20 July 2017
EMA/153102/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tecentriq

International non-proprietary name: atezolizumab

Procedure No. EMEA/H/C/004143/0000

Note

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

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List of abbreviations

1L	first-line treatment
2L	second-line treatment
2L+	≥ second-line treatment
AC	acceptance criterion
AE	adverse event
AESI	adverse event of special interest
ADCC	antibody-dependent cell-mediated cytotoxicity
ADE	acceptable daily exposure
AST	aspartate aminotransferase
ATA/ATAG	anti-therapeutic antibody
AUC	area under the curve
BCG	Bacillus Calmette-Guerin
BSC	best supportive care
BOR	best overall response
CL	clearance
Cmax	maximum observed serum concentration
Cmin	trough or minimum serum concentration
CPP	critical process parameter
CQA	critical quality attribute
CQA-AC	critical quality attribute acceptance criteria
CQA-TR	critical quality attribute target range
CR	complete response
CSR	clinical study report
DCR	disease control rate
DoE	design of experiment
DOR	duration of response
EAU	European Association of Urology
ECG	electrocardiography
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
ER	exposure-response

ES	exposure-safety
ESMO	European Society of Medical Oncology
HR	hazard ratio
IC	tumor-infiltrating immune cell
Ig	immunoglobulin
IHC	immunohistochemistry
IND	Investigational New Drug (application)
IRF	Independent Review Facility
IUO	Investigational Use Only
IV	intravenous
LFT	liver function test
LOQ	limit of quantification
MAA	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities
NCA	noncompartmental analysis
NCCN	National Comprehensive Cancer Network
NOR	normal operating range
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PALM	post-approval lifecycle management
PAR	proven acceptable range
pCPP	potential critical process parameter
pCQA	potential critical quality attribute
pCQA-TR	potential critical quality attribute target range
PD	Pharmacodynamic
PD	Progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
popPK	population pharmacokinetics
PFS	progression-free survival
PK	pharmacokinetic

PS	performance status
PR	partial response
q3w	every 3 weeks
QA	quality attribute
QbD	Quality by Design
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAT	severe acute toxicity
SD	stable disease
SOC	system organ class
TCC	transitional cell carcinoma
TIR	time in response
TTOR	time to onset of response
UC	urothelial carcinoma
Vss	volume of distribution at steady state

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration Limited submitted on 20 April 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Tecentriq, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 December 2014.

The applicant applied for the following indications

- Tecentriq is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy or who are considered cisplatin ineligible.
- Tecentriq is indicated for the treatment of adult patients with locally advanced or metastatic non small cell lung cancer (NSCLC) after prior chemotherapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that atezolizumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decisions PIP P/0220/2015 on the agreement of a paediatric investigation plan (PIP).

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

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance atezolizumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice/Protocol Assistance

The applicant received Scientific Advice from the CHMP on 25 April 2013, 26 June 2014, 25 March 2015, 28 January 2016 and 15 December 2016. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

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 26 April 2016.
- The procedure started on 19 May 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 August 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 5 August 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 19 August 2017.
- During the meeting on 15 September 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 February 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 28 March 2017.
- During the PRAC meeting on 6 April 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 21 April 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 May 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 8 June 2017 and on 16 June 2017.
- During the CHMP meeting on 20 June 2017 outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 17-20 July 2017, 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 20 July 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

NSCLC

Data to support the application for atezolizumab monotherapy in patients with locally advanced or metastatic NSCLC after prior chemotherapy are derived from two pivotal studies POPLAR and BIRCH, and two supportive Studies FIR and PCD4989g NSCLC Cohort. During the procedure the Applicant provided the results from the phase III OAK study. The Applicant seeks the following indication:

Tecentriq is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.

UC

Data to support the application for atezolizumab monotherapy in patients with locally advanced or metastatic UC or who are considered cisplatin ineligible are derived primarily from two studies: Pivotal Phase II Study IMvigor 210 and a supportive Phase Ia Study (PCD4989g). In addition, the applicant provided efficacy results of Study IMvigor 211. The Applicant seeks the following indication:

Tecentriq is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy or who are considered cisplatin ineligible.

2.1.2. Epidemiology

NSCLC

Lung cancer remains the leading cause of cancer deaths worldwide in men and the second leading cause of cancer deaths worldwide in women. It accounted for approximately 13% of all new cancers in 2012 (Torre et al. 2015). Non-small cell lung cancer is the predominant subtype, accounting for approximately 85% of all cases (Howlader et al. 2014; Molina et al. 2008).

UC

Urothelial carcinoma presents the highest recurrence rate among solid tumors and is the second leading cause of death in genitourinary cancers. Despite recent advances in the understanding of the pathophysiology of the disease, the management of UC patients remains a clinically challenging problem (Siegel et al. 2014).

Approximately 10%-15% of patients present with metastatic UC at the time of diagnosis. Despite the low frequency of de novo disease, approximately half of the patients with locally advanced UC progress to metastatic disease within two years of cystectomy.

2.1.3. Biologic features, aetiology and pathogenesis

Identification of cancer T-lymphocyte inhibitory signals, including PD-L1, has led to an important milestone in the development of effective cancer immunotherapies. These immune checkpoint inhibitors can prevent tumours from eluding immunosurveillance by removing an inhibitory signal

provided to T lymphocytes, thereby allowing their activation and consequently a cytotoxic attack on tumour cells. Checkpoint proteins that are targeted by checkpoint inhibitors in the clinic include cytotoxic T-lymphocyte (CTL)–associated antigen 4 (CTLA4), PD-1, and PD-L1. Immune checkpoint inhibitors, including anti-PD-L1 antibodies, have shown impressive clinical activity as monotherapy in a broad range of tumors, including NSCLC and UC. Atezolizumab targets human PD-L1 on ICs as well as TCs and inhibits its interaction with its receptors, PD-1 and B7.1 (CD80, B7-1). Both these interactions are reported to provide inhibitory signals to T lymphocytes. Therapeutic blockade of PD-L1 by atezolizumab is expected to reinvigorate and enhance the magnitude of tumour specific T-lymphocyte responses, resulting in improved anti-tumour activity. In addition, inhibition of the interaction between PD-L1 and B7.1 may also aid in the priming of new anti-tumour immune responses. Expression of PD-L1 within the tumour microenvironment has been observed to be focal in nature, consistent with the hypothesis that PD-L1 expression reflects areas of interaction between TCs and ICs. Programmed death ligand 1 expression likely represents a feedback mechanism, functioning at multiple levels to dampen T-helper type 1 (Th1)/CTL-driven immune responses. Treatment with inhibitors of PD-L1 can lead to further anti-tumour immune activity and spread of PD-L1 expression within the tumour microenvironment. Thus, the presence of PD-L1 in the tumour microenvironment may act as an indicator of the presence of an active anti-tumour immune response and/or an anti-tumour immune response that is being repressed by the presence of PD-L1.

2.1.4. Clinical presentation, diagnosis

NSCLC

The overall 5-year survival rate for advanced NSCLC is 2%-4%, depending on geographic location (Cetin et al. 2011). Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor performance status (PS), and a history of unintentional weight loss. More than half of the patients with NSCLC are diagnosed with distant metastatic disease, which directly contributes to poor survival prospects.

UC

The overall 5-year survival rate for patients diagnosed with metastatic UC is approximately 5.5% (Surveillance, Epidemiology, and End Results [SEER] 2015). Poor prognostic factors for survival in patients with metastatic UC include advanced stage of disease at the time of initial diagnosis, Karnofsky Performance Status (KPS) <80%, and visceral metastasis (i.e., lung, liver, or bone; Bajorin et al. 1999).

The presence of these unfavorable features was associated with a median survival of 4 months compared with 18 months in patients without these features (Bellmunt et al. 2010; Loehrer et al. 1992).

2.1.5. Management

NSCLC

Outcomes are poor for patients with previously treated, advanced or metastatic NSCLC; systemic chemotherapy (e.g., docetaxel) or erlotinib provides only modest benefit (Al-Farsi and Ellis 2014; Stinchcombe and Socinski 2008). Cancer immunotherapy represents a new treatment option for these patients. Despite improvements in the 1L treatment of patients with advanced NSCLC that have resulted in longer survival times and reduced disease-related symptoms, nearly all patients experience disease progression. Docetaxel, pemetrexed, and erlotinib are three single agents approved by the

European Medicines Agency (EMA) for use in the second-line and beyond (2L+) setting for an unselected population. Docetaxel was the first agent to demonstrate a survival benefit, with respect to best supportive care (BSC) in patients with relapsed NSCLC following 1L therapy and was associated with objective response rates (ORR) in the range of 6% to 11% and an estimated median overall survival (OS) of 6 to 10 months (Taxotere EPAR). Pemetrexed appeared non-inferior to docetaxel on efficacy outcomes as 2L therapy in advanced NSCLC (all histologies); subsequent subgroup analysis revealed improved survival in patients with non-squamous histologies, thus limiting its approval to patients with non-squamous NSCLC (Alimta EPAR). Improved OS was observed with erlotinib compared to BSC in a randomized study that included patients with poor Eastern Cooperative Oncology Group Performance Status (ECOG PS) (Tarceva EPAR). Erlotinib has therefore often been used for patients, who cannot receive cytotoxic chemotherapy due to poor performance status.

