), and programmed death-ligand 1 (PD-L1)-positive status defined as PD-L1 stained tumour-infiltrating immune cell (IC) covering ≥1% of the tumour area (yes vs. no).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	First patient randomized: 23 June 2015 Last patient randomized: 24May 2017 Not applicable Not applicable
Hypothesis	Superiority trial	
Treatments groups (PD-L1 positive)	Placebo + nab-paclitaxel (Pl+nP)	Placebo Q2W + nab-paclitaxel 100mg/m2 day 1, 8 and 15 of 28 days cycle
	Atezolizumab + nab-paclitaxel (Atezo+nP)	Atezolizumab 840mg Q2W + nab-paclitaxel 100mg/m2 day 1, 8,5 of 28 days cycle

Endpoints and definitions	Co-Primary endpoint	PFS	Investigator according to RECIST 1.1 ITT population
	Co-Primary endpoint	OS	Overall survival ITT population
	Secondary endpoint	ORR	Overall response rate
	Secondary endpoint	DOR	Duration of response
Database lock	02 January 2019		

<u>Results and Analysis</u>

Analysis description	**Updated PFS analysis and 2nd Interim OS analysis**			
Analysis population and time point description	Intent to treat and PD-L1-positive population (≥1%)			
Descriptive statistics and estimate variability	Treatment group	ITT Pl+nP vs Atezo+nP	PD-L1-positive Pl+nP	PD-L1-positive Atezo+nP
	Number of subject	N=451 vs N=451	N=184	N=185
	Co-primary endpoint PFS (months)	5.5 vs 7.2	5.3	7.5
	Co-primary endpoint OS (months)	17.6 vs 21.3	18.0	25.0
	ORR (%)	45.9 vs 56.0	42.6	58.9
	DOR (months)	5.6 vs 7.4	5.5	8.5

Effect estimate per comparison	Co-Primary endpoint PFS	Comparison groups	PD-L1-positive group
		HR	0.63
		95% CI	0.50, 0.80
		P-value	<0.0001
	Co-Primary Endpoint OS	Comparison groups	PD-L1-positive group
		HR	0.71
		95% CI	0.54, 0.93
		P-value	0.0133*
	Secondary endpoint DOR	Comparison groups	PD-L1-postive
		HR	0.62
		95% CI	0.44, 0.86
		P-value	0.0044*
Notes	* not formally tested		

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

Not applicable

Clinical studies in special populations

No specific studies have been submitted.

Supportive studies

Single drug contribution - atezolizumab

Atezolizumab was initially investigated as a single agent in patients with locally advanced or metastatic solid tumours or hematologic malignancies in a Phase Ia first-inhuman dose-escalation study PCD4989g (also referred to as GO27831). The expansion stage of this study included a cohort of 116 patients with TNBC, 21 of whom received atezolizumab as 1L therapy for metastatic disease. Results in this cohort of TNBC patients showed atezolizumab monotherapy to be well tolerated with objective clinical activity and durable clinical benefit (Schmid et al. 2017). Among 115 ORR-evaluable patients, INV-assessed confirmed ORR was 10% (95%CI: 5, 16) with 3 CR and 8 PR. Among the PD-L1-positive patients (IC1/2/3), ORR were reported in 12% of patients (95%CI: 6, 21) and no PD-L1-negative patients responded. Median DOR was 21 months (range: 3-38), and median OS was 8.9 months (95%CI: 7.0, 12.6) for all patients with a median FU of 25.3 months. Median PFS was 1.4 months (95%CI: 1.3, 1.6)

The safety and efficacy of atezolizumab in combination with chemotherapy with or without bevacizumab in patients with locally advanced or metastatic solid tumours was investigated in Study GP28328, a multi-arm, Phase Ib study. Arm F of this study tested the combination of atezolizumab (800 mg q2w) with nab-paclitaxel (125 mg/m2 weekly on a 3-weeks on/1-week off schedule) in female patients with TNBC who received no more than two prior therapies for metastatic or locally advanced disease (n=32). Results from this single arm demonstrated that atezolizumab plus nab-paclitaxel was tolerable with promising activity in mTNBC, both in patients who received atezolizumab plus nab-paclitaxel as 1L therapy and those who received study treatment as 2L+ therapy (Pohlmann et al. 2018).

Table 34: Phase 1/1b Cross-Trial Comparison of Atezolizumab Monotherapy (Study PCD4989g) Versus Combination Therapy with Nab-Paclitaxel (Study GP28328) in Clinically Relevant mTNBC Subgroups

	PCD4989g (1L) n=21	GP28328 (1L) n=13	PCD4989g PD-L1+ patients (IC 1/2/3) n=91	GP28328 PD-L1+ patients (IC 1/2/3) n=12
ORR (RECIST) (%)	24.0	53.8	12.0	41.7
PFS median (months)	1.6	8.6	1.4	6.9
OS median (months)	17.6	24.2	10.1	21.9

1L=first-line; IC=immune cells; mTNBC = metastatic triple-negative breast cancer; PD-L1=programmed death-ligand 1; PFS=progression-free survival; ORR=objective response rate; OS=overall survival; RECIST=Response Evaluation Criteria in Solid Tumours
Sources: Emens et al. 2018 (eTable 5 in Supplement 2), Adams et al. 2018 (Table 3 and eTable1 in Suppl 2)

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy assessment is based on a single, pivotal, international, multicenter, randomized, placebo-controlled, double-blinded, two-arm phase III Study WO29522 (hereinafter referred to as IMpassion130), which is evaluating the efficacy and safety of atezolizumab + nP compared with placebo plus nab-paclitaxel (hereinafter referred to as pl+nP) in patients with locally advanced or metastatic TNBC, who have not received prior chemotherapy for metastatic breast cancer.

The study comprises 902 patients in total and of these, 369 patients had PD-L1 positive tumours (target population). The patients were recruited from 246 centres in 41 countries over approximately 2 years. Patients were treatment-naïve in the metastatic setting. The rate of screen failure was approximately a quarter of the screened patients, and this is acceptable in this setting. Only approximately 5% of the patients were lost to follow up, which is acceptable for this patient population.

The inclusion and exclusion criteria are generally acceptable. However, the selection of patients could have been more detailed so that knowledge of BRCA mutation status and basal-like tumours could have been available for analyses. These tumour characteristics may be considered prognostic as well as predictive factors for treatment with atezolizumab. It is acceptable that patients with known CNS disease (except for treated asymptomatic CNS metastases) were excluded, indicating that patients, who were stable could be included. CNS metastases are frequent in this patient population, and a requested subgroup analyses of patients with treated asymptomatic CNS metastases present included only 26 patients (7%) of the PD-L1 positive population, which is a too limited sample size for any firm conclusion (see efficacy data and additional analyses).

The amendments and protocol violations of the pivotal study are deemed unlikely to have a relevant impact on the integrity of the study.

The single pivotal study was both placebo-controlled and double-blinded which is endorsed. The sample size was large. However, the applied indication is for patients with PD-L1-positive tumours (n=369) and of these 185 patients were randomized to receive atezolizumab.

At the final PFS analysis and pre-specified first interim analysis for OS, the iDMC recommended that the aggregated patient data be unblinded to the Sponsor to fully analyse the data because the pre-specified boundary for the co-primary endpoint of PFS in the ITT population and in the PD-L1-positive subgroup had been met. The Sponsor endorsed this recommendation and therefore presented these analyses as primary analysis for efficacy.

The investigators were blinded to the PD-L1 status of the patient to minimize the effect of potential investigator-bias in PFS and ORR. The adverse reaction profile, which could potentially break the blinding for some individuals in case of immune-related AEs are expected to lead to bias in some cases, but this is difficult to avoid. However, this is not expected to have a major impact on the results, and therefore it is acceptable. In addition, the immune-related AE's were rarely observed. Overall, the blinding strategy is considered adequate.

Stratification factors were presence of liver metastases, prior taxane treatment, and tumour PD-L1 status, which are considered clinically relevant in this setting because they are probably negative prognostic factors. Of note, prior taxane treatment is an indicator of prior (neo)-adjuvant treatment more than 12 months earlier, because the patients with early relapse (before 12 months) and a very poor prognosis were already excluded. In addition, the nature of TNBC is very aggressive causing a higher incidence of inoperable primary tumours that require neo-adjuvant pre-operative treatment before resection. Hence, the study population may not properly reflect the patient population of TNBC in the clinic. Relevant inclusion and exclusion criteria have been reflected in section 5.1 of the SmPC.

The applicant has adequately justified the choice of PD-L1 cutoff and the relevance of combination therapy. In the pivotal study IMpassion130, there were very few patients who had tumours with high PD-L1 expression (IC≥10%, n=35) i.e. IC3. The applicant has shown efficacy in the IC≥1% and <5% group (IC1), IC≥5% and IC<10% (IC2), so the chosen cut-off point of IC ≥1% is considered justified. The applicant has also clearly demonstrated that PD-L1 negative patients do not derive any benefit by addition of atezolizumab, which also supports the chosen cutoff. With regards to the relevance of the combination therapy, data presented from two studies (PCD4989g and GP28328) showed that atezolizumab monotherapy only had a modest efficacy in the mTNBC setting.

The evaluation of biomarkers has been listed as exploratory endpoint (including tumour biopsies at the time of radiographic disease progression, if clinically feasible and optional biopsies pre-dose on Cycle 2 for separately consenting patients). The MAH clarified that the additional biomarker analyses will be performed in Q1 2021 as a recommendation andas part of the final CSR.

Nab-paclitaxel has been questioned as the comparator because it is not standard of care in the treatment of breast cancer in Europe. However, the MAH has justified the appropriateness of nab-paclitaxel as comparator and in particular use of the applied dose regimen in the pivotal trial. It is acknowledged that, at the time of designing the pivotal trial Impassion130, the general hypothesis was that the immunosuppressive effects of steroids could potentially inhibit the immune-mediated anti-tumour activity of PD-L1 blockade with immunotherapies such as atezolizumab explaining the choice of a steroid sparing chemotherapy such as nab-paclitaxel. The applicant argues that this could particularly apply for TNBC, because of its lower immunogenicity and mutational burden compared with other immunotherapy-responsive cancers (e.g., melanoma, lung, and bladder cancers). This hypothesis is not considered substantiated at the present time (Postow et al. N Engl J Med 2018; 378:158-168), but it was a major concern when immunotherapy emerged and at the time of choosing nab-paclitaxel as the comparator. In addition, nab-paclitaxel is directly recommended in the NCCN clinical practice guidelines and indirectly by the ESMO guidelines, who recommends taxane-based regimens in general in the first-line setting of HER2-negative mBC. The used dosing regimen of 100mg/m^2 weekly Q3W is partly supported by a recent publication (Arpino et al. 2016). More importantly, the efficacy outcome of the control arm in IMpassion130 is comparable to historical controls, so no detrimental effects of this dosing schedule is evident. Overall, it is acknowledged that a steroid sparing chemotherapy such as nab-paclitaxel was used based on the available knowledge about steroids impact on efficacy at the time of the choice of comparator. Hence, the choice of nab-paclitaxel as comparator and its dosing regimen is acceptable. In addition, the applicant will provide results by June 2021 from the ongoing study that is currently studying paclitaxel instead of nab-paclitaxel using the same study design (Impassion 131).

Baseline demographics were well balanced regarding age, age-groups, sex, race, and PS. Only two patients had PS 2, which is not reflective of the general patient population, but considered acceptable in a clinical study. The majority of women were post-menopausal (59.5%) even though TNBC is more common in young, premenopausal women. Overall, patient demographics and baseline tumour disease in patients with PD-L1 expression ≥1% were generally representative of the broader study population (see SmPC section 5.1).

Half of the patients had received prior taxane treatment, but this is considered acceptable as the taxane was given as an (neo)-adjuvant treatment ≥12 months prior to randomization, and it was a stratification factor. Almost a third of the patients had liver metastases, half had lung metastases and 2/3 of the patients had chemotherapy before in the (neo)-adjuvant setting, which is considered reflective of TNBC as an aggressive breast cancer subtype with a poor prognosis and visceral metastases are often present at the time of metastatic disease. Only approximately 7% of patients had brain metastases at baseline, probably because known CNS disease, except for treated asymptomatic CNS metastases were an exclusion criterion. This is understandable since these patients have a very poor prognosis but it is not reflective of the patient population as the risk of CNS metastasis is high with TNBC in the metastatic setting. However, due to randomisation and that the incidence was well-balanced between the arms, it is considered acceptable. Furthermore, patients excluded from clinical trials have been adequately reflected in section 4.4 of the SmPC, i.e. patients with a history of autoimmune disease, history of pneumonitis, active brain metastasis, HIV, hepatitis B or hepatitis C infection, significant cardiovascular disease and patients with inadequate hematologic and end-organ function; patients who were administered a live, attenuated vaccine within 28 days prior to enrolment; systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to study entry.

PFS and OS were co-primary endpoints and this is acceptable and in line with previous advice. To detect investigator bias of PFS, independent review of the imaging data was performed and this is endorsed. The secondary endpoints of ORR, DOR, and time to deterioration of global health status (TTD) are clinically relevant as well, and especially TTD is considered indicative of detrimental effects on QOL.

Efficacy data and additional analyses

The clinical cut-off was 17 April 2018 for the analyses presented initially corresponding to the protocol-defined final analysis of PFS and 1st interim analysis of OS. Updated efficacy data were submitted with a data cut-off 2 January 2019 consisting in results from the second interim analysis for OS along with updated PFS and DOR results.

The median number of treatment cycles was 7 for atezolizumab and 6 for nab-paclitaxel in each treatment arm.

The final analysis of PFS in the ITT population is the co-primary endpoint and it was met. In addition, there were approximately 80% PFS events in the atezo-arm, so the data for PFS are considered mature. Median duration of survival follow-up was ~19 months (range 0.0-40.8) in the PD-L1 positive population.

Relevant for the applied indication is primarily the results from the PD-L1-positive population, where updated PFS was 7.5 months vs 5.3 months, HR 0.63 (95%CI: 0.50, 0.80), which is statistically significant. This result is also considered clinically relevant because the curves clearly separate, suggesting long-term benefit in a subgroup of patients as often observed with immunotherapy. This is now supported by more mature OS data. Promising long-term benefit is also reflected by the updated 1-year event-free rate in the atezo-arm (30.3% vs 17.3%). PFS by IRC show a similar result: PFS HR 0.63 (95%CI: 0.49, 0.81), which adds to the robustness of data.

Optimally, the benefitting subgroup could be better defined than by PD-L1 ≥ 1%. However, no better biomarker has been identified at the present time and this is acknowledged. OS in the ITT population is the other co-primary endpoint and it was not met in either the first or second IA. However, there were ~50% events in the atezo-arm of the PD-L1 positive population at data cut-off 2 January 2019, so the data are now considered more mature. Moreover, the relevant OS data for the applied indication is primarily the results from the PD-L1 positive population, where OS was improved to 25 months vs 18 months, HR 0.71 (95%CI: 0.54, 0.93), but this result could not be formally tested, because OS in the ITT population was not statistically significant. The median OS of the control arm of the ITT population (18.7 months) and historical data are similar (17.5 months, Miles et al. 2013). Even though the result of OS cannot be formally tested, the numerical difference of 7 months is considered clinically relevant. As with PFS, the OS curves clearly separate, demonstrating a long-term benefit for this subgroup of patients. This is also reflected by the 2-year event-free rate in the atezo-arm (36.9% vs 50.7%).

Overall, sensitivity analyses for PFS and OS (including IRC assessment and different censoring rules for PFS) were consistent with those observed in the primary analysis. Only very few patients (3% in each arm) had received a checkpoint inhibitor post-PD at the time of data cut-off.

From a statistical point of view, it is noticed that the time points chosen for the different interim and final analyses for OS are variable and depend on the results of PFS and ORR. In other words, unblinded data is used to select the number of events used in the interim analyses for OS. There is uncertainty whether this adaptive feature affects the type I error. Given a moderate maximal increase in the effective sample size for OS of around 5%, the issue is considered to not impact the PFS results in a meaningful way. However, the MAH will be expected to show that the type 1 error is strongly controlled in case the OS results for the ITT population turn out to be statistically significant at a later stage, when submitting the final CSR. The hierarchical testing for ORR is agreed and the use of the LanDeMets function to adjust the alpha level within the OS interim analyses seems appropriate.

ORR in the ITT population was higher in the atezo-arm, mainly due to an increased rate of CR (7.1% vs 1.6%). In the PD-L1-positive population, a difference of ~15% was observed with an ORR of 58.4% vs 42.6%, Odds ratio 1.96 (95%CI: 1.29-2.98). The complete response rate and PR was also increased to CR 10.3% and PR 48.6% in the atezo-arm. Another ~20% of the patients had stable disease with atezolizumab. This is considered clinically relevant as these patients have multiple sites of metastases and a high incidence of visceral metastases, so the improved response rate will most likely translate into improved clinical benefit by the relief of symptoms and decreased disease manifestations. In addition, the applicant provided data on the clinical benefit rate (CBR) of the treatment arms in the PD-L1-positive population, using confirmed rates of CR+PR+SD>6 months for the calculation, and the difference of 20.7% (95%CI: 10.1; 31.2) in favour of the atezolizumab arm is considered supportive of the co-primary endpoints.