The choice of agent used for patients being treated in the 2L setting depends on a number of factors, including tumour histology, the patient's comorbidities, toxicity from previous treatments, toxicity profile for a given agent, smoking history, and patient preference. Overall, the therapeutic index of these 2L NSCLC therapies has been restricted both by limited survival benefit and significant toxicities such as myelosuppression and neuropathy (docetaxel), diarrhoea (pemetrexed, erlotinib), and rash (erlotinib) (Stinchcombe and Socinski 2008).

Most recently, EMA and the FDA approved nivolumab and pembrolizumab for the treatment of metastatic 2L NSCLC with an improvement in OS.

UC

First-line Treatment for Metastatic Urothelial Carcinoma

Cisplatin-based chemotherapy is the preferred 1L therapy and has been shown to improve survival in patients with previously untreated metastatic UC (Loehrer et al. 1992; von der Maase et al. 2005). Cisplatin and gemcitabine (in combination with cisplatin; European Union only) are approved for 1L therapy; however, there are currently no approved 1L therapies for patients who have a contraindication to cisplatin or who are otherwise medically unfit for a cisplatin-based regimen.

Treatments Available for Patients with Previously Untreated Cisplatin-Ineligible Metastatic Urothelial Carcinoma: Historical Evidence and Treatment Guidelines

Patients who are medically unfit for cisplatin constitute a heterogeneous population, ranging from those who can tolerate the toxicity of combination chemotherapy to those who invariably cannot tolerate chemotherapy. This includes patients who are frail due to preexisting co-morbidities such as renal impairment, myelosuppression or hearing impairment, as well as those with a history of an allergy to cisplatin or other platinum containing regimens. While allergies to cisplatin are infrequent in the first cycle, the incidence increases significantly with subsequent cycles.

For patients who are unable to receive cisplatin, options comprise a carboplatin-based regimen (carboplatin plus gemcitabine or carboplatin, gemcitabine plus paclitaxel), non-platinum based combination (e.g., paclitaxel plus gemcitabine), single-agent chemotherapy, BSC, and inclusion in clinical studies. According to the European Association of Urology (EAU) guidelines (Witjes et al. 2015), there is no defined standard chemotherapy for cisplatin-ineligible (medically unfit) patients with advanced or metastatic UC (level of evidence 2B), and the guidelines recommend the use of carboplatin combination chemotherapy or single agents, (Grading of Recommendation C). Treatment with carboplatin-containing combination chemotherapy, preferably with gemcitabine/carboplatin, is also recommended for patients with PS2 or impaired renal function, as well as for patients with 0 or 1 poor Bajorin prognostic factors and impaired renal function (Grading of Recommendation B; Witjes et al. 2015).

Similarly, the ESMO guidelines (Bellmunt et al. 2014) recommend use of carboplatin-based regimens or single agents (taxane, gemcitabine) for cisplatin ineligible patients and BSC or inclusion in a clinical study for patients with PS >=2 and poor renal function. The National Comprehensive Cancer Network (NCCN) guidelines (2015) recommend participation in clinical studies or carboplatin- or taxane-based regimens, based on 2B level of evidence.

Second-Line Treatment for Metastatic Urothelial Carcinoma

Despite the efficacy of 1L regimens for patients treated with cisplatin-based regimens, responses showed limited durability, with nearly all patients experiencing disease progression. There is currently only one approved 2L therapy in the European Union (vinflunine). The approval of vinflunine was based on data from a single randomized Phase III study that compared vinflunine plus BSC with BSC alone in 370 patients with advanced UC progressing after a platinum-containing therapy. Taxanes (paclitaxel and docetaxel) are commonly used as 2L therapy in patients with locally advanced or metastatic UC.

About the product

Atezolizumab targets human PD-L1 on ICs and TCs and inhibits its interaction with its receptors, PD-1 and B7.1 (CD80, B7-1). Clinical studies utilizing anti-PD-1 antibodies (nivolumab, pembrolizumab) have established the therapeutic value of targeting the PD-L1/PD-1 pathway (Borghaei et al. 2015; Brahmer et al. 2015; Garon et al. 2015; Herbst et al. 2015).

The authorised indications for atezolizumab are:

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy or who are considered cisplatin ineligible.

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving Tecentriq.

Atezolizumab must be initiated and supervised by physicians experienced in the treatment of cancer.

The recommended dose of atezolizumab is 1,200 mg administered intravenously every three weeks.

It is recommended that patients are treated with atezolizumab until loss of clinical benefit (see section 5.1) or unmanageable toxicity.

If a planned dose of atezolizumab is missed, it should be administered as soon as possible; it is recommended not to wait until the next planned dose. The schedule of administration must be adjusted to maintain a 3-week interval between doses.

Dose reductions of atezolizumab are not recommended.

Table 1 - Dose modification advice for specified adverse drug reactions

Adverse reaction	**Severity**	**Treatment modification**
Pneumonitis	Grade 2	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4	Permanently discontinue Tecentriq

Adverse reaction	Severity	Treatment modification
Hepatitis	Grade 2: (ALT or AST > 3 to 5 x upper limit of normal [ULN] *or* blood bilirubin > 1.5 to 3 x ULN)	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4: (ALT or AST > 5 x ULN *or* blood bilirubin > 3 x ULN)	Permanently discontinue Tecentriq
Colitis	Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) *or* Symptomatic Colitis	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone equivalent per day
	Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)	Permanently discontinue Tecentriq
Hypothyroidism or hyperthyroidism	Symptomatic	Withhold Tecentriq *Hypothyroidism:* Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing *Hyperthyroidism:* Treatment may be resumed when symptoms are controlled by antithyroid medicinal product and thyroid function is improving
Adrenal insufficiency	Symptomatic	Withhold Tecentriq Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy
Hypophysitis	Grade 2 or 3	Withhold Tecentriq Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy
	Grade 4	Permanently discontinue Tecentriq
Type 1 diabetes mellitus	Grade 3 or 4 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L)	Withhold Tecentriq Treatment may be resumed when metabolic control is achieved on insulin replacement therapy
Infusion-related reactions	Grade 1 or 2	Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved
	Grade 3 or 4	Permanently discontinue Tecentriq
Rash	Grade 3	Withhold Tecentriq

Adverse reaction	Severity	Treatment modification
		Treatment may be resumed when rash is resolved and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4	Permanently discontinue Tecentriq
Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis	All Grades	Permanently discontinue Tecentriq
Pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis	Withhold Tecentriq Treatment may be resumed when serum amylase and lipase levels improve to Grade 0 or Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue Tecentriq

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Event Version 4.0 (NCI-CTCAE v.4.).

Atezolizumab should be permanently discontinued:

- For Grade 4 toxicities except for endocrinopathies that are controlled with replacement hormones
- For any recurrent event at Grade ≥ 3 severity
- If a treatment-related toxicity does not resolve to Grade 0 or Grade 1 within 12 weeks after adverse reaction onset date
- If a corticosteroid dose of > 10 mg prednisone or equivalent per day is required for treatment-related toxicity beyond 12 weeks after adverse reaction onset date.

Type of Application and aspects on development

The company has received the following scientific advice from the SAWP with regard the design and clinical development of atezolizumab in NSCLC and UC.

Meeting Date	Key Agreements
NSCLC	
11 January 2013	Advice was sought from the Committee for Medicinal Products for Human Use (CHMP) to discuss the clinical data from an ongoing Phase Ia (PCD4989g) study and to obtain feedback regarding the proposed designs of the BIRCH, POPLAR, FIR, and OAK studies with respect to their ability to support a MAA for the treatment of patients with locally advanced or metastatic NSCLC with PD-L1-positive tumor status, after failure of a platinum-containing chemotherapy regimen (procedure number EMEA/H/SA/2522/1/2013/III).

29 January 2015	Follow-up CHMP scientific advice was sought for OAK and BIRCH (Procedure No. EMEA/H/SA/2522/1/FU/1/2015/II).
UC	
7 May 2014	Advice from the Scientific Advice Working Party (SAWP) was sought for the development of atezolizumab for patients with metastatic UC (Procedure No. EMEA/H/SA/2522/2/2014/II).
28 January 2016	Advice was sought from the CHMP to discuss the design of the proposed Phase III Study IMvigor 130 (Procedure No.: EMEA/H/SA/2522/6/2015/II). IMvigor 130 is a Phase III, multicenter, randomized, placebo-controlled, double-blind study planning to evaluate the safety and efficacy of atezolizumab + gemcitabine/carboplatin versus gemcitabine/carboplatin alone in patients with locally advanced or metastatic UC who have not received prior systemic therapy and who are ineligible to receive cisplatin-based therapy.