The duration of response in the atezolizumab arm of the ITT population was 7.4 months, which is statistically significantly longer than with placebo (5.6 months). This difference was even greater in the PD-L1 population (8.5 vs 5.5 months) and this is considered clinically relevant. The DOR was updated and considered mature as ~70% of patients were responders with a subsequent event and ~28% of the patients have an ongoing response at data cut-off in the PD-L1 positive population.

The time to deterioration (a sustained ≥ 10-point decline from baseline score) of patient-reported global health status/health-related quality of life as measured by the EORTC QLQ-C30 was similar in each treatment group indicating that all patients maintained their baseline HRQoL for a comparable duration of time (see SmPC section 5.1).

Patients with PD-L1 expression <1% did not show improved PFS when atezolizumab was added to nab-paclitaxel (HR of 0.94, 95% CI 0.78, 1.13) (see SmPC section 5.1).

Exploratory subgroup analyses were performed in patients with PD-L1 expression ≥ 1%, exploring prior (neo)adjuvant treatment, BRCA1/2 mutation and asymptomatic brain metastases at baseline.

In the IMpassion130 study, of the 614 patients tested, 89 (15%) carried pathogenic BRCA1/2 mutations. From the PD-L1+/BRCA1/2 mutant subgroup, 19 patients received atezolizumab plus nab-paclitaxel and 26 placebo plus nab-paclitaxel. Based on exploratory analysis and acknowledging the small sample size, the presence of BRCA1/2 mutation does not seem to impact the PFS clinical benefit of atezolizumab and nab-paclitaxel. (see SmPC section 5.1).

There was no evidence of efficacy in patients with asymptomatic brain metastases at baseline, although the number of patients treated was small; the median PFS was 2.2 months in the atezolizumab plus nab-paclitaxel arm (n=15) compared to 5.6 months in the placebo plus nab-paclitaxel arm (n=11) (HR 1.40; 95% CI 0.57, 3.44).

In patients who had received prior (neo) adjuvant treatment (n=242), the hazard ratio for PFS was 0.79 and 0.82 for OS while in patients who had not received prior (neo)adjuvant treatment (n=127), the hazard ratio for PFS was 0.44 and 0.53 for OS (see SmPC section 5.1). In these patients only a small benefit regarding OS was demonstrated by the addition of atezolizumab to nab-paclitaxel compared to patients who were chemotherapy-naïve. This was evident both for patients who had prior anthracycline and/or prior taxane.

New analyses with adjustments for strong prognostic factors show that the PFS for the PD-L1 positive taxane-pretreated patients was still statistically significant, which is encouraging. Although the improvement of PFS in the taxane-pretreated patients was less than in the taxane-naïve patients, this analysis is considered supportive of the indication claimed. The subgroup analyses of patients who were anthracycline-pretreated were difficult to assess, as most of these patients (85%) were also taxane-pretreated patients, and anthracycline pre-treatment was not a stratification factor. It is agreed that there is no sign of lack of efficacy regarding PFS of nab-paclitaxel after prior exposure to taxane and

no concerning signals regarding safety were observed. Given the demonstrated PFS benefit and the lack of a detrimental effect on OS, it is agreed that patients with prior (neo) adjuvant treatment should not be excluded from the proposed indication. Furthermore since the above information is considered clinically relevant for individual treatment decisions it has been reflected in the SmPC (see section 5.1).

Due to a very small sample size of the target population (n=21) it is not possible to draw any firm conclusions regarding the impact of ADA status on efficacy in the PD-L1-positive populations of the pivotal study. However, the applicant will provide immunogenicity data further to a recommendation by the CHMP.

2.5.4. Conclusions on clinical efficacy

The results from the pivotal study demonstrate benefit of atezolizumab in combination with nab-paclitaxel for the first-line treatment of patients with advanced or metastatic TNBC through a clinically meaningful and statistically significant PFS advantage compared to the comparator arm. This is supported by a clinically meaningful improvement of ORR, DOR and OS benefit for the targeted population.

2.6. Clinical safety

Patient exposure

Safety data were provided for 890 safety-evaluable patients (all patients who have received at least one dose of study treatment) from the pivotal Study IMpassion130: n=438 pl+nP and n=452 atezo+nP (Table 4).

Pooled monotherapy data were also presented for 3178 atezolizumab-treated patients (all patients who received at least one dose of atezolizumab). The monotherapy population was the largest pooled population available to date for atezolizumab, and the majority was patients with second-line and beyond (2L+) urothelial carcinoma (UC) and non-small cell lung cancer (NSCLC) (Table 37). Study PCD4989g, however, enrolled patients with a variety of solid tumours and hematological malignancies, including 116 patients with first-line and beyond (1L+) mTNBC.

Table 35: Summary of Studies Contributing to Safety Evaluation

Study No.	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	CCOD
Pivotal Study					
IMpassion130 (WO29522)	Phase III, global, multicenter, double-blind, two-arm, randomized, placebo-controlled study	Patients with unresectable, locally advanced or mTNBC who have not received prior systemic therapy for mBC. Patients were stratified by the presence of liver metastases (yes vs. no), prior taxane treatment (yes vs. no), tumor PD-L1 status (IC0 vs. IC1/2/3).	n=452 atezo+nP n=438 pl+nP	atezo 840 mg IV q2w + nP 100 mg/m² qw (3wks on/1 wk off) vs. pl IV q2w + nP 100 mg/m² qw (3wks on/1 wk off)	17 April 2018 (primary analysis)
Atezolizumab Monotherapy Studies					
IMvigor211 (GO29294)	Phase III, global, open-label, multicenter, randomized study	Patients with locally advanced or metastatic UC who have progressed during or following a platinum-containing regimen (2L/3L). Patients were stratified by chemotherapy (vinflunine vs. taxane, PD-L1 status (IC0/1 vs. IC2/3), number of risk factors, and presence of liver metastases.	n=459 atezo [a]	atezo 1200 mg IV q3w vs. docetaxel 75 mg/m² q3w or paclitaxel 175 mg/m² q3w or vinflunine 320 mg/m² q3w	13 March 2017 (primary analysis)

Study No.	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	CCOD
IMvigor210 (GO29293)	Phase II, global, multicenter, two-cohort, single-arm trial	Patients with locally advanced or 1L metastatic UC (no prior chemotherapy in the metastatic setting and ineligible for cisplatin-based chemotherapy). 2L+ patients with locally advanced or metastatic UC (patients who failed a prior platinum-based therapy or progressed within 12 months of a platinum-containing treatment administered in the neoadjuvant or adjuvant setting). Approximately 30% of the patient population was planned to be PD-L1 selected (IC2/3).	n=429 atezo	atezo 1200 mg IV q3w	4 July 2016 (updated analysis)
OAK (GO28915)	Phase III, global, open-label, multicenter, randomized study	Patients with locally advanced, metastatic, or recurrent non-squamous and squamous NSCLC who have failed a prior platinum-containing regimen (2L and 3L). Patients were stratified by PD-L1 status (IC0/1/2/3), number of prior chemotherapy regimens (1 vs. 2), histology (non-squamous vs. squamous).	n=609 atezo [b]	atezo 1200 mg IV q3w vs. docetaxel 75 mg/m^2 q3w	7 July 2016 (primary analysis)
POPLAR (GO28753)	Phase II, global, multicenter, open-label, randomized, controlled trial	Patients with locally advanced, metastatic, or recurrent non-squamous and squamous NSCLC who have failed a prior platinum-containing regimen (2L and 3L). Patients were stratified by PD-L1 status (IC0/1/2/3), number of prior chemotherapy regimens (1 vs. 2), histology (non-squamous versus squamous).	n=142 atezo [c]	atezo 1200 mg IV q3w vs. docetaxel 75 mg/m^2 q3w	1 December 2015 (updated analysis)

Study No.	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	CCOD
BIRCH (GO28754)	Phase II, global, multicenter, three-cohort, single-arm trial	Patients with locally advanced or metastatic NSCLC who were treatment-naïve in the metastatic setting (1L), or had progressed during or following treatment with one platinum-based regimen (2L), or had progressed during or following at least 2 regimens (3L+), one of which had to have been a platinum-containing regimen for advanced disease. Patients were PD-L1 selected (TC2/3 or IC2/3).	n = 659 atezo	atezo 1200 mg IV q3w	1 December 2015 (updated analysis)
FIR (GO28625)	Phase II, global, multicenter, three-cohort, single-arm trial	Patients with locally advanced or metastatic NSCLC who were treatment-naïve in metastatic setting (1L, Cohort 1) or progressed during or following a prior platinum-based chemotherapy regimen without restriction to the maximum number of prior therapies (i.e., 2L+; Cohort 2), or 2L+ patients with previously treated brain metastases (Cohort 3). Patients were PD-L1 selected (TC2/3 or IC2/3).	n=137 atezo	atezo 1200 mg IV q3w	7 January 2015 (primary analysis)

Study No.	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	CCOD
IMmotion150 (WO29074)	Phase II, global, open-label, multicenter, randomized study	Patients with histologically confirmed, inoperable, locally advanced or metastatic RCC who have not received prior systemic therapy either in the adjuvant or metastatic setting. Patients were stratified by prior nephrectomy (yes vs. no), PD-L1 status (IC2/3 vs. IC0/1/unevaluable), and MSKCC (Motzer) risk score (low, intermediate, or high risk; 0, 1–2, or ≥3).	n=103 atezo [d]	atezo 1200 mg IV q3w vs. atezo 1200 mg IV q3w + bevacizumab 15 mg/kg IV q3w vs. sunitinib 50 mg/day (4 wks on/2wks off)	17 October 2016 (primary analysis)
Study PCD4989g (GO27831)	Phase I, open-label, dose-escalation and dose-expansion stages	Patients with locally advanced or metastatic solid tumors and hematologic malignancies.	n=640 atezo mTNBC=116 [e]	atezo ≤1, 3, 10, 15, 20 mg/kg and 1200 mg IV q3w	31 March 2016 (interim analysis)

1L=first-line; 2L=second-line; 2L+=second-line and beyond; 3L=third-line; 3L+=third-line and beyond; atezo=atezolizumab; CCOD=clinical cutoff date; IC=tumor-infiltrating immune cell; IHC=immunohistochemistry; IV=intravenous; mBC=metastatic breast cancer; mTNBC=metastatic triple negative breast cancer; NSCLC=non–small cell lung cancer; q3w=every 3 weeks; qw=weekly; PD-L1=programmed death–ligand 1; RCC=renal cell carcinoma; TC=tumor cell; UC=urothelial carcinoma; wk=week.

[a] A total of 443 patients were treated with chemotherapy (vinflunine=242, paclitaxel=148, docetaxel=53) in IMvigor211.

[b] A total of 578 patients were treated with docetaxel 75 mg/m^2 q3w in OAK.

[c] A total of 135 patients were treated with docetaxel 75 mg/m^2 q3w in POPLAR.

[d] A total of 100 patients were treated with sunitinib 50 mg/day (4wks on/2 weeks off) and 101 patients were treated with atezolizumab 1200 mg q3w + bevacizumab 15 mg/kg IV q3w in IMmotion150.

[e] Includes 1L, 2L, and 3L+ mTNBC patients.

Safety data from the pl+nP and the atezo+nP arms of IMpassion130 are presented side-by-side with the atezolizumab monotherapy population, where applicable, to allow for a comprehensive characterization of the safety risk profile of atezo+nP.

Table 36: Exposure to atezolizumab, placebo and nab-paclitaxel (safety-evaluable population) - Study IMpassion130

	pl+nP (N=438)		atezo+nP (N=452)	
	nab-Paclitaxel	Placebo	nab-Paclitaxel	Atezolizumab
Treatment Duration (wks)	n=438	n=438	n=452	n=452
Mean (SD)	23.9 (18.5)	26.9 (21.9)	27.6 (20.0)	31.6 (24.7)
Median	21.8	22.1	22.1	24.1
Min–Max	0–103	0–109	0–137	0–139
Treatment Duration	n=438	n=438	n=452	n=452
≤8 weeks	425 (97.0%)	424 (96.8%)	436 (96.5%)	426 (94.2%)
≤12 weeks	338 (77.2)	338 (77.2%)	387 (85.6%)	383 (84.7%)
≤16 weeks	316 (72.1%)	316 (72.1%)	361 (79.9%)	355 (78.5%)
≤6 months	257 (58.7%)	259 (59.1%)	315 (69.7%)	311 (68.8%)
≤9 months	145 (33.1%)	170 (38.8%)	181 (40.0%)	215 (47.6%)
≤12 months	75 (17.1%)	108 (24.7%)	100 (22.1%)	138 (30.5%)
≤18 months	44 (10.0%)	63 (14.4%)	53 (11.7%)	89 (19.7%)
>18 months	7 (1.6%)	15 (3.4%)	12 (2.7%)	25 (5.5%)
Dose Intensity (%)	n=438	n=0	n=452	n=452
Mean (SD)	90.4 (15.1)	NE	87.7 (17.8)	95.8 (10.4)
Median	100.0	NE	95.8	100.0
Min–Max	27–100	NE	8–107	15–100
Number of Cycles	n=438	n=438	n=452	n=452
Mean (SD)	6.4 (4.5)	7.2 (5.4)	7.2 (4.8)	8.2 (6.0)
Median	6.0	6.0	6.0	7.0
Min–Max	1–26	1–28	1–34	1–35
Total Cumulative Dose (mg)	n=438	n=438	n=452	n=452
Mean (SD)	1764.4 (1238.3)	0	1980.0 (1303.1)	13237.8 (9880.4)
Median	1500.0	0	1725.0	10080.0
Min–Max	98–7500	0–0	100–7425	840–57960

NE=not estimable.

Sources: t_ex_atezo_SE_17APR2018_29522 , t_ex_plac_SE_17APR2018_29522 , t_ex_nabpac_SE_17APR2018_29522

Adverse events

Table 37: Overview of safety in any population – Study Impassion130 and atezolizumab monotherapy pooled dataset

	IMpassion130		Atezolizumab Monotherapy (N=3178)
	pl+nP (N=438)	Atezo+nP (N=452)	
Number of Adverse Event	5942	7497	33365
Total number of patients with at least one:			
Adverse Event	429 (97.9%)	449 (99.3%)	3051 (96.0%)
Treatment Related AE	410 (93.6%)	436 (96.5%)	2167 (68.2%)
Grade 3−4 AE	185 (42.2%)	220 (48.7%)	1564 (49.2%)
Treatment Related Grade 3-4 AE	132 (30.1%)	179 (39.6%)	505 (15.9%)
Grade 5 AE	3 (0.7%)	6 (1.3%)	120 (3.8%)
Treatment Related Grade 5 AE	1 (0.2%)	3 (0.7%)	11 (0.3%)
Serious AE	80 (18.3%)	103 (22.8%)	1309 (41.2%)
Treatment Related Serious AE	32 (7.3%)	56 (12.4%)	353 (11.1%)
AE leading to discontinuation of:			
Any study treatment	36 (8.2%)	72 (15.9%)	226 (7.1%)
Atezo/placebo	6 (1.4%)	29 (6.4%)	226 (7.1%)
Nab-paclitaxel	36 (8.2%)	72 (15.9%)	N/A
AE leading to any dose modification/interruption of:			
Any study treatment	177 (40.4%)	212 (46.9%)	882 (27.8%)
AE leading to any dose interruption of atezo/placebo	103 (23.5%)	139 (30.8%)	882 (27.8%)
AE leading to any dose modification/interruption of nab-paclitaxel	172 (39.3%)	195 (43.1%)	N/A
AESIs	183 (41.8%)	259 (57.3%)	1098 (34.6%)

AE=adverse event ; AESI=adverse event of special interest; atezo=atezolizumab; N/A=not applicable; nP=nab-paclitaxel; pl=placebo.