2.2. Quality aspects

2.2.1. Introduction

Atezolizumab is an Fc-engineered, humanised IgG1 anti-programmed death-ligand 1 (PD-L1) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. PD-L1 may be expressed on tumour cells and/or tumour-infiltrating immune cells, and can contribute to the inhibition of the anti-tumour immune response in the tumour microenvironment.

The proposed mechanism of action of atezolizumab involves a direct binding of atezolizumab to the PD-L1 interface of the PD-L1:PD-1 and PD-L1:B7.1 binding sites, thus blocking the ability of PD-L1 to interact with these receptors. Disrupting the PD-L1/PD-1 and PD-L1/B7.1 pathways abrogates inhibition of antitumor T-cell activity.

Tecentriq is presented as concentrate for solution for infusion. One vial of 20 mL concentrate contains 1,200 mg atezolizumab, corresponding to a concentration before dilution of 60 mg/mL. Atezolizumab is formulated with L-histidine, glacial acetic acid, sucrose, polysorbate 20 and water for injections.

2.2.2. Active Substance

General information

Atezolizumab is a humanised monoclonal antibody based on a human immunoglobulin G1 (IgG1) framework that contains heavy chain V_HIII and light chain V_κI subgroup sequences. The recombinant

antibody is produced in CHO cells and consists of two heavy chains (448 amino acid residues each) and two light chains (214 amino acid residues each).

By design, atezolizumab incorporates an amino acid substitution (asparagine to alanine) at position 298 in the CH2 domain of each heavy chain. This substitution results in a non-glycosylated antibody that has minimal binding to Fcγ receptors and thereby prevents Fc-effector function and depletion of cells expressing programmed death-ligand 1 (PD-L1) at expected concentrations in humans.

Product variants resulting from the post-translational modifications commonly present in CHO-derived monoclonal antibodies are observed for atezolizumab.

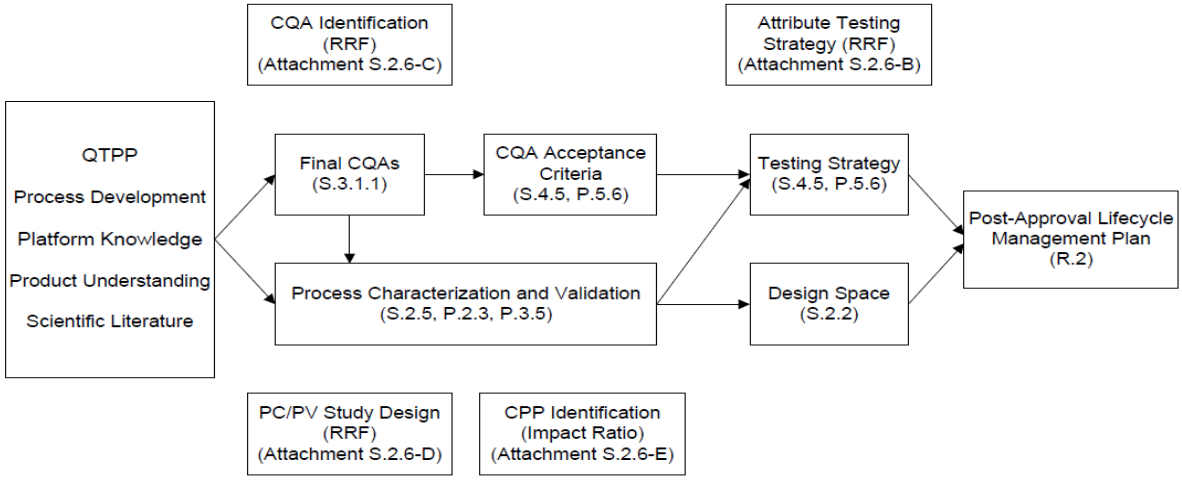
Manufacture, characterisation and process controls

Introduction to the Quality by Design (QbD) approach

It should be noted that the QbD approach applied for Tecentriq (**Figure 1** is comparable to the one that has been used for the product and process development of two of Roche's licensed products (Perjeta and Gazyvaro).

Overall, the design space claimed is based on the outcome of the process characterisation / process validation (PC/PV) studies as well as platform knowledge, product characterisation and identified critical quality attributes (CQAs).

The PALM plan (post-approval lifecycle management plan) for atezolizumab will contain elements covering process monitoring, control system updating and technical change management similar to the plans proposed for Perjeta and Gazyvaro. The approach provides assurance the process consistently produces material that meets all its CQAs and control strategy requirements throughout the product lifecycle.



Note: References in parentheses are to the relevant dossier sections and attachments for the different elements of the QbD approach (e.g., the design space is described in Section S.2.2 *Description of the Manufacturing Process and Process Controls*).
Abbreviations: ATS = attribute testing strategy; CPP = critical process parameter; CQA = critical quality attribute; PC/PV = process characterization and validation; QbD = Quality by Design; QTPP = quality target product profile; RRF = risk ranking and filtering.

Figure 1 - QbD approach for Tecentriq

Manufacture and process controls

Manufacturer

The active substance is manufactured at F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, CH-4070 Basel, Switzerland.

Cell culture and harvest

Atezolizumab is produced in a fed-batch process The source of cells is either the Master Cell Bank (MCB) or a Working Cell Bank (WCB) derived from the MCB. The cell culture process consists of three stages: seed train, inoculum train, and production culture. Upon completion of the production culture, atezolizumab in the cell culture fluid is physically separated from the CHO cells by harvesting via centrifugation and filtration.

Purification

Atezolizumab in the harvested cell culture fluid is initially purified by affinity chromatography, the recovered low pH pool is held to ensure potential viruses are inactivated, the pH adjusted affinity pool is further purified over a cation and anion chromatography step, and the pH adjusted anion exchange pool is filtered over a virus removal filter. The final step in the active substance purification process is concentration and buffer exchange to obtain the active substance specification (60 mg/mL atezolizumab in histidine acetate, sucrose, and polysorbate 20). The pool is 0.22 µm filtered into a sterilised storage tank, frozen, and stored at ≤ -20^{0}C.

Control of critical steps

To ensure the quality of the active substance, in-process controls (IPCs) have been established. IPC tests and limits apply to the cell culture and harvest process steps and the purification process steps.

Control of materials

Atezolizumab is produced using a stably transfected CHO cell line. One of the clones resulting from this transfection was selected as the host cell for production cell-line construction. A two-tier cell banking system of master cell bank and working cell bank was developed and characterised in accordance with ICH guidelines.

Process validation

Development, characterisation, and validation of the atezolizumab process are based on a QbD approach. An overview of the QbD tools used is presented in Figure 1.

Process characterisation and validation (PC/PV) studies were designed to demonstrate manufacturing process consistency for relevant product quality attributes and key performance indicators (KPIs) for CPPs and non-CPPs. These studies include a combination of qualified scale-down models and equipment and site-specific validation studies conducted at manufacturing scale.

The results from characterisation studies are used to identify CPPs and support acceptable parameter ranges for commercial production. These studies were designed based on process understanding developed during process development, platform knowledge, and scientific and engineering principles.

Manufacturing process development

During pharmaceutical development, different versions of the active substance manufacturing process were used to manufacture atezolizumab for clinical trials. The manufacturing process is based on the Applicant's CHO antibody manufacturing platform.

The process changes occurring during development have been assessed for impact to product quality, and the atezolizumab manufactured at the commercial manufacturing site has been demonstrated to be comparable to the material used for clinical trials.

Characterisation

Atezolizumab was extensively characterised in terms of physicochemical, biological, and immunochemical characteristics.

Summary of physicochemical characteristics

Atezolizumab is a humanized monoclonal antibody based on an IgG1 (kappa) framework containing humanised heavy chain V_HIII and light chain V kappa I subgroup sequences. The recombinant antibody is produced in CHO cells and consists of two heavy chains (448 amino acid residues each) and two light chains (214 amino acid residues each) with inter- and intrachain disulfide bonds that are typical of IgG1 antibodies. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 in the CH2 domain of the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and consequently eliminates detectable Fc-effector functions and depletion of cells expressing PD-L1 at expected concentrations in humans. Orthogonal physicochemical methods were developed to characterise atezolizumab attributes and product variants. These methods include control system release assays that were validated following ICH guidance and extended characterisation.

Summary of biological and immunochemical characteristics

A number of *in vitro* assays were developed to reflect the proposed mode of action for atezolizumab. Additionally, assays to assess effector function and evaluate the binding of atezolizumab to FcRn were developed. These assays were used to assess the bioactivity of the active substance batches and to characterise the product, product variants, and stress samples. The suitability of these methods were either validated following ICH guidance or qualified for their intended purposes.

Summary of CQA assessment

CQAs identified for atezolizumab are divided into the following categories: product variants, process-related impurities and obligatory CQAs. A CQA cut off score was determined by applying a CQA RRF tool to several examples of known high- and known low-risk quality attributes and establishing that the risk scores of known high-risk attributes were above the cut off. Quality attributes with moderate, high, and very high impact assessments will remain CQAs; reduced uncertainty will not move such attributes into the low-risk attribute category without corresponding low impact scores.