Table 38: Adverse Events with an incidence of at least 10% in any treatment group by preferred terms (Safety-Evaluable Population) - Study Impassion130 and atezolizumab monotherapy pooled dataset

MedDRA Preferred Term	IMpassion130 Placebo + NabPac (N=438)	IMpassion130 Atezo + NabPac (N=452)	Atezo Monotherapy Population (N=3178)
ALOPECIA	252 (57.5%)	255 (56.4%)	37 (1.2%)
FATIGUE	196 (44.7%)	211 (46.7%)	1142 (35.9%)
NAUSEA	167 (38.1%)	208 (46.0%)	747 (23.5%)
DIARRHOEA	150 (34.2%)	147 (32.5%)	624 (19.6%)
ANAEMIA	115 (26.3%)	125 (27.7%)	505 (15.9%)
CONSTIPATION	108 (24.7%)	113 (25.0%)	652 (20.5%)
COUGH	83 (18.9%)	112 (24.8%)	660 (20.8%)
HEADACHE	96 (21.9%)	105 (23.2%)	352 (11.1%)
NEUROPATHY PERIPHERAL	97 (22.1%)	98 (21.7%)	101 (3.2%)
NEUTROPENIA	67 (15.3%)	94 (20.8%)	36 (1.1%)
DECREASED APPETITE	79 (18.0%)	91 (20.1%)	810 (25.5%)
VOMITING	74 (16.9%)	88 (19.5%)	480 (15.1%)
PYREXIA	47 (10.7%)	85 (18.8%)	638 (20.1%)
ARTHRALGIA	70 (16.0%)	81 (17.9%)	442 (13.9%)
RASH	72 (16.4%)	78 (17.3%)	358 (11.3%)
DYSPNOEA	64 (14.6%)	72 (15.9%)	653 (20.5%)
PERIPHERAL SENSORY NEUROPATHY	52 (11.9%)	72 (15.9%)	43 (1.4%)
BACK PAIN	58 (13.2%)	69 (15.3%)	487 (15.3%)
OEDEMA PERIPHERAL	68 (15.5%)	66 (14.6%)	332 (10.4%)
MYALGIA	67 (15.3%)	64 (14.2%)	194 (6.1%)
DIZZINESS	47 (10.7%)	63 (13.9%)	250 (7.9%)
DYSGEUSIA	60 (13.7%)	62 (13.7%)	98 (3.1%)
HYPOTHYROIDISM	15 (3.4%)	62 (13.7%)	137 (4.3%)
PRURITUS	45 (10.3%)	62 (13.7%)	401 (12.6%)
NEUTROPHIL COUNT DECREASED	48 (11.0%)	57 (12.6%)	5 (0.2%)
ASTHENIA	50 (11.4%)	56 (12.4%)	461 (14.5%)
URINARY TRACT INFECTION	46 (10.5%)	53 (11.7%)	338 (10.6%)
INSOMNIA	51 (11.6%)	51 (11.3%)	281 (8.8%)
NASOPHARYNGITIS	37 (8.4%)	49 (10.8%)	141 (4.4%)
PAIN IN EXTREMITY	43 (9.8%)	49 (10.8%)	261 (8.2%)
UPPER RESPIRATORY TRACT INFECTION	40 (9.1%)	48 (10.6%)	227 (7.1%)
ALANINE AMINOTRANSFERASE INCREASED	40 (9.1%)	47 (10.4%)	167 (5.3%)
ABDOMINAL PAIN	53 (12.1%)	46 (10.2%)	268 (8.4%)

Grade 5 AEs due to PD are excluded for studies GO27831 and GO28625.
Investigator text for AEs encoded using MedDRA version 21.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. Includes AEs with onset from first dose of study drug through the clinical cut-off.
GO27831=PCD4989g, GO28625=FIR, GO28753=POPLAR, GO28754=BIRCH, GO29293=IMvigor 210, GO28915=OAK, GO29294=IMvigor 211, WO29074=IMmotion 150, WO29522=IMpassion130. Data cutoffs: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04Jul2016, GO29294:13MAR2017, WO29074:17OCT2016, WO25922:17APR2018.

Table 39: Adverse Events with a difference of at least 5% between treatment arms (Safety-Evaluable Population) - Study IMpassion130

MedDRA Preferred Term	Placebo + nab-Paclitaxel (N=438)	Atezolizumab + nab-Paclitaxel (N=452)
NAUSEA	167 (38.1%)	208 (46.0%)
COUGH	83 (18.9%)	112 (24.8%)
NEUTROPENIA	67 (15.3%)	94 (20.8%)
PYREXIA	47 (10.7%)	85 (18.8%)
HYPOTHYROIDISM	15 (3.4%)	62 (13.7%)

Investigator text for AEs encoded using MedDRA version 21.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. Includes AEs with onset from first dose of study drug through the clinical cut-off.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Table 40: Adverse Events with a ≥5% difference between Atezo+nP and Atezolizumab Monotherapy by Preferred Term (Safety-Evaluable Population) - Study Impassion130 and atezolizumab monotherapy pooled dataset

MedDRA Preferred Term	IMpassion130 Placebo + NabPac (N=438)	IMpassion130 Atezo + NabPac (N=452)	Atezo Monotherapy Population (N=3178)
ALOPECIA	252 (57.5%)	255 (56.4%)	37 (1.2%)
FATIGUE	196 (44.7%)	211 (46.7%)	1142 (35.9%)
NAUSEA	167 (38.1%)	208 (46.0%)	747 (23.5%)
DIARRHOEA	150 (34.2%)	147 (32.5%)	624 (19.6%)
ANAEMIA	115 (26.3%)	125 (27.7%)	505 (15.9%)
HEADACHE	96 (21.9%)	105 (23.2%)	352 (11.1%)
NEUROPATHY PERIPHERAL	97 (22.1%)	98 (21.7%)	101 (3.2%)
NEUTROPENIA	67 (15.3%)	94 (20.8%)	36 (1.1%)
DECREASED APPETITE	79 (18.0%)	91 (20.1%)	810 (25.5%)
RASH	72 (16.4%)	78 (17.3%)	358 (11.3%)
PERIPHERAL SENSORY NEUROPATHY	52 (11.9%)	72 (15.9%)	43 (1.4%)
MYALGIA	67 (15.3%)	64 (14.2%)	194 (6.1%)
DIZZINESS	47 (10.7%)	63 (13.9%)	250 (7.9%)
DYSGEUSIA	60 (13.7%)	62 (13.7%)	98 (3.1%)
HYPOTHYROIDISM	15 (3.4%)	62 (13.7%)	137 (4.3%)
NEUTROPHIL COUNT DECREASED	48 (11.0%)	57 (12.6%)	5 (0.2%)
NASOPHARYNGITIS	37 (8.4%)	49 (10.8%)	141 (4.4%)
ALANINE AMINOTRANSFERASE INCREASED	40 (9.1%)	47 (10.4%)	167 (5.3%)
STOMATITIS	22 (5.0%)	44 (9.7%)	85 (2.7%)
WHITE BLOOD CELL COUNT DECREASED	21 (4.8%)	37 (8.2%)	25 (0.8%)
NAIL DISCOLOURATION	31 (7.1%)	34 (7.5%)	4 (0.1%)
EPISTAXIS	40 (9.1%)	33 (7.3%)	48 (1.5%)
HOT FLUSH	32 (7.3%)	30 (6.6%)	42 (1.3%)
DRY EYE	16 (3.7%)	29 (6.4%)	33 (1.0%)
LEUKOPENIA	23 (5.3%)	28 (6.2%)	9 (0.3%)
LYMPHOEDEMA	31 (7.1%)	27 (6.0%)	16 (0.5%)
BREAST PAIN	23 (5.3%)	26 (5.8%)	10 (0.3%)

Grade 5 AEs due to PD are excluded for studies GO27831 and GO28625.
Investigator text for AEs encoded using MedDRA version 21.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
GO27831=PCD4989g, GO28625=FIR, GO28753=POPLAR, GO28754=BIRCH, GO29293=IMvigor 210, GO28915=OAK, GO29294=IMvigor 211, WO29074=IMmotion 150, WO29522=IMpassion130. Data cutoffs: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04Jul2016, GO29294:13MAR2017, WO29074:17OCT2016, WO25922:17APR2018.

Note: ≥5% difference does not apply to the IMpassion130 pI+nP arm. This arm has been included for comparison purposes.

Table 41: Grade 3–4 Preferred Terms Reported in ≥2% of patients in any Treatment Group (Safety-Evaluable Population) – Study Impassion130 and atezolizumab monotherapy pooled dataset

MedDRA System Organ Class MedDRA Preferred Term	IMpassion130 Placebo + NabPac (N=438)	IMpassion130 Atezo + NabPac (N=452)	Atezo Monotherapy Population (N=3178)
Total number of patients with at least one adverse event	185 (42.2%)	220 (48.7%)	1564 (49.2%)
Overall total number of events	395	522	3366
INVESTIGATIONS			
NEUTROPHIL COUNT DECREASED	15 (3.4%)	21 (4.6%)	2 (<0.1%)
ASPARTATE AMINOTRANSFERASE INCREASED	9 (2.1%)	9 (2.0%)	46 (1.4%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
NEUTROPENIA	36 (8.2%)	37 (8.2%)	11 (0.3%)
ANAEMIA	13 (3.0%)	13 (2.9%)	160 (5.0%)
NERVOUS SYSTEM DISORDERS			
NEUROPATHY PERIPHERAL	12 (2.7%)	25 (5.5%)	2 (<0.1%)
INFECTIONS AND INFESTATIONS			
PNEUMONIA	3 (0.7%)	10 (2.2%)	89 (2.8%)
URINARY TRACT INFECTION	2 (0.5%)	4 (0.9%)	72 (2.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
FATIGUE	15 (3.4%)	18 (4.0%)	109 (3.4%)
METABOLISM AND NUTRITION DISORDERS			
HYPOKALAEMIA	4 (0.9%)	10 (2.2%)	32 (1.0%)
HYPONATRAEMIA	6 (1.4%)	3 (0.7%)	98 (3.1%)
GASTROINTESTINAL DISORDERS			
DIARRHOEA	9 (2.1%)	6 (1.3%)	36 (1.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
DYSPNOEA	3 (0.7%)	4 (0.9%)	117 (3.7%)
VASCULAR DISORDERS			
HYPERTENSION	11 (2.5%)	4 (0.9%)	42 (1.3%)

Investigator text for AEs encoded using MedDRA version 21.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. GO27831=PCD4989g, GO28625=FIR, GO28753=POPLAR, GO28754=BIRCH, GO29293=IMvigor 210, GO28915=OAK, GO29294=IMvigor 211, WO29074=IMmotion 150, WO29522=IMpassion130. Data cutoffs: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04Jul2016, GO29294:13MAR2017, WO29074:17OCT2016, WO25922:17APR2018.

Table 42: Treatment Related AEs reported in at least 10% patients in any treatment arm (Safety-Evaluable Population) - Study Impassion130

MedDRA System Organ Class MedDRA Preferred Term	Placebo + nab-Paclitaxel (N=438)	Atezolizumab + nab-Paclitaxel (N=452)
Total number of patients with at least one adverse event	400 (91.3%)	427 (94.5%)
Overall total number of events	2044	2472
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total number of patients with at least one adverse event	278 (63.5%)	286 (63.3%)
Total number of events	371	394
ALOPECIA	251 (57.3%)	253 (56.0%)
RASH	54 (12.3%)	59 (13.1%)
PRURITUS	36 (8.2%)	46 (10.2%)

MedDRA System Organ Class MedDRA Preferred Term	Placebo + nab-Paclitaxel (N=438)	Atezolizumab + nab-Paclitaxel (N=452)
GASTROINTESTINAL DISORDERS		
Total number of patients with at least one adverse event	230 (52.5%)	250 (55.3%)
Total number of events	492	609
NAUSEA	148 (33.8%)	186 (41.2%)
DIARRHOEA	108 (24.7%)	106 (23.5%)
CONSTIPATION	52 (11.9%)	59 (13.1%)
VOMITING	49 (11.2%)	53 (11.7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total number of patients with at least one adverse event	199 (45.4%)	226 (50.0%)
Total number of events	296	340
FATIGUE	167 (38.1%)	181 (40.0%)
OEDEMA PERIPHERAL	44 (10.0%)	41 (9.1%)
PYREXIA	23 (5.3%)	48 (10.6%)
NERVOUS SYSTEM DISORDERS		
Total number of patients with at least one adverse event	194 (44.3%)	211 (46.7%)
Total number of events	291	336
NEUROPATHY PERIPHERAL	94 (21.5%)	98 (21.7%)
PERIPHERAL SENSORY NEUROPATHY	52 (11.9%)	71 (15.7%)
DYSGEUSIA	57 (13.0%)	56 (12.4%)
HEADACHE	42 (9.6%)	47 (10.4%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total number of patients with at least one adverse event	143 (32.6%)	172 (38.1%)
Total number of events	315	372
ANAEMIA	99 (22.6%)	112 (24.8%)
NEUTROPENIA	66 (15.1%)	93 (20.6%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total number of patients with at least one adverse event	77 (17.6%)	81 (17.9%)
Total number of events	113	116
MYALGIA	50 (11.4%)	49 (10.8%)
ARTHRALGIA	42 (9.6%)	51 (11.3%)
METABOLISM AND NUTRITION DISORDERS		
Total number of patients with at least one adverse event	58 (13.2%)	70 (15.5%)
Total number of events	61	87
DECREASED APPETITE	58 (13.2%)	70 (15.5%)
INVESTIGATIONS		
Total number of patients with at least one adverse event	47 (10.7%)	57 (12.6%)
Total number of events	93	155
NEUTROPHIL COUNT DECREASED	47 (10.7%)	57 (12.6%)
ENDOCRINE DISORDERS		
Total number of patients with at least one adverse event	12 (2.7%)	57 (12.6%)
Total number of events	12	63
HYPOTHYROIDISM	12 (2.7%)	57 (12.6%)

Investigator text for AEs encoded using MedDRA version 21.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes AEs with onset from first dose of study drug through the clinical cut-off.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Adverse Events of Special interest (AESI)

Adverse events of special interest for atezolizumab were selected based on the mechanism of action of atezolizumab. These AESIs were summarized by medical concepts. The medical concepts included atezolizumab-associated important identified risks, potential risks and class effects reported with other immune-checkpoint inhibitors.

Table 43: Overall Summary of AESIs (Safety-Evaluable Population) - Study Impassion130 and atezolizumab monotherapy pooled dataset

	IMpassion130		Atezolizumab Monotherapy (N=3178)
	pI+nP (N=438)	Atezo+nP (N=452)	
AESIs (any grade)	183 (41.8%)	259 (57.3%)	1098 (34.6%)
Grade 1–2	163 (37.2%)	224 (49.6%)	846 (26.6%)
Grade 3–4	19 (4.3%)	34 (7.5%)	248 (7.8%)
Grade 5	1 (0.2%)	1 (0.2%)	4 (0.1%)
Serious AESIs	6 (1.4%)	19 (4.2%)	151 (4.8%)
AESIs leading to placebo/atezolizumab withdrawal	2 (0.5%)	8 (1.8%)	58 (1.8%)
AESIs leading to placebo/atezolizumab interruption	12 (2.7%)	44 (9.7%)	210 (6.6%)
AESIs of patients who received systemic corticosteroid [a] within 30 days of AESI onset	28 (6.4%)	59 (13.1%)	247 (7.8%)
Grade 1–2	21 (4.8%)	46 (10.2%)	127 (4.0%)
Grade 3–4	6 (1.4%)	13 (2.9%)	119 (3.7%)
Grade 5	1 (0.2%)	0	1 (<0.1%)

AESI = adverse event of special interest.

[a] Per the programmatic derivation used, if a corticosteroid was available in multiple formulations and the formulation or route was not specified, it was assumed to be systemic.

Table 44: Summary of AESIs by medical concept (Safety Evaluable Population) - Study Impassion130 and atezolizumab monotherapy pooled dataset

	IMpassion130		Atezolizumab Monotherapy (N=3178)
	pl+nP (N=438)	Atezo+nP (N=452)	
Important AESIs			
Immune-related hypothyroidism	19 (4.3%)	78 (17.3%)	164 (5.2%)
Immune-related hepatitis (diagnosis and lab abnormal)	62 (14.2%)	69 (15.3%)	343 (10.8%)
Immune-related hepatitis (lab abnormal)	58 (13.2%)	62 (13.7%)	315 (9.9%)
Immune-related hepatitis (diagnosis)	7 (1.6%)	10 (2.2%)	62 (2.0%)
Immune-related hyperthyroidism	6 (1.4%)	20 (4.4%)	30 (0.9%)
Immune-related pneumonitis	1 (0.2%)	14 (3.1%)	87 (2.7%)
Infusion-related reactions	5 (1.1%)	5 (1.1%)	34 (1.1%)
Immune-related colitis	3 (0.7%)	5 (1.1%)	34 (1.1%)
Immune-related meningoencephalitis	2 (0.5%)	5 (1.1%)	13 (0.4%)
Immune-related adrenal insufficiency	0	4 (0.9%)	12 (0.4%)
Immune-related pancreatitis	0	2 (0.4%)	18 (0.6%)
Immune-related diabetes mellitus	2 (0.5%)	1 (0.2%)	11 (0.3%)
Immune-related nephritis	0	1 (0.2%)	3 (<0.1%)
Immune-related Guillain-Barre syndrome	0	0	5 (0.2%)
Immune-related hypophysitis	0	0	2 (<0.1%)
Immune-related myasthenic syndrome/myasthenia gravis	0	0	1 (<0.1%)
Other AESIs			
Immune-related rash	114 (26.0%)	154 (34.1%)	620 (19.5%)
Immune-related ocular inflammatory toxic	2 (0.5%)	3 (0.7%)	16 (0.5%)
Immune-related severe cutaneous reaction	3 (0.7%)	2 (0.4%)	22 (0.7%)
Rhabdomyolysis	0	1 (0.2%)	5 (0.2%)

AESI=adverse event of special interest.

Note: There were no reported events of immune–related hypophysitis, immune–related Guillain–Barre syndrome, immune–related myasthenic syndrome/myasthenia gravis, and immune–related myocarditis.

Immune-related hepatitis as a clinical diagnosis was observed in 17 patients (7 in pl+nP arm and 10 in atezo+nP arm). Three patients in the atezo arm had autoimmune hepatitis (2 grade 3 and 1 grade 5). Serious events were rare but more frequent in the atezo arm (1.3% vs. 0.7%) and less than 1% discontinued any treatment due to immune-related hepatitis. Eleven patients in the atezo arm required treatment with systemic corticosteroids.