The CQA acceptance criteria (CQA-AC) corresponds to the limit each CQA must meet throughout the finished product shelf life, independent of whether the CQA is routinely tested, tested through monitoring, or not tested. To meet the CQA-AC, restrictions have been included in the specifications of the finished product (release) and active substance (release and stability) based on the knowledge acquired on the process and stability for atezolizumab. For CQAs that are critical for bioactivity or pharmacokinetics (PK), CQA-ACs are established to ensure that CQA levels stay within the cumulative impact ranges for bioactivity and PK.

Specification

The release specifications for atezolizumab active substance have been suitably justified and are supported by consistent data from multiple lots. The specifications contain test for pharmacopoeial methods as well as specific methods to ensure sufficient safety and quality with respect to identity, purity, potency and other general tests.

Reference standard

A two-tiered approach was established for the commercial Reference Standard whereby the primary Reference Standard will be used to qualify future Reference Standards. The secondary Reference

Standard is used as the working Reference Standard for testing of the active substance and finished product in all assays requiring a Reference Standard. Qualification of the commercial Reference Standards was conducted by release testing and extensive characterisation.

Stability

A shelf life of 24 months at ≤ -20^{0}C is claimed for the active substance based on stability data obtained with four batches manufactured using the commercial manufacturing process and is supported by data from five representative batches manufactured using the clinical manufacturing process..

Batches obtained with the clinical manufacturing process are comparable and considered representative of the commercial process. The comparability exercise did not show any significant difference between batches manufactured by the clinical and commercial process.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Description and composition of the finished product

Atezolizumab finished product is provided as a sterile, single-use, colorless to slightly yellow solution for intravenous infusion and does not contain preservatives.

Each 20 mL vial contains 1200 mg of atezolizumab, a nominal fill volume of 20 mL, at a target pH of 5.8. The finished product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% (w/v) polysorbate 20, pH 5.8.

The container closure system consists of a Type I glass vial sealed with a rubber stopper and crimped with an aluminium seal fitted with a plastic flip-off cap.

Pharmaceutical Development

The finished product for commercial use contains 60 mg/mL atezolizumab in histidine acetate, sucrose, and polysorbate 20. These excipients are commonly used in formulation of biotech products. The Applicant established a quality target product profile (QTPP) which describes the desired performance characteristics of the product's requirements with respect to quality, efficacy, and patient safety. Elements of the QTPP include requirements from the target product profile, scientific and technical knowledge, legal requirements (e.g. pharmacopeias and guidelines published by Health Authorities or ICH), and intrinsic drug substance properties. The QTPP also influences evaluation of CQAs and drives active substance/finished product process and formulation development.

Manufacturing process development

During development the finished product manufacturing was transferred to a different site. The finished product manufacturing process at both sites remained the same with some facility fit adaptations.

Container closure system

The finished product container closure system consists of the following components:

- 20 mL Type I glass vial (Ph. Eur.);

- 20 mm fluororesin-laminated rubber stopper (Ph. Eur.);

- Aluminium seal fitted with a plastic flip-off cap.

The 20 mL glass vial size selected as the primary packaging of the finished product is pharmaceutical grade and meets pharmacopeial standards. The 20 mm fluororesin-laminated liquid-type rubber stopper meets pharmacopeial requirements for container closure. Compatibility of the vial and stopper with the finished product is demonstrated by the long-term finished product stability data. The container closure system has been validated by container closure integrity testing. In addition, the primary packaging components (vial and stopper) for the finished product were selected from standard components that have been implemented for numerous other commercial products manufactured by the Applicant.

Manufacture of the product and process controls

Manufacture and process controls

The finished product was developed using a QbD approach and used the same RRF tools to define CQA-ACs, CPPs and the control strategy. However, no design space is claimed for the finished product manufacturing process.

The commercial manufacturing process consists of thawing active substance, bioburden reduction and sterile filtrations, aseptic filling into glass vials, stoppering, capping and crimping, and visual inspection, including vial integrity testing.

In-process controls composed of action limits and acceptance criteria for manufacture of the finished product are in place.

Process validation

The finished product process validation was performed on batches manufactured with the commercial process at the commercial site.

Product specification

The finished product specification includes pharmacopoeial methods as well as specific methods for control of identity, purity, potency.

The control strategy for the finished product was developed using an approach similar to that used for the active substance.

The Reference Standard used for finished product release and stability testing is the same as that used for the active substance

Stability of the product

The finished product stability claim of 24 months at 2-8^{0}C is based on primary stability data from three primary stability product Batches, which are considered representative of the commercial product.

Commercial batches have been included in the stability program and will be monitored up to 48 months in a long-term study. Also, one commercial batch will be added to the stability program annually if commercial production occurs during the calendar year.

The compatibility/in-use study demonstrated that the finished product diluted solutions were physicochemically stable for 24 hours at 2-8^{0}C and 8hours at 30^{0}C in ambient room light conditions.

Adventitious agents

The risk of transmitting adventitious agents to humans, including transmissible spongiform encephalopathy (TSE), is thoroughly managed through the combination of control of raw and starting materials, process controls, and process understanding.

There are no raw materials of human origin in the entire process. Raw materials of animal origin that are used in the commercial manufacturing process include recombinant human insulin and simethicone emulsion. Heat treatment, irradiation, and filtration of animal-derived raw materials, together with filtration and/or heat treatment steps, ensure control of non-viral and viral adventitious agents. All other raw materials used in the cell culture and purification process are not of animal or recombinant origin and are therefore safe with regard to contamination with agents causing TSE.

All cell banks have been tested for non-viral and viral adventitious agents according to ICH Q5A and were found to be free of detectable adventitious viruses, as well as bacterial, fungal, and mycoplasma contamination. Results of routine testing of the active substance demonstrate that all batches produced are free from mycoplasma and within the acceptable limits set for bioburden and endotoxins.

The process characterisation studies used to establish the design space includes the evaluation of four steps with regards to virus clearance and inactivation.

Through systematic controls and comprehensive testing, as well as through the demonstration of clearance/inactivation included when moving within the design space, it can be ensured that the atezolizumab manufacturing process is safe with regard to potential viral and non-viral adventitious agent contamination.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

No Major Objection has been identified. The data presented on the chemical, pharmaceutical and biological aspects is very detailed and of high quality. Relevant guidelines and monographs have been taken into account. The development of the manufacturing process and the control strategy is based on a QbD approach and is generally considered properly described and justified. The dossier includes a post-approval lifecycle management (PALM) plan as well as Established Conditions.

Critical process parameters (CPPs) are identified based on impact to critical quality attributes (CQAs). The process parameter classification and the defined ranges are acceptable and supported by process evaluation and/or validation.

The Applicant demonstrated that due to the amino acid substitution atezolizumab has minimal binding to Fc receptors and consequently no detectable Fc-effector functions such as ADCC or CDC

The commercial specification for the active substance for release and end-of-shelf-life are provided and based on the proposed control strategy.

Stability data were provided to support the proposed shelf lives for active substance and finished product.

Established conditions

The Applicant has proposed Established Conditions (ECs) according to the draft ICH Q12 guidance on "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management". The proposed definition of ECs is that they are legally binding information defined in a Marketing Authorisation Application. As a consequence, any change to an EC initiates a variation. Any change to a non-established condition does not require regulatory action. The proposed ECs represent the final outcome of many supportive activities such as validation, risk mitigation, characterisation, etc.

Overall the attempt of the Applicant is very much appreciated and might trigger further discussion regarding product lifecycle management and dossier content. However, until the ICH Q12 discussions

are finalised and a consensus is reached, the Applicant was asked to remove the reference to Established Conditions from the Module 3.2.R of the dossier. This request has been met.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Tecentriq is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications.

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

The overall quality of Tecentriq is considered acceptable when used in accordance with the conditions defined in the SmPC.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Expression of programmed death–ligand 1 (PD-L1) is prevalent in many human tumours (Dong et al. 2002), and its overexpression is associated with poor prognosis for patients with any of several epithelial cancers (Thompson et al. 2006; Hamanishi et al. 2007; Okazaki and Honjo 2007; Hino et al. 2010). Elevated expression of PD-L1 on tumour cells has been reported to impede anti-tumour immunity, resulting in immune evasion by tumour cells. PD-L1 is one of two ligands that regulate the activity of programmed cell death–1 (PD-1), an inhibitory receptor that modulates T-cell signalling and whose expression is induced on T cells following activation and sustained in sites of chronic stimulation such as the tumour microenvironment (Blank and Mackensen 2007). Ligation of PD-1 impairs the capacity of chronically activated T cells to proliferate, produce cytokines, or effectively kill target cells in response to their cognate antigen. Atezolizumab (MPDL3280A) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that targets PD-L1 and inhibits its interaction with PD-1. Atezolizumab was engineered with an amino acid substitution at position 298, resulting in a non-glycosylated antibody, to impair Fcγ receptor binding and to prevent Fc-mediated depletion of cells expressing PD-L1.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Studies were conducted to characterize the *in vitro* and *in vivo* pharmacological activity of atezolizumab. Nonclinical *in vitro* and *in vivo* pharmacology studies with atezolizumab are summarized in the table below.

Study No.	Study Title
Primary Pharmacodynamics:	
***In Vitro* Studies**	
09-0426	*In Vitro* Binding and Biological Activity of MPDL3280A (rhuMAb PD-L1)
15-0984	*In Vitro* Binding Affinity of MPDL3280A
15-2718	Non-Clinical Biomarker Study in Paediatric Tumour Tissue
***In Vivo* Studies: Syngeneic Tumour Models**	
08-1033 E	Evaluation of the Anti-Tumour Efficacy of Anti–PD-L1 Monoclonal Antibody in the Syngeneic MC38.OVA Colorectal Cancer Model in C57BL/6 Mice
10-1883	Evaluation of the Anti-Tumour Efficacy of Anti–PD-L1 Monoclonal Antibody in the Syngeneic MC38 Colorectal Model in C57BL/6 Mice
08-1734 D	Evaluation of the Anti-Tumour Efficacy of Anti–PD-L1 Monoclonal Antibody in the Syngeneic CT26 Colorectal Cancer Model in Balb/c Mice
09-2165 I	Evaluation of the Anti-Tumour Efficacy of Anti–PD-L1 Monoclonal Antibody in the Syngeneic Cloudman S91 Melanoma Model in DBA/2 Mice
In Vivo Studies: LCMV	
08-0559A [a]	Evaluation of the Immune Response to LCMV in Mice Treated with Anti–PD-L1 Antibodies
08-0559B [a]	Testing Different Anti–PDL-1 Antibodies and Times of Intervention in Mice Infected with LCMV
08-1160 [a]	Evaluation of Anti–PD-L1 Antibody Dose Response in Mice Infected with Chronic LCMV Clone 13
09-2500 09-2500 B 09-2501 09-2501 A	Evaluation of the Host Response to Armstrong and CL-13 LCMV Infection in Mice following Administration of a Single Dose of Anti–PD-L1 Antibody at Different Times during Infection
10-1394	Studies to Address Mechanism of Anti–PD-L1 Enhanced Pathology LCMV Infection: Comparisons between Clone-13 and Armstrong Strains
08-1309 A	Evaluation of the Combined Effects of Adenovirus Expressed Interferon-alpha (IFN-a) and Anti–PD-L1 mAb in Mice Infected with LCMV

In Vitro Binding of Atezolizumab and the Chimeric Derivatives (PRO304397 and PRO314483) to PD-L1 (Studies 09-0426 and 15-0984)

In vitro tumour studies

Equilibrium binding studies were performed to determine binding affinity (K_d) values of CHO-derived atezolizumab and its chimeric derivative (PRO304397) to human and mouse PD-L1 expressed on 293 cells. The K_d values are presented in Table 2.

Table 2 Binding of Atezolizumab and the Chimeric Derivative to Transfected Human and Murine PD-L1 in Equilibrium Binding Assays (Studies 09-0426 and 15-0984)

	K_d (nM)	
Test Material	Binding to Human PD-L1	Binding to Murine PD-L1
Atezolizumab Lot 729339 [a]	0.433; 0.400 [b, c]	0.134; 0.120 [b]
Atezolizumab Lot 729341 [a, d]	0.228 ±0.095 [e]	Not done
Atezolizumab Lot 602044 [f]	0.255 ±0.018 [e]	Not done
PRO304397 [g]	0.374; 0.336 [b]	0.147; 0.188 [b]

CHO = Chinese hamster ovary; GLP = good laboratory practice; K_d = dissociation constant; PD-L1 = programmed death–ligand 1; v = version.
Note: Atezolizumab Lot 729339 and PRO304397 were used in Study 09-0426; atezolizumab Lots 729341 and 602044 were used in Study 15-0984.
[a] Manufactured using v0.1 process for toxicology. The same source material was used for GLP Study 08-1148.
[b] n = 2. Data shown are results from individual experiments.
[c] Initial measurement of v0.1 process material (Study 09-0426).
[d] Repeat measurement of v0.1 process material, done along with v0.3 process material (Study 15-0984).
[e] n = 3.
[f] Manufactured using v0.3 process used for clinical (Phase I/II and Phase III) studies.
[g] The same lot of material was used for Study 08-1946 (CHO-produced reverse chimera).

Blocking of PD-L1 Binding to PD-1 and to B7-1 by Atezolizumab (Study 09-0426)

The blocking activity of atezolizumab and its chimeric derivatives (PRO304397 and PRO314483) was assessed by competitive ELISAs using human and murine recombinant proteins PD-1, PD-L1, and B7-1; the binding selectivity and IC_{50} were determined.

Table 3 Atezolizumab and its Chimeric Derivatives Block the Binding of PD-L1 to Recombinant B7-1 and PD-1 (Study 09-0426)

	IC_{50} ± SD (pM, n = 3)			
Test Material	huB7-1/ huPD-L1	huPD-1/ huPD-L1	muB7-1/ muPD-L1	muPD-1/ muPD-L1
Atezolizumab [a]	48.4 ± 25.9	82.8 ± 40.3	75.6 ± 14.8	104 ± 38.7
PRO304397 [b]	47.5 ± 26.3	77.5 ± 25.2	79.4 ± 15.5	113 ± 31.5
PRO314483 [c]	41.0 ± 15.8	78.9 ± 31.0	96.6 ± 27.2	125 ± 16.5

CHO = Chinese hamster ovary; GLP = good laboratory practice; hu = human; IC50 = 50% inhibitory concentration; mu = murine; PD-L1 = programmed death–ligand 1.
a Lot 729339, the same source material was used for GLP Study 08-1148.
b CHO-produced lot of reverse chimera, PRO304397, was used in Study 08-1946.
c Escherichia coli-produced lot of reverse chimera, PRO314483.

Binding of Atezolizumab to FcγRs (Study 09-0426)

The ability of atezolizumab to bind to human Fcγ receptors was assessed using a panel of in vitro ELISAs. Atezolizumab exhibited minimal binding to each of the human Fcγ receptors tested (as shown in representative binding curves in Figure 1and Figure 2), relative to the humanized IgG1 control, trastuzumab, which bound to all Fcγ receptors tested.

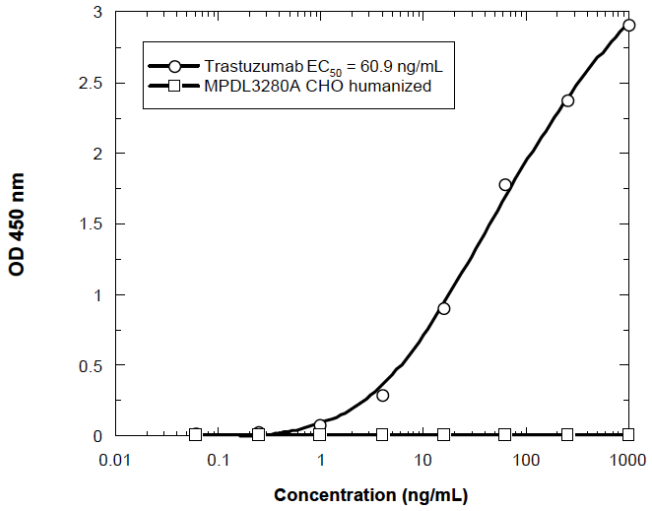


Figure 1 Binding of Atezolizumab and Trastuzumab to FcγRIA (Study 09-0426)

CHO = Chinese hamster ovary; EC50 = 50% effective concentration; OD = optical density; FcγR = Fc gamma receptor.
Notes: MPDL3280A CHO humanized is synonymous with atezolizumab.
The figure depicts binding curves showing binding of control antibody to the FcγR and reduced binding by atezolizumab. The mean absorbance values (OD 450 nm) from duplicates of sample dilutions were plotted against the test antibody or control concentration (in ng/mL)

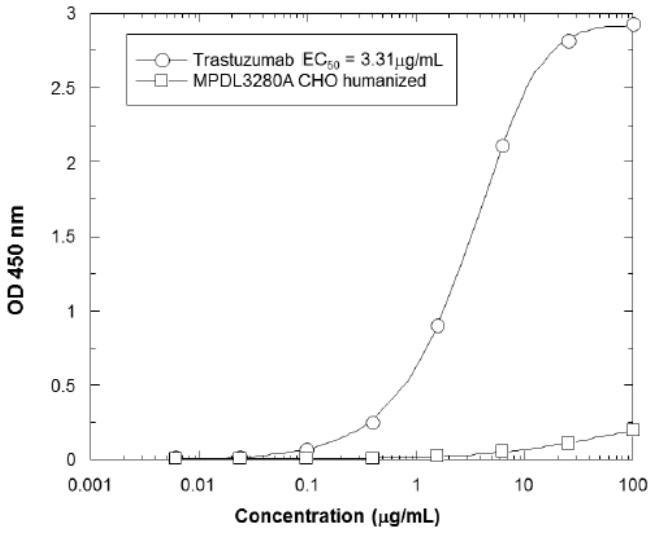


Figure 2 Binding of Atezolizumab and Trastuzumab to FcγRIIIA-F158 (Study 09-0426)

CHO = Chinese hamster ovary (cell); EC50 = 50% effective concentration; FcγR = Fc gamma receptor; OD = optical density.
Notes: MPDL3280A CHO humanized is synonymous with atezolizumab.
Example binding curves showing binding of control antibody to the FcγR and reduced binding by atezolizumab. The mean absorbance values (OD 450 nm) from duplicates of sample dilutions were plotted against the test antibody or control concentration (in µg/mL).