Immune-related hyperthyroidism was observed in 4.4% of patients in the atezo arm, only 1 patient had a <grade 3 event and overall the event was clinically manageable.

Immune-related pneumonitis was observed in 3.1% of patients in the atezo arm (n=14), and only 1 patient had a <grade 3 event, which required discontinuation of atezolizumab. Overall, the event was clinically manageable.

Infusion-related reactions were rarely observed (1.1%, n=5) in the atezo arm, and all events were of low grade. The number of events were similar in both treatment arms and none caused treatment

discontinuation. In addition, there were no cases of cytokine release syndrome, which is observed in 1 patient in the monotherapy population. Hence, the event was clinically manageable.

Immune-related colitis is a known ADR to atezolizumab and the rate was similar to the rate in the mono-therapy population (1.1%, n=5). One patient discontinued treatment and there were no fatal events. The event was clinically manageable.

Immune-related meningo-encephalitis rarely occurred and in the pivotal study, none had more than grade 1-2 events. There were no discontinuations due to this event, which was clinically manageable.

Immune-related adrenal insufficiency was rare in the atezo arm (0.9%, n=4), but there was one patient with acute adrenal insufficiency which required discontinuation. The patient had recovered by clinical cut-off date (CCOD).

The rate of immune-related pancreatitis was very rare (0.4%, n= 2) in the atezo arm and did not cause clinical symptoms or discontinuations. The events were clinically manageable.

Immune-related diabetes occurred in 1 patient in the atezo arm, which corresponds to the incidence in the monotherapy population. Grade 3 ketoacidosis was observed, which had resolved by the CCOD and did not cause discontinuation. The event was overall considered clinically manageable.

Immune-related nephritis was observed in one patient in the atezo arm and required discontinuation.

Immune-related rash was very common in the atezo arm and was observed in a third of the patients. One patient had a serious event and 6.2% (n=28) of patients required treatment with systemic corticosteroids. The overall risk was lower in the monotherapy population (19.5% vs 34.1%). Serious events and discontinuations were similar in the pivotal study and the monotherapy population. One patient discontinued treatment in the pivotal study.

Immune-related ocular inflammatory toxicity were observed in 3 patients (0.7%) in the atezo arm, leading 2 more than grade 3 events. No patients required discontinuation of treatment and 1 patient received corticosteroids.

Immune-related severe cutaneous reactions were reported rarely and in similar numbers between the treatment arms and the monotherapy population. There were no serious events nor any discontinuations. One patient required corticosteroids.

Rhabdomyolysis was observed in one patient in the atezo arm, and the event was not-resolved at CCOD and lead to dose interruption.

Safety in PD-L1 positive patients

Table 45: Overview of exposure and AE incidence in the safety-evaluable (Study IMpassion130) and PD-L1-positive populations

	Safety-Evaluable Population		PD-L1–Positive SE Population [a]	
	pl+nP (N=438)	atezo+nP (N=452)	pl+nP (N=181)	atezo+nP (N=185)
Exposure				
Median treatment duration (weeks) (range)				
Atezolizumab/placebo	pl: 22.1 (0–109)	atezo: 24.1 (0–139)	pl: 16.1 (0 –109)	atezo: 26.4 (0–139)
nab-paclitaxel	21.8 (0–103)	22.1 (0–137)	16.1 (0–103)	22.7 (0–137)
Median number of cycles (range)				
Atezolizumab/placebo	pl: 6 (1–28)	atezo: 7 (1–35)	pl: 5 (1–28)	atezo: 7 (1–35)
nab-paclitaxel	6 (1–26)	6 (1–34)	5 (1–26)	6 (1–34)
Adverse Events				
Total number of patients with at least one AE (any grade)	429 (97.9)	449 (99.3)	177 (97.8)	185 (100)
Total number of deaths	203 (46.3)	181 (40.0)	88 (48.6)	63 (34.1)
Total number of patients with at least one:				
Grade 5 AE	3 (0.7)	6 (1.3)	1 (0.6)	2 (1.1)
Related Grade 5 AE	1 (0.2)	3 (0.7)	0	1 (0.5)
Grade 3–4 AE	185 (42.2)	220 (48.7)	72 (39.8)	95 (51.4)
Related Grade 3–4 AE	132 (30.1)	179 (39.6)	49 (27.1)	76 (41.1)
SAE	80 (18.3)	103 (22.8)	31 (17.1)	42 (22.7)
Related SAE	32 (7.3)	56 (12.4)	14 (7.7)	21 (11.4)
AE leading to discontinuation of any study treatment	36 (8.2)	72 (15.9)	14 (7.7)	37 (20.0)
AE leading to discontinuation of atezolizumab/placebo	6 (1.4)	29 (6.4)	4 (2.2)	12 (6.5)
AE leading to discontinuation of nab-paclitaxel	36 (8.2)	72 (15.9)	14 (7.7)	37 (20.0)
AE leading to dose interruption of atezolizumab/placebo	103 (23.5)	139 (30.8)	38 (21.0)	60 (32.4)

atezo=atezolizumab; PD-L1=programmed death-ligand 1; pl=placebo; SE=safety-evaluable.

[a] The PD-L1–positive SE population includes patients in the safety-evaluable population who are PD-L1–positive.

Table 46: Overview of AESIs in the Safety-Evaluable and PD-L1 Positive Populations - Study Impassion130

	Safety-Evaluable Population		PD-L1–Positive SE Population [a]	
	pl+nP (N=438)	atezo+nP (N=452)	pl+nP (N=181)	atezo+nP (N=185)
Total number of patients with at least one AESI (any grade)	183 (41.8)	259 (57.3)	66 (36.5)	105 (56.8)
Total number of patients with at least one Grade 3–4 AESI	19 (4.3)	34 (7.5)	7 (3.9)	10 (5.4)
Important AESIs by Medical Concept				
Immune-related hypothyroidism	19 (4.3)	78 (17.3)	6 (3.3)	38 (20.5)
Immune-related hepatitis (diagnosis and laboratory)	62 (14.2)	69 (15.3)	18 (9.9)	19 (10.3)
Immune-related hyperthyroidism	6 (1.4)	20 (4.4)	1 (0.6)	6 (3.2)
Immune-related pneumonitis	1 (0.2)	14 (3.1)	0	4 (2.2)
Infusion-related reactions	5 (1.1)	5 (1.1)	4 (2.2)	3 (1.6)
Immune-related colitis	3 (0.7)	5 (1.1)	1 (0.6)	2 (1.1)
Immune-related meningoencephalitis	2 (0.5)	5 (1.1)	1 (0.6)	5 (2.7)
Immune-related adrenal insufficiency	0	4 (0.9)	0	3 (1.6)
Immune-related pancreatitis	0	2 (0.4)	0	2 (1.1)
Immune-related diabetes mellitus	2 (0.5)	1 (0.2)	1 (0.6)	0
Immune-related nephritis	0	1 (0.2)	0	0
Other AESIs by Medical Concept				
Immune-related rash	114 (26.0)	154 (34.1)	46 (25.4)	69 (37.3)
Immune-related ocular inflammatory toxicity	2 (0.5)	3 (0.7)	1 (0.6)	1 (0.5)
Immune-related severe cutaneous reaction	3 (0.7)	2 (0.4)	1 (0.6)	0
Rhabdomyolysis	0	1 (0.2)	0	0
Systemic immune activation	0	1 (0.2)	0	1 (0.5)
Immune-related myositis	1 (0.2)	0	1 (0.6)	0
Immune-related vasculitis	1 (0.2)	0	1 (0.6)	0
Autoimmune hemolytic anemia	1 (0.2)	0	0	0

atezo=atezolizumab; PD-L1=programmed death-ligand 1; pl=placebo; SE=safety-evaluable.

[a] The PD-L1–positive SE population includes patients in the safety-evaluable population who are PD-L1–positive.

Adverse drug reactions

The safety of Tecentriq in combination with other agents is based on pooled data from IMpassion130, IMpower150 Arms A+B, IMmotion 150/151 and IMpassion130).

Table 47: Pooled population for the safety of Tecentriq in combination with other agents

Pooled Population	Patients Included	Number of Patients (N)
RCC Combination (All ATZ+BEV)	Patients treated with ATZ+BEV pooled from Studies IMmotion151 and IMmotion150	552
Non-squamous NSCLC (ATZ+BEV+CP)	Patients treated with ATZ+BEV+CP from Study IMPower150	393
Non-squamous NSCLC (ATZ+CP)	Patients treated with ATZ+CP from Study IMPower150	400
TNBC combination (ATZ+NabPac)	Patients treated with ATZ+NabPac from study IMPassion130	552
Total	Patients treated with ATZ in combination with other agents from studies IM	1797

The safety of atezolizumab given in combination with other agents, has been evaluated in 1797 patients across multiple tumour types. The most common adverse reactions (≥ 20%) were fatigue (36.6%), nausea (34.2%), peripheral neuropathy (31.8%), rash (31.3%), diarrhea (28.8%), constipation (24.3%), anaemia (24.2%), arthralgia (23.0%), neutropenia (22.8%), decreased appetite (22.5%), musculoskeletal pain (22.0%) and cough (20.6%).

Table 48: ADRs for the atezolizumab monotherapy and combination safety data sets (pooled data sets)

Atezolizumab monotherapy (n=3178)		**System Organ Class ADR**	Atezolizumab in combination therapy (n=1797)	
Frequency (All Grades)	Incidence % (All Grades)		Frequency (All Grades)	Incidence % (All Grades)
Infections and infestations				
very common	368 (11.6%)	Urinary tract infection [a]		
Blood and Lymphatic System Disorders				
-	-	Anaemia	very common	434 (24.2%)
-	-	Neutropenia [c]	very common	410 (22.8%)
common	115 (3.6%)	Thrombocytopenia [b]	very common	223 (12.4%)
Immune System Disorders				
common	36 (1.1%)	Hypersensitivity		
Endocrine Disorders				
uncommon	11 (0.3%)	Adrenal insufficiency [g]		
uncommon	11(0.3%)	Diabetes mellitus [f]		
uncommon	30 (0.9%)	Hyperthyroidism [e]		
rare	2 (<0.1%)	Hypophysitis		
common	164 (5.2%)	Hypothyroidism [d]	very common	302 (16.8%)
Metabolism and nutrition disorders				
very common	809 (25.5%)	Decreased appetite	very common	404 (22.5%)
common	138 (4.3%)	Hypokalemia	common	100 (5.6%)
-	-	Hypomagnesaemia	common	132 (7.3%)
common	169 (5.3%)	Hyponatremia	common	89 (5.0%)
common	103 (3.2%)	Hyperglycaemia		
Nervous System Disorders				
uncommon	5 (0.2%)	Guillain-Barré syndrome [i]	-	-
uncommon	13 (0.4%)	Meningoencephalitis [j]		
rare	1 (<0.1%)	Myasthenic syndrome	-	-
-	-	Peripheral neuropathy [h]	very common	572 (31.8%)
Cardiac Disorders				
rare	0 (<0.1%)	Myocarditis [k]	-	-
Vascular Disorders				
common	102 (3.2%)	Hypotension		
Respiratory, Thoracic, and Mediastinal Disorders				
very common	660 (20.8%)	Cough	very common	371 (20.6%)
very common	653 (20.5%)	Dyspnoea	very common	288 (16.0%)
		Dysphonia	common	132 (7.3%)
common	73 (2.3%)	Hypoxia		

Atezolizumab monotherapy (n=3178)		**System Organ Class ADR**	Atezolizumab in combination therapy (n=1797)	
Frequency (All Grades)	Incidence % (All Grades)		Frequency (All Grades)	Incidence % (All Grades)
common	101 (3.2%)	Nasal congestion		
common	141 (4.4%)	Nasopharyngitis		
common	87 (2.7%)	Pneumonitis [l]		
Gastrointestinal Disorders				
common	268 (8.4%)	Abdominal pain		
common	34 (1.1%)	Colitis [n]		
-	-	Constipation	very common	436 (24.3%)
very common	626 (19.7%)	Diarrhoea [m]	very common	518 (28.8%)
common	82 (2.6%)	Dysphagia		
common	130 (4.1%)	Oropharyngeal pain [o]		
very common	747 (23.5%)	Nausea	very common	614 (34.2%)
uncommon	18 (0.6%)	Pancreatitis [p]		
-	-	Stomatitis	common	176 (9.8%)
very common	480 (15.1%)	Vomiting		
Hepatobiliary Disorders				
common	167 (5.3%)	ALT increased		
common	180 (5.7%)	AST increased		
common	62 (2.0%)	Hepatitis [q]		
Skin and Subcutaneous Tissue Disorders				
very common	401 (12.6%)	Pruritus	very common	273 (15.2%)
very common	620 (19.5%)	Rash [r]	very common	563 (31.3%)
Musculoskeletal and Connective Tissue Disorders				
very common	443 (13.9%)	Arthralgia	very common	414 (23.0%)
very common	487 (15.3%)	Back pain		
very common	417 (13.1%)	Musculoskeletal pain[w]	very common	395 (22.0%)
Uncommon	12 (0.4%)	Myositis [s]		
Renal Disorders				
		proteinuria [t]	very common	202 (11.2%)
rare	3 (<0.1%)	Nephritis [u]		
General Disorders and Administration				
very common	461 (14.5%)	Asthenia		
common	207 (6.5%)	Chills		
very common	1142 (35.9%)	Fatigue	very common	657 (36.6%)
common	186 (5.9%)	Influenza like illness		
common	34 (1.1%)	Infusion related reactions[v]		
very common	638 (20.1%)	Pyrexia	very common	309 (17.2%)
		Headache	very common	336 (18.7%)

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 thrombocytopenia and platelet count decreased.
c. Includes reports of neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic sepsis.
d. 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, thyroxine free increased, thyroid disorder, thyroxine free decreased, thyroxine increased, tri-iodothyronine decreased, tri-iodothyronine increased.
e. Includes reports of hyperthyroidism, endocrine ophthalmopathy, and exophthalmos.
f. Includes reports of diabetes mellitus, type 1 diabetes mellitus, diabetic ketoacidosis and ketoacidosis.
g. Includes reports of adrenal insufficiency and primary adrenal insufficiency.
h. Includes reports of neuropathy peripheral, autoimmune neuropathy, peripheral sensory neuropathy, polyneuropathy, herpes zoster, peripheral motor neuropathy, neuralgic amyotrophy, peripheral sensorimotor neuropathy, toxic neuropathy, axonal neuropathy, lumbosacral plexopathy, neuropathic arthropathy.
i. Includes reports of Guillain-Barré syndrome and demyelinating polyneuropathy.
j. Includes reports of encephalitis, meningitis, photophobia.
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 diarrhoea, defaecation urgency, frequent bowel movements, and gastrointestinal hypermotility.
n. Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic, colitis ulcerative.
o. Includes reports of oropharyngeal pain, oropharyngeal discomfort and throat irritation.
p. Includes reports of pancreatitis, pancreatitis acute, lipase increased and amylase increased.
q. 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.
r. 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, dermatitis exfoliative generalised.
s. Includes reports of myositis, rhabdomyolysis, polymyalgia rheumatica, dermatomyositis, myoglobin urine present.
t. Includes reports of proteinuria, protein urine present, haemoglobinurea, nephrotic syndrome.
u. Includes report of Henoch-Schonlein Purpura nephritis.
v. Includes infusion-related reaction and cytokine release syndrome.
w. Includes reports of musculoskeletal pain and myalgia.