Non-Clinical Biomarker Study in Paediatric Tumour Tissue (Study 15-2718)

Paediatric tumour samples were assessed for PD-L1 expression using an anti–PD-L1–specific immunohistochemistry (IHC) assay that can measure PD-L1 expression on tumour cells (TCs) and on

tumour-infiltrating lymphocytes (ICs) in human formalin-fixed, paraffin-embedded (FFPE) tumour tissues. The findings were assessed using available demographic and baseline information. Overall, PD L1 prevalence was low in the assessed patient samples across four of five indications.

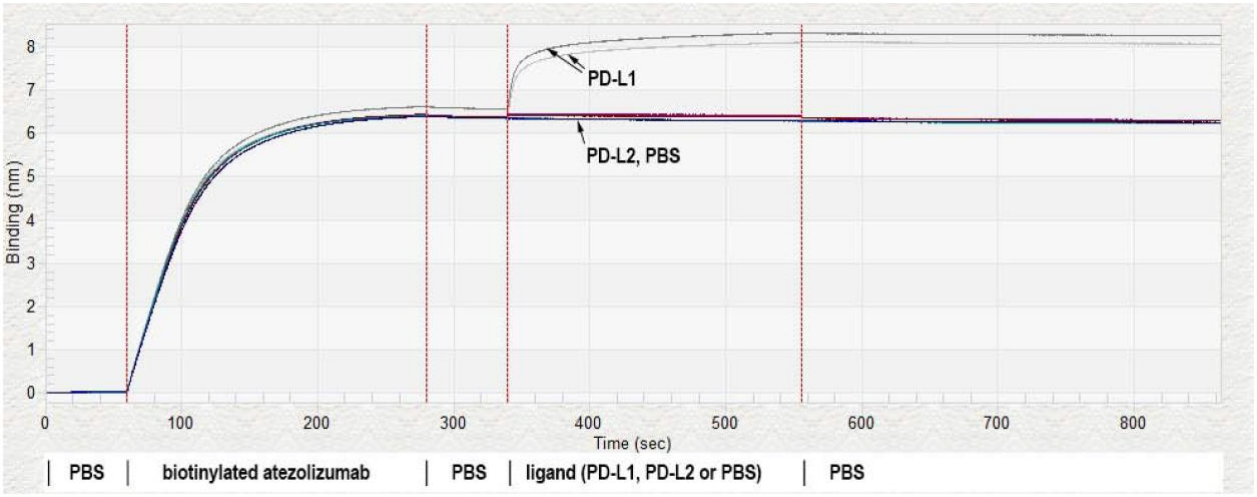
Table 4 PD-L1 Protein Expression across Paediatric Indications

Indication	TC0, IC0	TC0, IC1	TC0, IC2	TC2, IC0
Ewing Sarcoma	19	—	1	—
Medulloblastoma	19	1	—	—
Neuroblastoma	18	2	—	—
Osteosarcoma	19	1	—	—
Rhabdomyosarcoma	14	2	—	4

— = not applicable; IC = immune cell; PD-L1 = programmed death-ligand 1; TC = tumor cell.

Binding of Atezolizumab to PD-1/PD-L2 (study 16-3192)

Molecular interaction analysis was performed on a ForteBio Octet platform using streptavidin probes by capturing biotinylated atezolizumab and then detecting any binding of PD-L1 or PD-L2 to atezolizumab. Clear binding was detected when atezolizumab was tested with PD-L1, but PD-L2 showed no detectable binding to atezolizumab.



PBS = phosphate-buffered saline; PD-L1 = programmed death–ligand 1; PD-L2 = programmed death–ligand 2.
Data are based on a single experiment.

Figure 3 Binding interaction sensorgram for atezolizumab with PD-L1-Fc and PD-L2-Fc

In vivo tumour studies

Evaluation of the Antitumor Efficacy of Anti-PD-L1 MAb in mice models (Studies 08 1033 E, 10 1883, Study 08-1734 D and 09-2165 I).

The primary pharmacology of the mouse chimeric mAB derivative PRO314483 (atezolizumab PD-L1 binding variable region set in a mouse IgG2a framework), also exhibit impaired Fc-mediated effector function) was studied in several syngeneic mouse models, in both colorectal tumours (MC38, MC38.OVA and CT 26) as well as one melanoma model (Cloudman S91). In the four studies, all treated groups showed improved average time to progression, and in MC38.OVA complete remission was observed in all treated animals with three weekly IP injections of 10 mg/kg PRO314483 for one up to 3 weeks. In the study with melanoma (Cloudman S91), two (of 10) animals showed partial remission, however in all four studies tumour growth inhibition of 76% and above was observed.

A summary of the designs and results from the *in vivo* tumour studies is provided in Table 5.

Table 5 Design of *In Vivo* Studies with Response Data

Study No.	Model	Schedule	% TGI	TTP5X [Days] (Treated/ Control)	Fold-Extension in Time To Progression (TTP5X Treated/ TTP5X Control)	PR	CR
08-1033 E	MC38.OVA	TIW × 1	118	NA/18	NA	0	10
		TIW × 2	116	NA/18	NA	0	10
		TIW × 3	119	NA/18	NA	0	10
10-1883	MC38	TIW × 1	76	23.5/16.5	1.4	1	0
		TIW × 2	98	37/16.5	2.2	3	3
		TIW × 3	103	50/16.5	3.0	3	3
08-1734 D	CT26	TIW × 3	92	27.5/11.5	2.4	1	1
09-2165 I	Cloudman S91	TIW × 3	78	14/8	1.75	2	0

CR = complete response; NA = not applicable; TIW = three times per week; PR = partial response; TGI = tumor growth inhibition; TTP = time to progression.

Evaluation of the Impact of Anti–PD-L1 in a Mouse Model of LCMV (Studies 08-0559A, 08-0559B, 08-1160, 09-2500, 09-2500 B, 09-2501, 09-2501 A, 10-1394, and 08-1309 A)

The objective of these studies was to evaluate the impact of atezolizumab in a mouse model of chronic viral infection (LCMV CL-13 model).

When administered approx. 2 weeks after the initial infection, anti-PD-L1 treatment enhanced virus-specific T cell function and reduced viral load without evidence of toxicity. Blockade of PD L1 at the peak of the acute T cell response and concomitant peak viremia following LCMV CL-13 infection (on Day 7) resulted in a mortality rate of 60%-100% (Study 08-0559B). Additional studies were conducted to determine the factors contributing to the enhanced disease and mortality in CL-13-infected mice following PD L1 blockade during peak viremia.

The mortalities observed in the acute CL 13 infection model resulted from enhanced $CD8^+$ T cell function in the setting of extremely high viral burden in multiple organs.

Mortality with PD-L1 blockade was not seen in other acute viral infections that elicit robust T-cell responses and produce high viral titres with more restricted tissue tropism (e.g., Armstrong LCMV, vaccinia, and Adeno-5 virus) (Studies 09-2500, 09-2500 B, 09-2501, 09-2501 A, and 08-1309 A; Ha et al. 2008).

Secondary pharmacodynamic studies

No specific secondary pharmacodynamics studies have been conducted.

In vitro tissue cross reactivity studies were conducted with MPDL3280A using a full panel of human and *Cynomolgus* monkey tissues (see Study 08-1174). In human tissues, biotin-MPDL3280A–specific staining was detected in the placenta, lymph node, tonsil, and thymus. Frequent, moderate, apical cytoplasmic and membranous staining was observed in syncytiotrophoblasts of the placenta. Very rare, minimal to mild, cytoplasmic staining was observed in sinusoidal cells of lymph nodes and tonsil. Rare to frequent, mild to moderate, cytoplasmic staining was observed in thymic cortical and medullary cells. In *Cynomolgus* monkey tissues, biotin-MPDL3280A–specific staining was detected only in the lymph node. Rare to frequent, minimal to moderate, cytoplasmic staining was observed in sinusoidal cells of lymph nodes.

Safety pharmacology programme

No specific safety pharmacology studies have been conducted.

Central nervous system, cardiovascular (telemetry and/or surface leads), and respiratory safety pharmacology parameters were evaluated as part of the 8- and 26-week GLP *Cynomolgus* monkey toxicology studies (Studies 08-1148 and 13-3278). No atezolizumab-related electrocardiographic findings were observed; all electrocardiograms evaluated in this study were qualitatively and quantitatively within normal limits. There were no changes in mean arterial blood pressure, heart rate, body temperature, respiratory rate, oxygen saturation, or neurological parameters observed at doses up to 50 mg/kg given intravenously weekly for 26 weeks (total of 27 doses).