Serious adverse events and deaths

Table 49: Serious adverse events reported in ≥ 1% of patients in either treatment arm (safety-evaluable population) - Study Impassion130

MedDRA System Organ Class MedDRA Preferred Term	Placebo + nab-Paclitaxel (N=438)	Atezolizumab + nab-Paclitaxel (N=452)
Total number of patients with at least one adverse event	9 (2.1%)	24 (5.3%)
Overall total number of events	10	28
INFECTIONS AND INFESTATIONS		
PNEUMONIA	5 (1.1%)	10 (2.2%)
URINARY TRACT INFECTION	0	5 (1.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
PYREXIA	3 (0.7%)	5 (1.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
DYSPNOEA	2 (0.5%)	5 (1.1%)

Investigator text for AEs encoded using MedDRA version 21.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes AEs with onset from first dose of study drug through the clinical cut-off.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Table 50: SAEs Related to any Study Treatment - Study Impassion130

	Placebo + nab-Paclitaxel (N = 438)	Atezolizumab + nab-Paclitaxel (N = 452)
Total number of patients with at least one adverse event	32 (7.3%)	56 (12.4%)
Overall total number of events	47	83
Pneumonia	2 (0.5%)	5 (1.1%)
Febrile neutropenia	1 (0.2%)	4 (0.9%)
Dyspnoea	1 (0.2%)	4 (0.9%)
Colitis	1 (0.2%)	3 (0.7%)
Cellulitis	1 (0.2%)	3 (0.7%)
Nausea	3 (0.7%)	2 (0.4%)
Mucosal inflammation	1 (0.2%)	2 (0.4%)
General physical health deterioration	0	2 (0.4%)
Autoimmune hepatitis	0	2 (0.4%)
Muscular weakness	0	2 (0.4%)
Pyrexia	2 (0.5%)	1 (0.2%)
Diarrhoea	3 (0.7%)	1 (0.2%)

SAEs = serious adverse events
Note: Includes AEs that occurred more than once in either arm
Source: t_ae_SER_REL_SE_17APR2018_29522

Table 51: Deaths and causes of death (safety-evaluable population) - Study Impassion130

Primary Cause of Death	Placebo + nab-Paclitaxel (N=438)	Atezolizumab + nab-Paclitaxel (N=452)
All Deaths	203 (46.3%)	181 (40.0%)
Adverse Event	3 (0.7%)	6 (1.3%)
Progressive Disease	186 (42.5%)	157 (34.7%)
Other*	14 (3.2%)	18 (4.0%)

*includes deaths due to AEs, unrelated, and those outside of the 30-day reporting period from the last dose.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Table 52: Fatal Adverse Events (Safety-Evaluable Population) - Study Impassion130

MedDRA System Organ Class MedDRA Preferred Term	Placebo + nab-Paclitaxel (N=438)	Atezolizumab + nab-Paclitaxel (N=452)
Total number of patients with at least one adverse event	3 (0.7%)	6 (1.3%)
Overall total number of events	3	7
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total number of patients with at least one adverse event	1 (0.2%)	1 (0.2%)[a]
Total number of events	1	2
DEATH	1 (0.2%)	1 (0.2%)
MUCOSAL INFLAMMATION	0	1 (0.2%)
HEPATOBILIARY DISORDERS		
Total number of patients with at least one adverse event	1 (0.2%)	1 (0.2%)
Total number of events	1	1
AUTOIMMUNE HEPATITIS	0	1 (0.2%)
HEPATIC FAILURE	1 (0.2%)	0
INFECTIONS AND INFESTATIONS		
Total number of patients with at least one adverse event	0	2 (0.4%)
Total number of events	0	2
PNEUMONIA	0	1 (0.2%)
SEPTIC SHOCK	0	1 (0.2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total number of patients with at least one adverse event	0	2 (0.4%)
Total number of events	0	2
ASPIRATION	0	1 (0.2%)
PULMONARY EMBOLISM	0	1 (0.2%)
CARDIAC DISORDERS		
Total number of patients with at least one adverse event	1 (0.2%)	0
Total number of events	1	0
ACUTE MYOCARDIAL INFARCTION	1 (0.2%)	0

Investigator text for AEs encoded using MedDRA version 21.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes AEs with onset from first dose of study drug through the clinical cut-off.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Laboratory findings

Table 53: Summary of Clinically Relevant Shifts from Baseline in Laboratory Safety Parameters (Safety-Evaluable Population) - Study Impassion130

Laboratory Test	Direction of Abnormality	Placebo + nab-Paclitaxel (N=438)	Atezolizumab + nab-Paclitaxel (N=452)
Chemistry			
Albumin	Low	4/435 (0.9%)	9/451 (2.0%)
	High	0/438	0/452
Alkaline Phosphatase	Low	0/438	0/452
	High	12/437 (2.7%)	16/452 (3.5%)
SGPT/ALT	Low	0/438	0/452
	High	12/437 (2.7%)	25/452 (5.5%)
SGOT/AST	Low	0/438	0/452
	High	16/436 (3.7%)	22/452 (4.9%)
Calcium	Low	11/438 (2.5%)	9/451 (2.0%)
	High	4/438 (0.9%)	6/452 (1.3%)
Creatinine	Low	0/438	0/452
	High	3/438 (0.7%)	4/452 (0.9%)
Glucose	Low	5/436 (1.1%)	2/451 (0.4%)
	High	0/438	0/452
Magnesium	Low	5/436 (1.1%)	2/451 (0.4%)
	High	11/434 (2.5%)	11/450 (2.4%)
Phosphorus	Low	16/432 (3.7%)	16/448 (3.6%)
	High	0/433	0/449
Potassium	Low	11/437 (2.5%)	18/452 (4.0%)
	High	8/438 (1.8%)	8/451 (1.8%)
Sodium	Low	16/434 (3.7%)	25/449 (5.6%)
	High	3/438 (0.7%)	1/452 (0.2%)
Bilirubin	Low	0/438	0/452
	High	13/437 (3.0%)	7/451 (1.6%)
Coagulation			
International Normalized Ratio	Low	0/436	0/450
	High	1/436 (0.2%)	2/449 (0.4%)
Activated Partial Thromboplastin Time	Low	0/431	0/449
	High	1/431 (0.2%)	3/449 (0.7%)
Hematology			
Hemoglobin	Low	16/437 (3.7%)	19/450 (4.2%)
	High	7/438 (1.6%)	8/452 (1.8%)
Lymphocytes Abs	Low	28/294 (9.5%)	44/313 (14.1%)
	High	2/298 (0.7%)	7/315 (2.2%)
Neutrophils, Total, Abs	Low	41/299 (13.7%)	43/316 (13.6%)
	High	0/300	0/316
Platelet	Low	8/437 (1.8%)	7/451 (1.6%)
	High	0/438	0/452
Total Leukocyte Count	Low	42/438 (9.6%)	61/450 (13.6%)
	High	3/438 (0.7%)	4/452 (0.9%)

For each patient, baseline is the last observation prior to initiation of study drug. For each laboratory test, patients with at least 1 post-baseline assessment are included in the analysis. For each cell, the denominator is the number of patients with baseline values with NCI-CTCAE Grade 0-2 in the specified direction of abnormality. Patients with missing baseline values are counted as Grade 0-2 at baseline.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Safety in special populations

Safety by age

Table 54: **Incidence of AEs by Age Group in Atezolizumab+Nab-Paclitaxel Arm, Safety Evaluable Population - Study Impassion130**

MedDRA Terms	Age <65 N = 348	Age 65-74 N = 83	Age 75-84 N = 21	Age 85+ N= 0
Total AEs	5613	1525	359	0
Serious AEs – Total	66 (19.0%)	26 (31.3%)	11 (52.4%)	0
Fatal	6 (1.7%)	0	0	0
Hospitalization/ prolong existing hospitalization	60 (17.2%)	24 (28.9%)	11 (52.4%)	0
Life-threatening	4 (1.1%)	2 (2.4%)	1 (4.8%)	0
Disability/incapacity	4 (1.1%)	0	1 (4.8%)	0
Other (medically significant)	4 (1.1%)	2 (2.4%)	0	0

AE leading to drop-out	14 (4.0%)	6 (7.2%)	9 (42.9%)	0
Psychiatric disorders	69 (19.8%)	18 (21.7%)	3 (14.3%)	0
Nervous system disorders	227 (65.2%)	62 (74.7%)	16 (76.2%)	0
Accidents and injuries	27 (7.8%)	14 (16.9%)	5 (23.8%)	0
Cardiac disorders	33 (9.5%)	4 (4.8%)	0	0
Vascular disorders	85 (24.4%)	19 (22.9%)	3 (14.3%)	0
Cerebrovascular disorders	2 (0.6%)	0	0	0
Infections and infestations	193 (55.5%)	51 (61.4%)	16 (76.2%)	0
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	See paragraph below			
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	52 (14.9%)	22 (26.5%)	2 (9.5%)	0

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities
Source: t_ae_aet01_aesi_A_SE

Table 55: Safety summary by age (Safety Summary by Age (<65 Years vs. ≥65 Years) (Safety-Evaluable Population in IMpassion130)

	pl+nP (N=438)		Atezo+nP (N=452)	
	<65 (n=324)	≥65 (n=114)	<65 (n=348)	≥65 (n=104)
Total number of patients with at least one Adverse event	318 (98.1%)	111 (97.4%)	345 (99.1%)	104 (100.0%)
Treatment−related AE	303 (93.5%)	107 (93.9%)	335 (96.3%)	101 (97.1%)
Grade 3−4 AE	126 (38.9%)	59 (51.8%)	148 (42.5%)	72 (69.2%)
Treatment−related Grade 3−4 AE	87 (26.9%)	45 (39.5%)	118 (33.9%)	61 (58.7%)
Grade 5 AE	3 (0.9%)	0	6 (1.7%)	0
Treatment−related Grade 5 AE	1 (0.3%)	0	3 (0.9%)	0
SAE	60 (18.5%)	20 (17.5%)	66 (19.0%)	37 (35.6%)
Treatment−related SAE	24 (7.4%)	8 (7.0%)	42 (12.1%)	14 (13.5%)
AE leading to withdrawal from any treatment	21 (6.5%)	15 (13.2%)	42 (12.1%)	30 (28.8%)
AE leading to any dose modification/ interruption	123 (38.0%)	54 (47.4%)	146 (42.0%)	66 (63.5%)
AESI	139 (42.9%)	44 (38.6%)	192 (55.2%)	67 (64.4%)
Grade 3−4 AESI	17 (5.2%)	2 (1.8%)	21 (6.0%)	13 (12.5%)
Grade 5 AESI	1 (0.3%)	0	1 (0.3%)	0

AE=adverse event; AESI=adverse events of special interest; atezo=atezolizumab; nP=nab-paclitaxel; pl=placebo; SAE=serious adverse event

Table 56: Grade 3-4 Events and Serious Adverse Events with a ≥2% difference in Preferred Terms between Patients Aged <65 and ≥65 Years in the Atezo+nP Arm (Safety-Evaluable Population)

MedDRA Preferred Term	Atezo+nP (N=452) <65 (n=348)	Atezo+nP (N=452) ≥65 (n=104)
Grade 3-4 Events		
Anaemia	8 (2.3%)	5 (4.8%)
Leukopenia	4 (1.1%)	4 (3.8%)
Aspartate Aminotransferase Increased	4 (1.1%)	5 (4.8%)
Peripheral Neuropathy	13 (3.7%)	12 (11.5%)
Poly Neuropathy	2 (0.6%)	4 (3.8%)
Fatigue	16 (4.6%)	2 (1.9%)
Urinary Tract Infection	0	4 (3.8%)
Upper Respiratory Infection	2 (0.6%)	3 (2.9%)
Diarrhoea	2 (0.6%)	4 (3.8%)
Hypertension	1 (0.3%)	3 (2.9%)
Serious Adverse Events		
Pneumonia	6 (1.7%)	4 (3.8%)
Urinary Tract Infection	1 (0.3%)	4 (3.8%)

Atezo=atezolizumab; MedDRA=Medical Dictionary for Regulatory Activitie; nP=nab-paclitaxel

Safety by Race

Table 57: Safety Summary by Race (Safety-Evaluable Population in IMpassion130)

	pl+nP (N=438)				Atezo+nP (N=452)			
	American Indian or Alaska Native (n=23)	Asian (n=74)	Black or African American (n=27)	White (n=296)	American Indian or Alaska Native (n=17)	Asian (n=84)	Black or African American (n=30)	White (n=306)
Total no. of patients with at least one Adverse event	21 (91.3%)	74 (100%)	27 (100%)	289 (97.6%)	17 (100%)	84 (100%)	30 (100%)	303 (99.0%)
Treatment-related AE	20 (87.0%)	72 (97.3%)	26 (96.3%)	275 (92.9%)	16 (94.1%)	79 (94.0%)	29 (96.7%)	297 (97.1%)
Grade 3–4 AE	11 (47.8%)	27 (36.5%)	14 (51.9%)	123 (41.6%)	9 (52.9%)	36 (42.9%)	16 (53.3%)	149 (48.7%)
Treatment-related Grade 3–4 AE	7 (30.4%)	24 (32.4%)	9 (33.3%)	83 (28.0%)	8 (47.1%)	29 (34.5%)	12 (40.0%)	122 (39.9%)
Grade 5 AE	0	0	0	3 (1.0%)	2 (11.8%)	0	0	4 (1.3%)
Treatment-related Grade 5 AE	0	0	0	1 (1.0%)	2 (11.8%)	0	0	1 (0.3%)
SAE	1 (4.3%)	7 (9.5%)	4 (14.8%)	67 (22.6%)	5 (29.4%)	9 (10.7%)	7 (23.3%)	80 (26.1%)
Treatment−related SAE	0	4 (5.4%)	2 (7.4%)	26 (8.8%)	5 (29.4%)	6 (7.1%)	4 (13.3%)	39 (12.7%)
AE leading to withdrawal from any treatment	3 (13.0%)	4 (5.4%)	2 (7.4%)	21 (7.1%)	1 (5.9%)	6 (7.1%)	5 (16.7%)	58 (19.0%)
AE leading to any dose modification/ interruption	8 (34.8%)	37 (50.0%)	7 (25.9%)	122 (41.2%)	4 (23.5%)	57 (67.9%)	9 (30.0%)	136 (44.4%)
AESI	9 (39.1%)	31 (41.9%)	11 (40.7%)	123 (41.6%)	7 (41.2%)	47 (56.0%)	10 (33.3%)	185 (60.5%)
Grade 3-4 AESI	0	3 (4.1%)	2 (7.4%)	14 (4.7%)	1 (5.9%)	3 (3.6%)	0	29 (9.5%)
Grade 5 AESI	0	0	0	1 (0.3%)	0	0	0	1 (0.3%)

AE=adverse event; AESI=adverse events of special interest; atezo=atezolizumab, nP=nab-paclitaxel; pl=placebo, SAE=serious adverse event.
Note: Other subgroups by race not included in the table are (numbers presented pl+nP and atezo+nP) Native Hawaiian or other Pacific Islander (0 and 1), multiple (3 and 2), and unknown (15 and 12).

Safety by region

Table 58: Safety Summary by Region (Safety-Evaluable Population in IMpassion130)

	pl+nP (N=438)					Atezo+nP (N=452)				
	Asia (n=65)	Australia (n=21)	Europe and Middle East (n=170)	Latin America (n=81)	North America (n=101)	Asia (n=78)	Australia (n=21)	Europe and Middle East (n=174)	Latin America (n=55)	North America (n=124)
Total no. of patients with at least one AE										
Adverse event	65 (100%)	21 (100%)	168 (98.8%)	74 (91.4%)	101 (100%)	78 (100%)	21 (100%)	171 (98.3%)	55 (100%)	124 (100%)
Treatment-related AE	63 (96.9%)	21 (100%)	159 (93.5%)	68 (84.0%)	99 (98.0%)	73 (93.6%)	21 (100%)	169 (97.1%)	52 (94.5%)	121 (97.6%)
Grade 3-4 AE	24 (36.9%)	9 (42.9%)	70 (41.2%)	31 (38.3%)	51 (50.5%)	32 (41.0%)	9 (42.9%)	79 (45.4%)	26 (47.3%)	74 (59.7%)
Treatment-related Grade 3-4	21 (32.3%)	6 (28.6%)	47 (27.6%)	21 (25.9%)	37 (36.6%)	26 (33.3%)	7 (33.3%)	66 (37.9%)	18 (32.7%)	62 (50.0%)
Grade 5 AE	0	0	1 (0.6%)	1 (1.2%)	1 (1.0%)	0	0	3 (1.7%)	2 (3.6%)	1 (0.8%)
Treatment-related Grade 5 AE	0	0	0	0	1 (1.0%)	0	0	0	2 (3.6%)	1 (0.8%)
SAE	7 (10.8%)	10 (47.6%)	35 (20.6%)	10 (12.3%)	18 (17.8%)	7 (9.0%)	6 (28.6%)	41 (23.6%)	13 (23.6%)	36 (29.0%)
Treatment-related SAE	4 (6.2%)	2 (9.5%)	12 (7.1%)	5 (6.2%)	9 (8.9%)	4 (5.1%)	2 (9.5%)	21 (12.1%)	9 (16.4%)	20 (16.1%)
AE leading to any study treatment discontinuation	3 (4.6%)	5 (23.8%)	15 (8.8%)	4 (4.9%)	9 (8.9%)	5 (6.4%)	8 (38.1%)	29 (16.7%)	6 (10.9%)	24 (19.4%)
AE leading to any study treatment dose modification or interruption	36 (55.4%)	7 (33.3%)	65 (38.2%)	26 (32.1%)	43 (42.6%)	54 (69.2%)	9 (42.9%)	78 (44.8%)	15 (27.3%)	56 (45.2%)
AESI	27 (41.5%)	6 (28.6%)	69 (40.6%)	26 (32.1%)	55 (54.5%)	44 (56.4%)	11 (52.4%)	100 (57.5%)	24 (43.6%)	80 (64.5%)
Grade 3-4 AESI	3 (4.6%)	0	7 (4.1%)	2 (2.5%)	7 (6.9%)	3 (3.8%)	3 (14.3%)	16 (9.2%)	3 (5.5%)	9 (7.3%)
Grade 5 AESI	0	0	0	0	1 (1.0%)	0	0	0	0	1 (0.8%)

AE=adverse event; AESI=adverse events of special interest; atezo=atezolizumab, nP=nab-paclitaxel; pl=placebo, SAE=serious adverse event.
Source: t_saf_sum_aesi_by_region_PA_SE, t_saf_sum_by_region_PA_SE