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies have been conducted.

2.3.3. Pharmacokinetics

The pharmacokinetics of atezolizumab was evaluated in a single-dose PK study in *Cynomolgus* monkeys. Repeat-dose toxicokinetics was assessed from the toxicity studies in *Cynomolgus* monkeys (8 and 26-weeks) and the exploratory toxicity study in mice (15 days). In addition, PK/PD of the chimeric anti-PD-L1 mAb PRO304397 was studied after single-dose administration in mice.

Indirect antigen ELISAs were used for detection of atezolizumab or a chimeric anti-PD-L1 mAb in mouse and *Cynomolgus* serum. Bridging ELISAs were used for detection of anti-atezolizumab antibodies in mouse and *Cynomolgus* serum. All assays used in the pivotal *Cynomolgus* toxicity studies were adequately validated.

In a PK/PD study in BALB/c mice, the PK of a chimeric anti-PD-L1 mAb and saturation of PD-L1 on peripheral blood T cells was evaluated after single IV doses from 1 to 30 mg/kg. The duration of PD-L1 saturation on CD8+ and CD4+ T cells was dose-dependent and correlated with the amount of anti-PD-L1 mAb in serum.

Kinetics of atezolizumab in mice (C57BL/6 and CD1) was evaluated after 3 weekly IV doses of 10 and 50 mg/kg. There was a dose-dependent increase in exposure after the first dose. However, atezolizumab serum concentrations dropped rapidly after the 3rd dose, which correlated with the presence of ATA in all mice after the 3rd dose.

Table 6: Summary of non-clinical PK and TK studies

Species	Study Type	Study Site [a]	Study No.	Title
Mouse	PK/PD	Genentech, Inc.	08-1946	Evaluation of Pharmacokinetics and Pharmacodynamics following Single-Dose IV Administration of an Anti–PD-L1 Reverse Chimera Antibody
Mouse	TK	Genentech, Inc.	08-0806	A 15-Day Pilot Toxicity Study of Anti–PD-L1 (MPDL3280A) Administered by IV Injection Once a Week for a Total of 3 Doses to Female C57Bl/6 and CD-1 Mice with 4 Weeks of Recovery
Cynomolgus monkey	PK	Charles River Labs	08-0598	A Single-Dose PK Study of MPDL3280A Administered by IV Injection to Cynomolgus Monkeys
Cynomolgus monkey	TK	Charles River Labs	08-1148 [b]	An Eight-Week Toxicity, TK, and Safety Pharmacology Study of MPDL3280A Administered by IV Injection or Subcutaneous Injection to Cynomolgus Monkeys, with a 12-Week Recovery Period
Cynomolgus monkey	TK	Covance	13-3278 [b]	A 26-Week Toxicity and TK Study with MPDL3280A, Administered by IV Injection to Cynomolgus Monkey with a 13-Week Recovery Phase

IV=intravenous; PD=pharmacodynamic; PK=pharmacokinetic; TK=toxicokinetic.
Note: Unless otherwise noted, all studies have been completed.
MPDL3280A is synonymous with atezolizumab.
[a] Genentech, Inc. is located in South San Francisco, CA. Charles River Laboratories is located in Sparks, NV. Covance is located in Munster, Germany.
[b] Study was conducted in accordance with Good Laboratory Practice regulations.

Kinetics of atezolizumab in *Cynomolgus* monkeys were evaluated after single IV doses (up to 20 mg/kg) and repeated IV and SC doses (up to 50 mg/kg). In all studies, a bi-phasic disposition was observed, with a rapid initial distribution phase followed by a slower elimination phase. The exposure was dose-proportional after the first dose in all dose groups, and in the mid- and high-dose group after the last dose.

In the chronic toxicity study, after repeated once weekly administration, there was moderate accumulation of atezolizumab consistent with a half-life of 11.8 – 23.5 days. Bioavailability after SC administration ranged from 51.8 to 54.3%. In all studies the majority of *Cynomolgus* monkeys developed ATA, with a greater incidence in the low-dose group than in the high-dose group. In a number of animals, a decrease in atezolizumab serum concentration was evident after detection of ATA; this was most evident in the low-dose group.

Studies on distribution, metabolism and excretion were not conducted.

Non-clinical PK drug interaction studies were not conducted.

2.3.4. Toxicology

Toxicity of atezolizumab was evaluated in mice and *Cynomolgus* monkeys. Both species can be considered relevant for testing of atezolizumab. The toxicity programme consisted of a 2-week non-GLP pilot study in mice, and 8-week and 26-week pivotal toxicity studies in *Cynomolgus* monkeys. In

Cynomolgus, the studies consisted of 3 dose groups in addition to a vehicle group; recovery animals were included in all dose groups. Local tolerance and immunotoxicity endpoints were evaluated as part of the repeat-dose studies. In addition, an *in vitro* cytokine release assay, a haemolytic potential and blood compatibility assay and a GLP tissue cross-reactivity study with human and *Cynomolgus* tissue was conducted.

Single dose toxicity

No single-dose toxicity studies were performed.

Repeat dose toxicity

The results of the repeat dose toxicity studies are summarised in the table below.

Table 7: **Overview of repeat-dose studies**

Study ID	Number/ group	Route / Dose (mg/kg)	Duration	NOAEL (mg/kg)	Major findings
08-0806	32 F	IV: 0, 10, 50	15 days; Q1W	Not determined	• Spleen weight and spleen to brain weight ratios from both C57BL/6 and CD-1 animals dosed 50 mg/kg of atezolizumab were greater compared to controls animals. No histology correlate to the weight change, finding is reversible; the significance of the weight change is uncertain. • Atezolizumab-related, minimal sciatic neuropathy in only C57BL/6 mice on days 17 and 43 in both dose groups (10 and 50 mg/kg).
08-1148	3/sex (main) 2/sex (recovery) 3/sex (telemetry)	IV: 0, 5, 15, 50 SC: 0, 15, 50	8 weeks Q1W	5 mg/kg	• Transiently reduced NK cell activity (day 3) @ 15 mg/kg SC; resolved by day 8; relationship to treatment uncertain • Atezolizumab-related arteritis/ periarteritis in various tissues (in few animals in the 15 mg/kg SC and in the 50 mg/kg SC and IV group) considered enhancement of autoreactivity in pre-disposed animals • Transient elevations in IL-12 p40, TNF-α, IFN-γ in 1 animal at 50 mg/kg IV, corresponding increase in activated Th cells on day 29 (reversible); finding likely associated with the arteritis • Atezolizumab-related, minimal cellular infiltrates at the SC injection sites (@ 15 and 50 mg/kg); reversible; not considered adverse

13-3278	3/sex (main) 2/sex (recovery)	IV: 0, 5, 15, 50	26 weeks Q1W	5 mg/kg	• Slight atezolizumab-related lower body weight gain (approx. -10 to -15%) in M, reversible, not considered adverse • Effect on menstrual cycles: irregular cycle pattern between weeks 8 and 14 in all F at 50 mg/kg; reversible • Minimal to slight, chronic-active, and multifocal arteritis/periarteritis in multiple organs of two animals (1 F each at 15 and 50 mg/kg) at the terminal phase necropsy; no arteritis/periarteritis in recovery animals • Minimal increases in neutrophils and lymphocytes, moderate increases in CRP in the 50 mg/kg F with arteritis • Immune mediated hypersensitivity reactions in 2 M (1x 5 mg/kg; 1x 15 mg/kg) on days 113 and141

Genotoxicity

No genotoxicity studies were performed.

Carcinogenicity

No carcinogenicity studies were performed.

Reproduction Toxicity

No reproductive and developmental toxicity studies were performed.

Female and male reproductive organ systems were assessed as part of the chronic toxicity study (*Study 13-3278, 26-Week Toxicity study in Cynomulgus monkeys*). In females, menstrual cycles were monitored by daily vaginal swabs. An effect was observed on menstrual cycles at 50 mg/kg, with an irregular cycle pattern during the dosing phase with disturbed cycles especially between Weeks 8 and 14. This finding correlated with an absence of fresh corpora lutea in the ovaries (lack of cycling activity) at the time of the terminal phase necropsy. This effect showed reversibility as the two females (from the recovery period) at 50 mg/kg demonstrated a return to normal menstrual cycling by vaginal swab data, and both animals had fresh corpus lutea at the recovery necropsy.

In males, semen assessments, testicular evaluations, and serum testosterone level measurements were performed; there was no effect of atezolizumab on any of these parameters.

Toxicokinetic data

The toxicokinetics of atezolizumab were investigated in the repeat-dose toxicity studies 08-1148 and 13-3278.

Exposure to atezolizumab increased with the increase in dose level from 5 to 50 mg/kg.

The group mean TK values for study 08-1148 are presented in the below table.