Safety by ECOG status

Table 59: Overview of Safety by ECOG PS - Study Impassion130

	Placebo + nab-Paclitaxel (N=438)		Atezolizumab + nab-Paclitaxel (N=452)	
	ECOG 0 (N=263)	ECOG 1 (N=173)	ECOG 0 (N=260)	ECOG 1 (N=191)
Total number of patients with at least one AE	257 (97.7%)	170 (98.3%)	258 (99.2%)	190 (99.5%)
Total number of AEs	3693	2214	4361	3132
Total number of deaths	96 (36.5%)	106 (61.3%)	84 (32.3%)	96 (50.3%)
Total number of patients with at least one				
AE with fatal outcome	0	3 (1.7%)	1 (0.4%)	4 (2.1%)
Related AE with fatal outcome	0	1 (0.6%)	0	2 (1.0%)
Grade 3-4 AE	101 (38.4%)	82 (47.4%)	118 (45.4%)	102 (53.4%)
Related Grade 3-4 AE	81 (30.8%)	50 (28.9%)	101 (38.8%)	78 (40.8%)
Serious AE	35 (13.3%)	43 (24.9%)	52 (20.0%)	50 (26.2%)
Related Serious AE	17 (6.5%)	14 (8.1%)	29 (11.2%)	26 (13.6%)
Related AE	248 (94.3%)	160 (92.5%)	255 (98.1%)	180 (94.2%)
AE leading to any study treatment discontinuation	19 (7.2%)	17 (9.8%)	44 (16.9%)	28 (14.7%)
AE leading to Atezolizumab/Placebo discontinuation	3 (1.1%)	3 (1.7%)	17 (6.5%)	12 (6.3%)
AE leading to Nab-paclitaxel discontinuation	19 (7.2%)	17 (9.8%)	44 (16.9%)	28 (14.7%)
AE leading to any study treatment dose modification or interruption	111 (42.2%)	64 (37.0%)	128 (49.2%)	84 (44.0%)
AE leading to dose interruption of Atezolizumab/Placebo	66 (25.1%)	35 (20.2%)	83 (31.9%)	56 (29.3%)
AE leading to dose reduction or interruption of Nab-paclitaxel	109 (41.4%)	61 (35.3%)	116 (44.6%)	79 (41.4%)

Investigator text for AEs is coded using MedDRA version 21.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately. Includes AEs with onset from first dose of study drug through the clinical cut-off.
ECOG scores of missing and 2 are not included in the table.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Safety by prior treatment with anthracyclines or taxane

Table 60: Overview of AE and AESI in Placebo + nab-Paclitaxel Arm with Prior Treatment with Anthracyclines or Taxane in Comparison to Safety Evaluable Population - Study

Impassion130

	AEs				AESIs			
	Safety Evaluable Population	Prior Taxane or Anthra-cycline	Prior Taxane	Prior Anthra-cycline	Safety Evaluable Population	Prior Taxane or Anthra-cycline	Prior Taxane	Prior Anthra-cycline
	pl+nP (N=438)	pl+nP (N=273)	pl+nP (N=224)	pl+nP (N=237)	pl+nP (N=438)	pl+nP (N=273)	pl+nP (N=224)	pl+nP (N=237)
AE with fatal outcome	3 (0.7%)	0	0	0	1 (0.2%)	0		0
Related AE with fatal outcome	1 (0.2%)	0	0	0	1 (0.2%)	0	0	0
Grade 3–4 AE	185 (42.2%)	114 (41.8%)	92 (41.1%)	93 (39.2%)	19 (4.3%)	9 (3.3%)	8 (3.6%)	7 (3.0%)
Related Grade 3–4 AE	132 (30.1%)	85 (31.1%)	69 (30.8%)	68 (28.7%)	14 (3.2%)	7 (2.6%)	6 (2.7%)	5 (2.1%)
Serious AE	80 (18.3%)	46 (16.8%)	35 (15.6%)	40 (16.9%)	6 (1.4%)	2 (0.7%)	2 (0.9%)	1 (0.4%)
Related Serious AE	32 (7.3%)	16 (5.9%)	14 (6.3%)	13 (5.5%)	6 (1.4%)	2 (0.7%)	2 (0.9%)	1 (0.4%)
Related AE	410 (93.6%)	259 (94.9%)	212 (94.6%)	226 (95.4%)	141 (32.2%)	87 (31.9%)	68 (30.4%)	76 (32.1%)
AE leading to any study treatment discontinuation	36 (8.2%)	26 (9.5%)	20 (8.9%)	23 (9.7%)	2 (0.5%)	1 (0.4%)	1 (0.4%)	1 (0.4%)

AE =adverse events; AESI =adverse events of special interest; nP =nab-paclitaxel; pl =placebo Source: t_saf_sum_PRANTAX_SE_17APR2018_29522, t_saf_sum_PRANTH_SE_17APR2018_29522, t_saf_sum_PRTAX_SE_17APR2018_29522, t_saf_sum_aesi_PRANTAX_SE_17APR2018_29522, t_saf_sum_aesi_PRANTH_SE_17APR2018_29522, t_saf_sum_aesi_PRTAX_SE_17APR2018_29522

Table 61: Overview of AE and AESI in Atezo + nab-Paclitaxel Arm with Prior Treatment with Anthracyclines or Taxane in Comparison to Safety Evaluable Population - Study Impassion130

	AEs				AESIs			
	Safety Evaluable Population	Prior Taxane or Anthra-cycline	Prior Taxane	Prior Anthra-cycline	Safety Evaluable Population	Prior Taxane or Anthra-cycline	Prior Taxane	Prior Anthra-cycline
	atezo+nP (N=452)	atezo+nP (N=274)	atezo+nP (N=232)	atezo+nP (N=242)	atezo+nP (N=452)	atezo+nP (N=274)	atezo+nP (N=232)	atezo+nP (N=242)
AE with fatal outcome	6 (1.3%)	4 (1.5%)	4 (1.7%)	3 (1.2%)	1 (0.2%)	1 (0.4%)	1 (0.4%)	0
Related AE with fatal outcome	3 (0.7%)	2 (0.7%)	2 (0.9%)	1 (0.4%)	1 (0.2%)	1 (0.4%)	1 (0.4%)	0
Grade 3–4 AE	220 (48.7%)	143 (52.2%)	117 (50.4%)	123 (50.8%)	34 (7.5%)	20 (7.3%)	17 (7.3%)	18 (7.4%)
Related Grade 3–4 AE	179 (39.6%)	114 (41.6%)	91 (39.2%)	94 (38.8%)	28 (6.2%)	17 (6.2%)	15 (6.5%)	15 (6.2%)
Serious AE	103 (22.8%)	63 (23.0%)	52 (22.4%)	54 (22.3%)	19 (4.2%)	11 (4.0%)	10 (4.3%)	10 (4.1%)
Related Serious AE	56 (12.4%)	34 (12.4%)	30 (12.9%)	29 (12.0%)	17 (3.8%)	10 (3.6%)	9 (3.9%)	9 (3.7%)
Related AE	436 (96.5%)	267 (97.4%)	226 (97.4%)	235 (97.1%)	214 (47.3%)	130 (47.4%)	108 (46.6%)	113 (46.7%)
AE leading to any study treatment discontinuation	72 (15.9%)	43 (15.7%)	36 (15.5%)	35 (14.5%)	11 (2.4%)	7 (2.6%)	7 (3.0%)	5 (2.1%)

AE =adverse event; AESI =adverse events of special interest; atezo =atezolizumab; nP =nab-paclitaxel
Source: t_saf_sum_PRANTAX_SE_17APR2018_29522, t_saf_sum_PRANTH_SE_17APR2018_29522, t_saf_sum_PRTAX_SE_17APR2018_29522, t_saf_sum_aesi_PRANTAX_SE_17APR2018_29522, t_saf_sum_aesi_PRANTH_SE_17APR2018_29522, t_saf_sum_aesi_PRTAX_SE_17APR2018_29522

Immunological events

Table 62: Safety summary in the atezo+nP arm by ADA status - Study Impassion130

	ADA- (N=377)	ADA+ (N=57)
Total number of patients with at least one AE	374 (99.2%)	57 (100%)
Total number of AEs	6494	829
Total number of deaths	147 (39.0%)	20 (35.1%)
Total number of patients with at least one		
AE with fatal outcome	4 (1.1%)	1 (1.8%)
Related AE with fatal outcome	2 (0.5%)	0
Grade 3-4 AE	184 (48.8%)	28 (49.1%)
Related Grade 3-4 AE	153 (40.6%)	23 (40.4%)
Serious AE	81 (21.5%)	16 (28.1%)
Related Serious AE	45 (11.9%)	9 (15.8%)
Related AE	369 (97.9%)	53 (93.0%)
AE leading to any study treatment discontinuation	60 (15.9%)	10 (17.5%)
AE leading to Atezolizumab/Placebo discontinuation	22 (5.8%)	6 (10.5%)
AE leading to Nab-paclitaxel discontinuation	60 (15.9%)	10 (17.5%)
AE leading to any dose reduction or study treatment interruption	179 (47.5%)	29 (50.9%)
AE leading to dose interruption of Atezolizumab/Placebo	115 (30.5%)	22 (38.6%)
AE leading to dose reduction or interruption of Nab-paclitaxel	163 (43.2%)	28 (49.1%)

ADA = Anti-Drug Antibodies (is also referred to as ATA, or Anti-Therapeutic Antibodies); ADA- = Without TX Enhanced/Induced; ADA+ = With TX Enhanced/Induced; TX = Treatment.
Investigator text for AEs is coded using MedDRA version 21.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately. Includes AEs with onset from first dose of study drug through the clinical cut-off.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Table 63: Summary of AESIs in the atezo+nP arm by ADA status - Study Impassion130

	ADA- (N=377)	ADA+ (N=57)
Total number of patients with at least one AE	221 (58.6%)	30 (52.6%)
Total number of AEs	451	69
Total number of deaths	147 (39.0%)	20 (35.1%)
Total number of patients with at least one		
AE with fatal outcome	1 (0.3%)	0
Related AE with fatal outcome	1 (0.3%)	0
Grade 3-4 AE	30 (8.0%)	4 (7.0%)
Related Grade 3-4 AE	26 (6.9%)	2 (3.5%)
Serious AE	16 (4.2%)	3 (5.3%)
Related Serious AE	14 (3.7%)	3 (5.3%)
Related AE	182 (48.3%)	26 (45.6%)
AE leading to any study treatment discontinuation	10 (2.7%)	1 (1.8%)
AE leading to Atezolizumab/Placebo discontinuation	7 (1.9%)	1 (1.8%)
AE leading to Nab-paclitaxel discontinuation	8 (2.1%)	1 (1.8%)
AE leading to any dose reduction or study treatment interruption	44 (11.7%)	6 (10.5%)
AE leading to dose interruption of Atezolizumab/Placebo	37 (9.8%)	6 (10.5%)
AE leading to dose reduction or interruption of Nab-paclitaxel	29 (7.7%)	3 (5.3%)
Medical concepts: patients with		
Immune-Related Hepatitis (Diagnosis and Lab Abnormalities)	56 (14.9%)	11 (19.3%)
Immune-Related Hypothyroidism	69 (18.3%)	8 (14.0%)
Immune-Related Hyperthyroidism	19 (5.0%)	1 (1.8%)
Immune-Related Adrenal Insufficiency	4 (1.1%)	0
Immune-Related Pneumonitis	11 (2.9%)	1 (1.8%)
Immune-Related Colitis	4 (1.1%)	1 (1.8%)
Immune-Related Guillain-Barre Syndrome	0	0
Immune-Related Myasthenia Gravis	0	0
Immune-Related Meningoencephalitis	3 (0.8%)	1 (1.8%)
Infusion-Related Reactions	5 (1.3%)	0
Immune-Related Pancreatitis	2 (0.5%)	0
Immune-Related Diabetes Mellitus	1 (0.3%)	0
Immune-Related Myositis	0	0
Immune-Related Nephritis	1 (0.3%)	0
Immune-Related Rash	136 (36.1%)	16 (28.1%)
Rhabdomyolysis	0	1 (1.8%)
Systemic Immune Activation	1 (0.3%)	0
Immune-Related Meningitis	3 (0.8%)	1 (1.8%)
Immune-Related Encephalitis	0	0
Immune-Related Ocular Inflammatory Toxicity	3 (0.8%)	0
Immune-Related Vasculitis	0	0
Immune-Related Hypophysitis	0	0
Immune-Related Myocarditis	0	0
Immune-Related Severe Cutaneous Reactions	2 (0.5%)	0
Autoimmune Hemolytic Anemia	0	0
Immune-Related Hepatitis (Diagnosis)	9 (2.4%)	1 (1.8%)
Immune-Related Hepatitis (Lab Abnormalities)	50 (13.3%)	10 (17.5%)

ADA = Anti-Drug Antibodies (is also referred to as ATA, or Anti-Therapeutic Antibodies); ADA- = Without TX Enhanced/Induced; ADA+ = With TX Enhanced/Induced; TX = Treatment.
Investigator text for AEs is coded using MedDRA version 21.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately. Includes AEs with onset from first dose of study drug through the clinical cut-off.
RAVE Data Snapshot Date: 05JUN2018. Data Cutoff Date: 17APR2018.

Safety related to drug-drug interactions and other interactions

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

Discontinuation due to AES

Table 64: Adverse Events Leading to Treatment Withdrawal in ≥2 Patients in Either Atezo+nP or Atezolizumab Monotherapy (Safety- Evaluable Population) - Study Impassion130

MedDRA System Organ Class MedDRA Preferred Term	Atezo+nP (N=452)	Atezolizumab Monotherapy (N=3178)
Total number of patients with at least one AE	29 (6.4%)	226 (7.1%)
Nervous System Disorders		
Neuropathy Peripheral	4 (0.9%)	0
Cerebral Vascular Accident	0	4 (0.1%)
Cognitive Disorder	0	2 (<0.1%)
Ischemic Stroke	0	2 (<0.1%)
Optic Neuritis	0	2 (<0.1%)
General Disorders and Administration Site Conditions		
Fatigue	2 (0.4%)	4 (0.1%)
General Physical Health Deterioration	2 (0.4%)	2 (<0.1%)
Death	0	8 (0.3%)
Pyrexia	0	2 (<0.1%)
Sudden Death	0	3 (<0.1%)
Infections and Infestations		
Lung Infection	1 (0.2%)	2 (<0.1%)
Pnuemonia	1 (0.2%)	12 (0.4%)
Meningitis	0	3 (<0.1%)
Sepsis	0	8 (0.3%)
Septic Shock	0	5 (0.2%)
Investigations		
Aspartate Aminotransferase Increased	2 (0.4%)	5 (0.2%)
Alanine Aminotransferase Increased	0	4 (0.1%)
Weight Decreased	0	2 (<0.1%)
Hepatobiliary Disorders		
Autoimmune Hepatitis	1 (0.2%)	2 (<0.1%)
Hepatitis	0	2 (<0.1%)
Injury, Poisoning and Procedural Complications		
Infusion Related Reaction	0	3 (<0.1%)
Skin and Subcutaneous Tissue Disorders		
Dermatitis Bullous	0	2 (<0.1%)

MedDRA System Organ Class MedDRA Preferred Term	Atezo+nP (N=452)	Atezolizumab Monotherapy (N=3178)
Blood and Lymphatic System Disorders		
Anaemia	0	3 (<0.1%)
Thrombocytopenia	0	4 (0.1%)
Gastrointestinal Disorders		
Colitis	1 (0.2%)	4 (0.1%)
Autoimmune Colitis	0	2 (<0.1%)
Diarrheoa	0	3 (<0.1%)
Pancreatitis	0	2 (<0.1%)
Metabolism and Nutrition Disorders		
Diabetes Mellitus	0	3 (<0.1%)
Hypercalcaemia	0	2 (<0.1%)
Respiratory, Thoracic and Mediastinal Disorders		
Pneumonitis	1 (0.2%)	9 (0.3%)
Dyspnoea	0	6 (0.2%)
Hypoxia	0	3 (<0.1%)
Interstitial Lung Disease	0	2 (<0.1%)
Pleural Effusion	0	4 (0.1%)
Pneumonia Aspiration	0	4 (0.1%)
Pulmonary Hypertension	0	2 (<0.1%)
Respiratory Distress	0	3 (<0.1%)
Respiratory Failure	0	4 (0.1%)
Cardiac Disorders		
Cardiac Arrest	0	3 (<0.1%)
Cardiac Failure	0	2 (<0.1%)
Myocardial Infarction	0	2 (<0.1%)
Pericardial Effusion	0	3 (<0.1%)
Immune System Disorders		
Hypersensitivity	0	3 (<0.1%)
Vascular Disorders		
Embolism	0	2 (<0.1%)

AE=adverse event; atezo=atezolizumb; MedDRA= Medical Dictionary for Regulatory Activities; nP=nab-paclitaxel.

AEs leading to dose interruption

Per protocol, dose reductions of placebo/atezolizumab were not permitted. A higher proportion of patients in the atezo+nP arm (30.8%) compared with the pl+nP arm (23.5%) experienced AEs leading to dose interruption of placebo/atezolizumab. The higher incidence in the atezo+nP arm was due to more patients experiencing AEs in the SOCs of General Disorders and Administration Site Conditions (e.g., pyrexia), Blood and Lymphatic System Disorders (neutropenia), Investigations (decreased neutrophil count), Respiratory, Thoracic and Mediastinal Disorders (pneumonitis) and Endocrine Disorders (hyperthyroidism and hypothyroidism). The most commonly reported (≥2% of patients in either arm) AEs leading to dose interruption of placebo/atezolizumab were neutropenia (1.8% pl+nP vs. 3.8% atezo+nP), neutrophil count decreased (1.4% vs. 2.7%), pyrexia (0.5% vs. 2.0%), and hyperthyroidism (0.2% vs. 2.0%).

A higher proportion of patients in the atezo+nP arm (43.1%) compared with the pl+nP arm (39.3%) experienced AEs leading to dose reduction or interruption of nab-paclitaxel. The most commonly reported (≥2% of patients in either arm) AEs leading to dose reduction or interruption of nab-paclitaxel were neutropenia (7.5% pl+nP vs. 9.3% atezo+nP), neutrophil count decreased (5.0% vs. 6.9%), peripheral sensory neuropathy (2.5% vs. 2.7%), pyrexia (0.9% vs. 2.7%), neutrophil count decreased (5.0% vs. 6.9%), neuropathy peripheral (3.0% vs. 2.4%), fatigue (1.6% vs. 2.4%), and leukopenia (0.7% vs.

2.0%). Events which contributed to the overall higher incidence in the atezo+nP arm included neutropenia/decreased neutrophil count, pneumonitis, and pyrexia.

Post marketing experience

As of 17 May 2018, a total of 20,783 patients had been exposed to atezolizumab monotherapy in the post-marketing setting. No new risks beyond those identified in the clinical trial setting have been identified so there are no major concerns related to the safety profile of atezolizumab.

2.6.1. Discussion on clinical safety

The safety database related to the proposed dosing regimen is 452 patients. The applicant presented pooled safety data from an "atezolizumab monotherapy" population of 3178 patients and pooled safety data from an "atezolizumab in combination therapy" population of 1797.

The applicant applies for a new dosing regimen and therefore safety data from the Impassion 130 will be the primary focus in this assessment of the safety profile of atezo + nP.

The median duration of treatment with both atezolizumab and nab-paclitaxel was approximately 5 months. Exposure to nab-paclitaxel was for the majority of patients approximately 9-12 months, which is consistent with the normal clinical use of chemotherapy in this target population, as chemotherapy is given until progression or intolerable toxicity. In the case of nab-paclitaxel, it is expected that maximum 12-15 months of therapy is tolerable and this is consistent with data available. The mean number of cycles and duration of therapy with nab-paclitaxel was similar in both arms. Exposure to atezolizumab was for 68.8% of the patients more than 6 months and 30.5% of the patients were exposed for more than 12 months. The mean number of cycles was slightly higher in the atezolizumab arm compared to placebo, so no detrimental effect is present. The overall exposure of atezolizumab is considered acceptable for an evaluation of the safety profile, considering the rate of progression in the targeted patient population.

Almost every patient (99.3%) in the atezolizumab arm experienced at least 1 adverse event and the majority were assessed to be treatment-related (96.5%). Grade 3-4 treatment-related events occurred in 39.6% in the atezolizumab arm compared to 15.9% of patients in the atezolizumab monotherapy pool, which is considered acceptable, as the majority were known chemotherapy-related ADRs. Serious adverse events were observed in more patients in the atezolizumab arm (22.8%), however, only 12.4% of these were treatment-related.

In the relevant arm (atezolizumab+nP), the most frequent AEs were chemotherapy-related, such as alopecia, fatigue, nausea, diarrhoea, anaemia, constipation and neutropenia. It is noted that more patients in the atezolizumab arm compared with placebo had nausea (46% vs 38%), cough (25% vs 19%), neutropenia (20.8% vs 15.3%) and peripheral sensory neuropathy (15.9% vs 11.9%). Notably more patients had hypothyroidism (13.7% vs 3.4%), and this is acceptable knowing this is a common ADR to atezolizumab and an adverse event of special interest (AESIs). The level of neutropenia, peripheral sensory neuropathy, and hypothyroidism is acceptable considering the severity of the treated disease and the palliative setting.

Clinically relevant grade 3-4 events were rare (~5% of patients per PT) and consisted of peripheral neuropathy (5.5%), pneumonia (2.2%), fatigue (4.0%), and diarrhea (1.3%) and there were no clinically meaningful difference between the treatment arms. The level of grade 3-4 events is also considered acceptable. Grade 3-4 treatment-related AEs that were reported at a higher frequency in the atezolizumab arm compared with the placebo were peripheral neuropathy (5.5% vs 2.7%) and decreased neutrophil count (4.6% vs 3.4%).

AESIs of low grade were observed in approximately half of the patients in the atezolizumab arm. This is acceptable as only 7.5% had grade 3-4 events and only 1 patient a grade 5 event. AESIs rarely led to withdrawal of any treatment (1.8%). Most common AESIs in the atezolizumab arm vs monotherapy were immune-related events such as rash (34.1% vs 19.5%), hypothyroidism (17.3% vs 5.2%), lab-abnormal hepatitis (13.7% vs 9.9%), and hyperthyroidism (4.4% vs 0.9%). The higher incidence of laboratory-abnormal hepatitis is most likely attributable to nab-paclitaxel and there are no signs of a synergistic toxicity. With regards to thyroid function, it is considered plausible that the more frequent monitoring of thyroid function may be the leading cause of the higher incidence of hypothyroidism or hyperthyroidism in the Impassion130 study. It cannot be ruled out that the addition of nab-paclitaxel increases the risk of immune-related rash. Overall, the events of laboratory-abnormal hepatitis, thyroid function, and rash are appropriately reflected in the SmPC.

Immune-related hepatitis as a clinical diagnosis was observed in 17 patients (7 in pl+nP arm and 10 in atezo+nP arm). This event was rare but maybe fatal and is already included as an 'Important identified risk' in the list of safety concerns with atezolizumab in the RMP.

Immune-related adrenal insufficiency was rare in the atezolizumab arm (0.9%, n=4), but there was one patient with acute adrenal insufficiency who required discontinuation. The patient had recovered by CCOD. This event is known with immunotherapy such as atezolizumab and there may be an increased focus on discovering such events early, which may cause more testing and diagnosing than previously, and this may explain the slight increase in incidence compared to the monotherapy safety population. In addition, these small numbers causes uncertainties and the low incidence observed is of no major concern. Overall, the events are clinically manageable when diagnosed.

Serious adverse events were rare but occurred more frequently in the atezolizumab arm (5.3% vs 2.1%). The most common SAEs in the atezolizumab arm were pneumonia (2.2%), urinary tract infection (1.1%), pyrexia (1.1%), and dyspnoea (1.1%). Especially the number of pneumonias was significantly increased in the atezolizumab arm. This may be due to the difficulty of diagnosing pneumonia vs pneumonitis, which is a known adverse effect of atezolizumab. The case of fatal pneumonia was clarified as not considered related to study drug which is reassuring. Overall, the SAEs are adequately categorized.

Overall, more deaths occurred in the placebo arm and the majority of patients died from progressive disease. However, more patients died due to an AE in the atezolizumab arm (1.3% vs 0.7%), but data are still considered immature regarding deaths. It was clarified that around 3-4% of the patients died from other causes and no deaths were due to treatment-related AEs. The vast majority of deaths categorised as other causes were due to disease progression on subsequent therapies.

Regarding shifts in laboratory safety parameters, the most concerning issues were the lowering of potassium, sodium, haemoglobin, and leukocytes. However, the differences were small and considered acceptable. No direct treatment-related case of Hy's law was observed in the study.

The incidence of adverse events was significantly increased in patients of more than 65 years of age. This included grade 3-4 AEs, SAEs, AESIs, and AEs leading to withdrawal from any treatment. The most common grade 3-4 events with increased incidence in the >65 year olds were peripheral neuropathy/polyneuropathy, AST increased, anaemia, leukopenia, and urinary tract infections (UTIs). All of the UTIs except 1 were in the older patient group. However, based on the provided data review and analysis of age-related risk factors including the effect of nab-paclitaxel in elderly patients, it is agreed that the observed differences are primarily due to nab-paclitaxel and are not due to a specific effect of the combination. Therefore, it is acceptable that no update to the SmPC for atezolizumab is provided in this regard.

There were limited sample sizes of the 75-84 years and ≥ 85 years subgroups in both treatment arms, therefore no firm conclusion can be drawn from these data. Data for patients ≥75 years of age are too limited to draw conclusions on this population (see section 4.8 of the SmPC).

Amongst 434 patients in study IMpassion130, 13% (n=57) tested positive for treatment-emergent antibodies (ADAs) at one or more post-dose time points. Overall, ADA status appeared to have no clinically relevant impact on safety. (see clinical pharmacology section and SmPC section 4.8). The overall safety profile was similar between the ADA-positive and ADA-negative patients, acknowledging the small sample size of ADA-positive patients (n=57). It is noted that 28.1% of ADA-positive patients versus 21.5% of ADA-negative patients experienced SAEs and that more ADA-positive patients discontinued atezo/placebo. The rates of grade 3-4 leukopenia and dyspnoea were also increased in the ADA-positive population. However, summary of AESIs according to ADA-status showed no clear pattern of change in the safety profile. Overall, ADA status appeared to have no clinically relevant impact on safety.

AEs leading to discontinuation of placebo/atezolizumab occurred in more patients in the atezolizumab arm (6.4% vs 1.4%). Most common AEs leading to withdrawal was neuropathy (6 vs 1 patients), which indicates that atezolizumab more frequently induces severe neuropathy than nab-paclitaxel alone. The risks are most likely related to the total exposure of drugs causing neuropathy, such as taxanes, and to the cumulative effect of these drugs. Unfortunately, no new information has emerged, so it is still primarily the known cumulative effect of taxanes that should be considered, when initiating nab-paclitaxel and atezolizumab and this is appropriately reflected in the nab-paclitaxel SmPC with a reference in the SmPC of atezolizumab (Section 4.4). Peripheral neuropathies will continue to be closely monitored.

AEs leading to discontinuation of nab-paclitaxel also occurred more frequently in the atezolizumab arm (15.9% vs. 8.2%). Even though more patients discontinue nab-paclitaxel due to AEs in the atezolizumab arm, the exposure to nab-paclitaxel was similar between the treatment arms, so this finding is acceptable. It is to be expected that an addition of therapy, in this case atezolizumab, causes more AEs, and there are no signs of a detrimental effect on exposure to chemotherapy in the presented data.

Comparing to the monotherapy population, the rate of discontinuations is similar (7.1%) and this is reassuring. Overall, there are no new safety signals in the pivotal study and the discontinuation rates of atezolizumab or nab-paclitaxel of 6.4% and 15.9%, respectively, are considered acceptable in this palliative setting.

AEs leading to dose interruption/modification of placebo/atezolizumab were more common in the atezolizumab arm (30.8% vs 23.5%), and the most common AEs were neutropenia (3.8% vs 1.8%), neutrophil count decreased (2.7% vs 1.4%), pyrexia (2.0% vs 0.5%), and hyperthyroidism (2.0% vs. 0.2%). A similar rate of dose reduction or interruption of nab-paclitaxel were observed between the treatment arms (43.1% vs 39.3%) and were mostly due to neutropenia, neuropathy, and pyrexia. Overall, the AEs leading to dose interruption/modification of atezolizumab or nab-paclitaxel were known with these treatments and the rate was acceptable for this palliative setting.

Section 4.4 of the SmPC of atezolizumab has been updated to reflect that neutropenia and peripheral neuropathies occurring during treatment with atezolizumab and nab-paclitaxel may be reversible with interruptions of atezolizumab and/or nab-paclitaxel. Physicians should consult the nab-paclitaxel summary of product characteristics (SmPC) for specific precautions and contraindications of this medicine (see SmPC section 4.4).

Regarding the PD-L1 positive group, **t**here was a lower number of deaths in the PD-L1-positive group in the atezolizumab arm in comparison to the safety evaluable population. This may be correlated to improved efficacy. Slightly more patients discontinued any study treatment, most often nab-paclitaxel. Otherwise, there were no clinically meaningful differences observed regarding treatment duration, AEs,

or SAEs between the subpopulation, which is reassuring. The PD-L1 positive population who received atezolizumab (n=185) had approximately the same rate of toxicity as the PD-L1 negative population who received atezolizumab, also indicating a similar safety profile regardless of PD-L1 status.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics. Section 4.8 of the SmPC has been updated with pooled data from IMpassion130, IMpower150 Arms A+B, IMmotion 150/151 and IMpassion130 in which atezolizumab was given in combination with other agents. This is considered acceptable. The same recommendations in terms of dose delay or discontinuation as for other approved indications apply (see Table 1 of SmPC section 4.2). Dose reductions of Tecentriq are not recommended. If a planned dose of Tecentriq is missed, it should be administered as soon as possible. The schedule of administration must be adjusted to maintain the appropriate interval between doses (see SmPC section 4.2).

The identified and potential risks for atezolizumab are well characterized from previous procedures. The indication assessed, for atezolizumab with nab-paclitaxel in TNBC brings no changes to the identified and potential risks and no newly identified safety concerns.

2.6.2. Conclusions on the clinical safety

The safety profile of the combination of atezolizumab and nab-paclitaxel is as expected and consists of a combination of chemotherapy and immune-related adverse drug reactions. There were no new safety signals and the toxicities were generally clinically manageable. The discontinuation rate is considered acceptable. In conclusion, the safety profile is considered overall acceptable in this treatment setting.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Immune-related hepatitis Immune-related pneumonitis Immune-related colitis Immune-related pancreatitis Immune-related endocrinopathies (Diabetes mellitus, Hypothyroidism, Hyperthyroidism, Adrenal Insufficiency, and Hypophysitis) Immune-related neuropathies (Guillain-Barré syndrome, and Myasthenic syndrome / myasthenia gravis) Immune -related meningoencephalitis Infusion-related reactions Immune-related myocarditis Immune-related nephritis Immune-related myositis
Important potential risks	Anti-drug antibodies Embryo-fetal toxicity
Missing information	Concomitant use with other immuno-modulatory drugs Long term use Concomitant or sequential use of atezolizumab with intra-vesical bacillus Calmette-Guérin vaccine for the treatment of urothelial carcinoma

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 ADAs against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy	Anti-therapeutic antibodies	Final CSR	December 2019
GO29322: A Phase IB Study of the Safety and Pharmacology of atezolizumab Administered with Ipilimumab or Interferon-Alpha in Patients with Locally Advanced or Metastatic Solid Tumors	To evaluate the safety and tolerability of atezolizumab and ipilimumab in combination in patients with advanced or	Concomitant use with other immunomodulatory drugs	Final CSR	March 2020

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Ongoing	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			
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 Ongoing	To evaluate the long-term safety of atezolizumab on the bases of the following endpoints: The incidence of all serious adverse events (SAEs) related to atezolizumab treatment and the incidence of immune-related adverse events (irAEs) related to atezolizumab treatment	Long-term use	Final CSR	May 2022

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
MO29983: An Open-Label, Single Arm, Multicenter, Safety Study of atezolizumab in Locally Advanced or Metastatic Urothelial or Non-Urothelial Carcinoma of the Urinary Tract Ongoing	To evaluate the safety of atezolizumab based on the following endpoints: Nature, severity, duration, frequency and timing of adverse events (AEs) and changes in vital signs, physical findings, and clinical laboratory results during and following atezolizumab administration.	Long-term use	Final CSR	Q1 2023
WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions Ongoing	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 endocrinopathies (Diabetes mellitus, Hypothyroidism, Hyperthyroidism, Adrenal insufficiency, and Hypophysitis) Immune-related neuropathies (Guillain-Barré syndrome, and Myasthenic syndrome / myasthenia gravis) Immune related meningoencephalitis Infusion-related reactions Immune-related myocarditis	Protocol submission Interim report Final Report	February 2018 December 2020 December 2022

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
		Immune-related nephritis		

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Immune-related Hepatitis	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects **Additional risk minimization measures:** • Educational materials for HCPs • Patient alert cards	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.
Immune-related Pneumonitis	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects **Additional risk minimization measures:** • Educational materials for HCPs • Patient alert cards	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.

Safety concern	Risk minimization measures	Pharmacovigilance activities
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:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis and infusion-related reactions.
Immune-related Pancreatitis	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects **Additional risk minimization measures:** • Educational materials for HCPs • Patient alert cards**.**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.

Safety concern	Risk minimization measures	Pharmacovigilance activities
Immune-related Endocrinopathies (Diabetes Mellitus, Hypothyroidism, Hyperthryroidism, Adrenal Insufficiency, and Hypophysitis)	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 – Undesirable effects **Additional risk minimization measures:** • Educational materials for HCPs • Patient alert cards**.**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis and infusion-related reactions.
Immune-related Neuropathies (Guillain-Barre Syndrome and Myasthenia Gravis)	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 – Undesirable effects **Additional risk minimization measures:** • Educational materials for HCPs • Patient alert cards**.**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.

Safety concern	Risk minimization measures	Pharmacovigilance activities
Immune-related Meningoencephalitis	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 – Undesirable effects **Additional risk minimization measures:** • Educational materials for HCPs • Patient alert cards**.**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.
Infusion-Related Reactions	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 – Undesirable effects **Additional risk minimization measures:** • Educational materials for HCPs • Patient alert cards**.**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.

Safety concern	Risk minimization measures	Pharmacovigilance activities
Immune-related Myocarditis	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 –Undesirable effects **Additional risk minimization measures:** • Educational materials for HCPs • Patient alert cards**.**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition of and intervention in the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.
Immune-related Nephritis	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 –Undesirable effects **Additional risk minimization measures:** • Educational materials for HCPs • Patient alert cards**.**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition of and intervention in the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.

Safety concern	Risk minimization measures	Pharmacovigilance activities
Immune-related Myositis	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 –Undesirable effects **Additional risk minimization measures:** • Educational materials for HCPs • Patient alert cards**.**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Anti-drug Antibodies	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.8 – Undesirable effects **No additional risk minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study GO28915 (OAK)
Embryo-fetal Toxicity	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.6 Fertility, pregnancy and lactation Section 5.3 Preclinical safety data **No additional risk minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
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:

Safety concern	Risk minimization measures	Pharmacovigilance activities
		• 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

Conclusion

No new safety concerns were identified as part of this line extension. The pharmacovigilance plan and risk minimisiations measures also remain unchanged.

The CHMP and PRAC considered that the risk management plan version 7.1 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Tecentriq 1200 mg concentrate for solution for infusion. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication for Tecentriq, 840 mg concentrate for solution for infusion, is in combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥1% and who have not received prior chemotherapy for metastatic disease.

Metastatic TNBC is incurable and the main goals with treatment are life-prolongation and palliation of symptoms. Compared to other subtypes of breast cancer, TNBC tumours are generally more aggressive leading to a high risk of visceral metastases and a very poor prognosis. The estimated 5-year survival rate for metastatic TNBC is 9% in the SEER database.

3.1.2. Available therapies and unmet medical need

Current treatment options for triple-negative metastatic breast cancer (mTNBC) is the use of sequential single-agent chemotherapy. No single chemotherapy-agent has demonstrated clear superiority and is considered the preferred agent in the first-line metastatic setting. There are several active agents considered appropriate for first-line chemotherapy, including taxanes, anthracyclines, capecitabine, gemcitabine, platinum-based compounds, vinorelbine, and ixabepilone. Several diverse genetic subtypes have been identified in TNBC. However, apart from BRAC1/2 there is still a lack of common targetable mutations. There are no immunotherapies approved for use in the treatment of TNBC. Recently PARP inhibitors have been approved for the treatment of advanced TNBC with germline BRCA1/2 mutations in patients who have been previously treated with an anthracycline and/or a taxane.

The disease usually progresses rapidly despite palliative chemotherapy, and multiple studies have shown a median PFS of approximately 6 months and a median OS of approximately 16 months (see 2.1.4. Clinical presentation, diagnosis and stage/prognosis). Hence, there is an unmet medical need for treatment of metastatic TNBC.

3.1.3. Main clinical studies

The pivotal study for this application is the Impassion130 study, which is a fully recruited, ongoing, international, multicenter, randomized, placebo-controlled, double-blinded, two-arm Phase III Study. The ITT population consisted of 902 patients, who were randomized 1:1 to receive atezolizumab + nab-paclitaxel compared with placebo plus nab-paclitaxel in patients with metastatic TNBC, who had not received prior chemotherapy for metastatic breast cancer (first-line setting). The pivotal study comprised 369 patients with PD-L1 ≥ 1% tumours, who were exposed to atezolizumab, which is the relevant study population for the applied indication that includes only this subgroup of patients.

The co-primary efficacy endpoints included investigator-assessed progression free survival (PFS) in the ITT population and in patients with PD-L1 expression ≥ 1% per RECIST v1.1 as well as overall survival (OS) in the ITT population and in patients with PD-L1 expression ≥ 1%. Secondary efficacy endpoints included objective response rate (ORR) and duration of response (DOR) per RECIST v1.1, and time to deterioration in global health status (TDD).

3.2. Favourable effects

The study met the co-primary endpoint of PFS in ITT and PD-L1-population. With a median follow up of 13 months, the study treatment resulted in a statistically significant and clinically relevant improvement of PFS in the PD-L1 ≥ 1% population from 5.3 months to 7.5 months, HR 0.63 (95%CI: 0.50-0.80). In addition, there were 80.5% PFS events in the atezo-arm, so the data for PFS are considered mature.

The co-primary endpoint of OS in the ITT population was not statistically significant, so it could not be statistically tested in the PD-L1 ≥ 1% population. However, OS in the PD-L1 ≥ 1% population was improved by 7 months from 18.0 months to 25.0 months, which is considered clinically relevant in the treatment of mTNBC.

Secondary endpoints were ORR, DOR, and TTD (Time to deterioration in global health status/HRQoL). ORR in the PD-L1 ≥ 1%population was 58.9% in the atezolizumab arm compared to 42.6% in the placebo arm. In the atezolizumab arm, CR and PR were increased from 1.1% to 10.3% and from 41.5% to 48.6%, respectively. DOR in the PD-L1 ≥ 1% population was improved from 5.5 months to 8.5 months, HR 0.62 (95%CI: 0.44, 0.86).

In the ITT population, there were no apparent differences in time to deterioration in global health status/HRQoL between the treatment arms (8.0 vs 8.3 months). This indicates that there are no detrimental effects of the added atezolizumab from this perspective.

3.3. Uncertainties and limitations about favourable effects

Optimally, the benefitting subgroup could be better defined than by PD-L1 ≥ 1%. However, no better biomarkers exist at the present time and this is acknowledged. In addition, chosen cut-off point has been adequately justified.

Patients with active brain metastases at baseline were excluded from the pivotal study while CNS metastases are frequent in this patient population. This is adequately reflected in the SmPC section 4.4. Furthermore, based on the exploratory subgroup analyses performed in patients with PD-L1 expression ≥ 1% and asymptomatic brain metastases at baseline, there was no evidence of efficacy in these patients, although the number of patients treated was small. This has been reflected in the SmPC, section 5.1.

3.4. Unfavourable effects

Almost every patient experienced at least 1 AE and the majority were assessed to be treatment-related. Grade 3-4 treatment-related events occurred in 39.6% in the atezolizumab arm compared to 15.9% of patients in the atezolizumab monotherapy pool and the majority were known chemotherapy-related ADRs. Serious adverse events were observed in more patients in the atezolizumab arm (22.8%), however, only 12.4% of these were treatment-related.

In the relevant arm (atezo+nP), the most frequent AEs were chemotherapy-related, such as alopecia, fatigue, nausea, diarrhoea, anaemia, constipation, and neutropenia. It is noted that more patients in the atezolizumab arm compared with placebo had nausea (46% vs 38%), cough (25% vs 19%), neutropenia (20.8% vs 15.3%) and peripheral sensory neuropathy (15.9% vs 11.9%). Notably more patients had hypothyroidism (13.7% vs 3.4%).

Clinically relevant grade 3-4 events were rare (~5% of patients per PT) and consisted of peripheral neuropathy (5.5%), pneumonia (2.2%), fatigue (4.0%), and diarrhoea (1.3%) and there were no clinically meaningful difference between the treatment arms.

The most common adverse events of special interest (AESIs) were immune-related events, such as rash (34.1%), hypothyroidism (17.3%), lab-abnormal hepatitis (13.7%), and hyperthyroidism (4.4%).

The most common SAEs in the atezolizumab arm were pneumonia (2.2%), urinary tract infection (1.1%), pyrexia (1.1%), and dyspnea (1.1%). The number of pneumonias was significantly increased in the atezolizumab arm compared with placebo.

Overall, more deaths occurred in the placebo arm and the majority of patients died from progressive disease. However, more patients died due to an AE in the atezolizumab arm (1.3% vs 0.7%).

The overall safety profile was similar between the ADA-positive and ADA-negative patients.

AEs leading to discontinuation of placebo/atezolizumab occurred in more patients in the atezolizumab arm (6.4% vs 1.4%). Most common AEs leading to withdrawal was neuropathy (6 vs 1 patients), which indicates that atezolizumab more frequently induces severe neuropathy than nab-paclitaxel alone. AEs leading to discontinuation of nab-paclitaxel also occurred more frequently in the atezolizumab arm (15.9% vs. 8.2%). Most common AEs were neuropathy, general disorders, GI toxicity, and infections. The rate of discontinuations in monotherapy population were similar (7.1%) which is reassuring.

3.5. Uncertainties and limitations about unfavourable effects

The vast majority of patients were of PS 0-1 in the pivotal study (see SmPC section 5.1), which is not reflective of the patient population in the real life setting, and in the daily clinic patients of PS 2 will also be treated and may have increased susceptibility to treatment toxicity, as observed in the patients of >65 years of age. This is adequately reflected in sections 4.4 and 5.1 of the SmPC.

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 65: Effects Table for addition of atezolizumab to nab-paclitaxel in the first-line treatment of mTNBC (data cut-off dates 17 April 2018; 02 January 2019)

Effect	Short Description	Unit	Treatment Tecentriq +nP N=185	Control Placebo+ nP N=184	Uncertainties/ Strength of evidence	References
Favourable Effects						
Co-primary endpoints PD-L1 ≥ 1% population[1]						
PFS	INV-assessed	Months	7.5	5.3	HR 0.63 (0.50-0.80) P<0.0001	
OS	INV-assessed	Months	25.0	18	HR 0.71 (0.54-0.93) Not formally tested	
Secondary endpoints PD-L1 ≥ 1% population[2]						
ORR	Overall response rate	N (%)	109 (58.9%)	78 (42.6%)	Difference 16.3% (5.7-26.9%)	
DOR	Duration of response	Months	8.5	5.5	HR 0.62 (0.44-0.86) P=0.0044	
Unfavourable Effects						

Effect	Short Description	Unit	Treatment Tecentriq +nP N=185	Control Placebo+ nP N=184	Uncertainties/ Strength of evidence	References
≥ AE		%	99.3	97.9		
Grade 3-4	ADR	%	48.7 (39.6)	42.2 (30.1)		
Grade 5	ADR	%	1.3 (0.7)	0.7 (0.2)		
SAEs	ADR	%	22.8 (12.4)	18.3 (7.3)		
AEs leading to discont.	ADR	%	15.9 (6.4)	8.2 (1.4)		
AESI	ADR	%	57.3	41.8		
Adverse events with a difference of at least 5% between treatment arms						
Nausea	ADR	%	46.0	38.1		
Cough	ADR	%	24.8	18.9		
Neutropenia	ADR	%	20.8	15.3		
Pyrexia	ADR	%	18.8	10.7		
Hypothyroidism	ADR	%	13.7	3.4		

Abbreviations: AE = Adverse event; ADR = treatment-related AE; SAE = Serious adverse event; discont. = discontinuation; AESI= Adverse events of special interest; HR-QoL = Health-related quality of life.
[1] at clinical cut off 17th April 2018; [2] at clinical cut off 2 January 2019

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The target population of mTNBC have a high unmet medical need as this is an aggressive life-threatening disease, and the currently available treatment options result in a median PFS of ~6 months and a median OS of ~ 16 months. The mean age of patients with mTNBC was in ~55 years in the study and more than 2/3 of the patients were in the age group of 41-64 years of age, so this is a relatively young patient population with a very poor prognosis. This is also reflected by the control arm of the study, where the observed mature median PFS is 5.3 months for the targeted PD-L1 ≥ 1% population.

Therefore, an improvement in PFS of 2.2 months (from 5.3 to 7.5 months) is relevant in the proposed population. It may be discussed, if the difference in terms of PFS is limited per se, but in the context of improved OS, ORR, and DOR, the PFS result is considered clinically relevant. It should be acknowledged that a PFS gain with immune therapy may not be large, but often results in a considerable OS benefit for the responding patients, maybe even long term.

The numerical OS gain of 7 months (median) is considered clinically relevant for this patient population, who have not seen any major advances of therapy in decades, although this result could not be formally statistically tested.

Efficacy data by PD-L1 expression status demonstrated that subjects with PD-L1 negative tumours (IC0) do not derive clinical benefit from the addition of atezolizumab to nab-paclitaxel (PFS HR 0.95; OS HR 1.04). PD-L1 status was prospectively centrally tested, implemented as stratification factor, and efficacy evaluation in the PD-L1 positive population (IC≥1) was pre-specified. Thus, limiting the indication to subjects with PD-L1 expression ≥ 1% is endorsed.

The secondary endpoint of ORR improved by 16% with atezolizumab, which is considered to translate into improved symptom relief and increased clinical benefit for the patients. It is considered important that 10% of the patients had a complete response, which is almost unseen with standard of care (chemotherapy as monotherapy). There were no detrimental effects on the reported quality of life measures (Time to deterioration in global health status/HRQoL), which is reassuring.

The safety profile of the combination of atezolizumab and nab-paclitaxel is as could be expected and consists ofa combination of chemotherapy and immune-related adverse drug reactions. There were no new safety signals. Most of the toxicities were clinically manageable and the discontinuation rate is considered acceptable. In conclusion, the safety profile is considered overall acceptable in this palliative treatment setting. Adequate measures are in place to manage the risks associated with atezolizumab in the RMP and relevant recommendations are included in the SmPC.

3.7.2. Balance of benefits and risks

Overall, the patients diagnosed with mTNBC have a very poor prognosis and there have not been any major advances in decades, hence, the standard of care is still chemotherapy as monotherapy. In addition, the safety profile of the combination therapy is considered overall acceptable in this palliative treatment setting. Therefore, the benefit-risk balance is considered favourable for the PD-L1 ≥ 1% population because updated mature data show clinically relevant differences in PFS and OS.

3.8. Conclusions

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

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tecentriq 840 mg concentrate for solution for infusion is favourable in the following indication:

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

The CHMP therefore recommends the extension of the marketing authorisation for Tecentriq subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

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

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

Additional risk minimisation measures

Prior to launch of Tecentriq in each Member State the marketing authorisation holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing awareness and providing information concerning the signs and symptoms of certain important identified risks of atezolizumab, including immune-related pneumonitis, hepatitis, colitis, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, and infusion related reactions, and how to manage them.

The MAH shall ensure that in each Member State where Tecentriq is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Tecentriq have access to/are provided with the following educational package:

- Physician educational material
- Patient Alert Card

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals

- **The Guide for healthcare professionals** shall contain the following key elements:
  - Relevant information (e.g. seriousness, severity, frequency, time to onset, reversibility as applicable) of the following safety concerns associated with the use of Tecentriq:
    - Immune-Related Hepatitis
    - Immune-Related Pneumonitis

- Immune-Related Colitis
- Immune-Related Pancreatitis
- Immune-Related Endocrinopathies (Type 1 Diabetes Mellitus, Hypothyroidism, Hyperthyroidism, Adrenal Insufficiency and Hypophysitis)
- Immune-Related Neuropathies (Guillain-Barre Syndrome, Myasthenic Syndrome / Myasthenia Gravis)
- Immune-Related Meningoencephalitis
- Immune-Related Myocarditis
- Immune-Related Nephritis
- Immune-Related Myositis
- Infusion-Related Reactions

- Description of the signs and symptoms of immune-related adverse reactions.
- Details on how to minimise the safety concerns through appropriate monitoring and management.
- Reminder to distribute the patient alert card to all patients receiving treatment with Tecentriq and to advise them to show it to any healthcare professional who may treat them.
- Reminder to educate patients/caregivers about the symptoms of immune-related adverse reactions and of the need to report them immediately to the physician.

The patient alert card shall contain the following key messages:

- Brief introduction to atezolizumab (indication and purpose of this tool)
- Information that atezolizumab can cause serious side effects during or after treatment, that need to be treated right away
- Description of the main signs and symptoms of the following safety concerns and reminder of the importance of notifying their treating physician immediately if symptoms occur, persist or worsen:
  - Immune-Related Hepatitis
  - Immune-Related Pneumonitis
  - Immune-Related Colitis
  - Immune-Related Pancreatitis
  - Immune-Related Endocrinopathies (Type 1 Diabetes Mellitus, Hypothyroidism, Hyperthyroidism, Adrenal Insufficiency and Hypophysitis)
  - Immune-Related Neuropathies (Guillain-Barre Syndrome, Myasthenic Syndrome / Myasthenia Gravis)
  - Immune-Related Meningoencephalitis
  - Immune-Related Myocarditis
  - Immune-Related Nephritis
  - Immune-Related Myositis
  - Infusion-Related Reactions
- Warning message for patients on the importance of consulting their doctor immediately in case they develop any of the listed signs and symptoms and on the important not attempting to treat themselves.
- Reminder to carry the Patient Alert Card at all times and to show it to all healthcare professionals that may treat them.
- The card should also prompt to enter contact details of the physician and include a warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Tecentriq.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further evaluate the efficacy of atezolizumab for the treatment of patients with locally advanced or metastatic urothelial cancer, the MAH should submit the final OS results of study IMvigor210.	Submission of study results: 30 June 2019
Post-authorisation efficacy study (PAES): In order to evaluate the efficacy of atezolizumab monotherapy versus atezolizumab plus carboplatin/gemcitabine versus placebo plus cisplatin/gemcitabine in patients with locally advanced or metastatic urothelial cancer who are	Submission of study results: 31 July 2021

platinum –ineligible and –eligible patients, the MAH should submit the final CSR of study IMvigor130.	

Additional Data exclusivity/Marketing protection

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