Table 8: Non-compartmental PK parameter estimates (mean ± SD) following 9 weekly doses of atezolizumab to cynomolgus [08-1148]

Parameter	Dose (mg/kg)				
	Intravenous Route			Subcutaneous Route	
	Group 2 (5 mg/kg)	Group 3 (15 mg/kg)	Group 4 (50 mg/kg)	Group 5 (15 mg/kg)	Group 6 (50 mg/kg)
AUC_{0-7} [a] (day • µg/mL)	486 ± 68.9	1860 ± 296	6990 ± 904	1010 ± 275	3620 ± 517
AUC_{0-56} [a] (day • µg/mL)	4870 ± 1630	28700 ± 8890	104000 ± 22200	11700 ± 10100	61400 ± 21700
AUC_{0-140} [b] (day • µg/mL)	5630 ± 3590	43800 ± 10300	170000 ± 37800	13400 ± 22900	115000 ± 21200
AUC_{last} [b] (day • µg/mL)	5220 ± 2360	35100 ± 13400	133000 ± 44300	14400 ± 15000	82100 ± 37300
AUC_{0-7}/Dose (day • µg/mL/mg/kg)	97.1	124	140	67.4	72.4
AUC_{0-56}/Dose (day • µg/mL/mg/kg)	957	1910	2080	781	1230
AUC_{0-140}/Dose (day • µg/mL/mg/kg)	1130	2920	3400	893	2300
AUC_{last}/Dose (day • µg/mL/mg/kg)	1040	2340	2660	958	1640
C_{max} [a] (µg/mL)	187 ± 44.0	959 ± 158	3310 ± 686	363 ± 230	1640 ± 486
t_{max} [a] (day)	NA	NA	NA	23.4 ± 20.8	47.6 ± 17.7
F (%)	NA	NA	NA	54.3	51.8

AUC_{0-7} = area under the serum concentration–time curve from time = 0 to Study Day 8 (TK Day 7); AUC_{0-56} = area under the serum concentration–time curve from time = 0 to time of the last measurable concentration just before terminal necropsy on Study Day 57 (TK Day 56); AUC_{0-140} = area under the serum concentration–time curve from time = 0 to time of the last measurable concentration just before terminal necropsy on Study Day 141 (TK Day 140); AUC/Dose = area under the serum concentration–time curve divided by the respective dose level; AUC_{last} = area under the serum concentration–time curve from time = 0 to the last measurable concentration; C_{max} = maximum observed concentration; F = bioavailability (calculated based on rounded table values); NA = not applicable; PK = pharmacokinetic; TK = toxicokinetic; t_{max} = time (days) to maximum observed concentration.

[a] n = 10.

[b] n = 4.

Toxicokinetic parameters from study 13-3278 are summarised in the below table.

Table 9: Summary of the mean TK parameters for atezolizumab in monkey plasma [13-3278]

Group	Dose Level (mg/kg)	Sex		First Dose C_{max} (µg/mL)	First Dose AUC_{0-3} (µg • day/mL)	Last Dose C_{max} (µg/mL)	Last Dose $AUC_{182-185}$ (µg • day/mL)	Accumulation Ratio C_{max}	Accumulation Ratio AUC
2	5	M	Mean	139	263	7.28	NC [a]	NA	NA
			SD	12.2	28.4	12.1	NA	NA	NA
		F	Mean	107	224	116	378	NA	NA
			SD	6.65	20.3	140	NA	NA	NA
		M and F Combined	Mean	123	243	61.4	378	NA	NA
			SD	19.5	31.2	107	NA	NA	NA
3	15	M	Mean	351	758	1220	4250	4.80	5.58
			SD	81	149	690	341	1.46	1.36
		F	Mean	251	629	1350	2810	5.56	4.47
			SD	35.7	32.4	1470	2740	6.12	4.25
		M and F Combined	Mean	301	693	1290	3350	5.28	4.89
			SD	79.2	122	1090	2210	4.71	3.34
4	50	M	Mean	1290	2880	4060	10100	3.19	3.50
			SD	109	178	754	1060	0.723	0.430
		F	Mean	1110	2690	3300	6740	3.00	2.51
			SD	71.1	218	515	1370	0.599	0.508
		M and F Combined	Mean	1200	2790	3680	8400	3.09	3.01
			SD	127	215	730	2100	0.634	0.684

AUC_{0-3} = area under the concentration–time curve from 0 to 3 days; $AUC_{182-185}$ = area under the concentration–time curve from 182 to 185 days; C_{max} = maximum observed concentration; NA = not applicable; NC = not calculated.

Note: Limited quantifiable data were available post the last dose at the 5 mg/kg dose level due to formation of anti-atezolizumab antibodies. Therefore, limited AUC data were available post the last dose.

First and last dose C_{max} and AUC values are presented here in micrograms, but listed as nanograms in the final report.

[a] Only one quantifiable concentration was observed from TK Day182 to 185 for Group 2 males; therefore, $AUC_{182-185}$ could not be calculated.

Local Tolerance

A separate local tolerance study of atezolizumab was not performed, as injection sites were examined macroscopically and microscopically as part of the 8- and 26-week repeat-dose *Cynomolgus* monkey toxicology studies (Studies 08-1148 and 13-3278, respectively). In Study 08-1148, a microscopic change related to the SC administration of atezolizumab was noted at terminal necropsy in 3 of 6 and 6 of 6 animals given 15 and 50 mg/kg atezolizumab, respectively. The lesion was characterised as a minimal, focal to multifocal, and often perivascular mononuclear cell infiltrate in the SC tissue of injection sites.

Other toxicity studies

- *In Vitro* Cytokine Release

Study 08-1827: *In Vitro* Cytokine Release Study with Anti–PD-L1 Antibody in Human PBMCs

The potential of atezolizumab to induce cytokine release from PBMCs (*peripheral blood mononuclear cells*) was evaluated *in vitro*. Isolated human PBMCs were cultured in the presence of solution-phase (soluble) or plate-bound (immobilised) atezolizumab at various concentrations (0.25-250 µg/mL) for 24 or 48 hours, and supernatants were analysed for the presence of several cytokines and chemokines.

Atezolizumab, over a concentration range of 0.25-250 µg/mL, did not induce cytokine release from isolated human PBMCs. The levels of GM-CSF, TNF-α, IL-8, IL-2, IFN-γ, IL-6, IL-1β, IL-10, IL-4, and IL-12 produced by PBMCs cultured with soluble or immobilized atezolizumab were comparable to those from PBMCs cultured in media alone or in the presence of the negative control antibody (anti-FGFR3) at both 24 and 48 hours.

- Haemolytic Potential

Study 08-1172: Haemolytic Potential Testing with atezolizumab in *Cynomolgus* Monkey and Human Blood

Atezolizumab, at concentrations up to 125 mg/mL (*the highest testable concentration*), did not cause haemolysis of human or cynomolgus monkey erythrocytes.

- Tissue Cross-Reactivity study

Tissue Cross-Reactivity of atezolizumab with Human and *Cynomolgus* Monkey Tissues *Ex Vivo* (Study 08-1174)

The cross-reactivity of biotinylated atezolizumab at concentrations of 0.25 and 1.25 µg/mL was evaluated immunohistochemically with cryosections of normal human and *Cynomolgus* monkey tissues.

In human tissues, biotin-atezolizumab-specific staining was detected in the placenta, lymph node, tonsil, and thymus. Frequent, moderate, apical cytoplasmic and membranous staining was observed in syncytiotrophoblasts of the placenta. Very rare, minimal to mild, cytoplasmic staining was observed in sinusoidal cells of lymph nodes and tonsil. Rare to frequent, mild to moderate, cytoplasmic staining was observed in thymic cortical and medullary cells.

In *Cynomolgus* monkey tissues, biotin-atezolizumab-specific staining was detected only in the lymph node. Rare to frequent, minimal to moderate cytoplasmic staining was observed in sinusoidal cells of lymph nodes.

- Immunogenicity

Specific immunogenicity study of atezolizumab was not performed. However presence of anti-therapeutic antibody (ATA) was investigated in studies 08-0806, 08-0598, 08-1148 and 13-3278.

In study 08-0806, ATAs were detected in all animals 3 days after the last dose and through the end of the study.

In study 08-0598, ATAs were observed post-dose in all animals given 0.5 mg/kg atezolizumab, all animals given 5 mg/kg atezolizumab, and all animals given 20 mg/kg atezolizumab at Day 14. All but one animal (in the 20 mg/kg group) remained ATA positive until the end of the study.

In study 08-1148, 50 of 56 (89%) *Cynomolgus* monkeys dosed with atezolizumab developed ATA responses. Of these 50 ATA-positive *Cynomolgus* monkeys dosed with atezolizumab, 25 were female and 25 were male.

Table 10: Non-compartmental PK parameter estimates (mean±SD) comparing ATA-positive and ATA-negative *Cynomolgus* monkeys following nine weekly doses of atezolizumab (study 08-1148)

	Intravenous Group 4 (50 mg/kg)		Subcutaneous Group 6 (50 mg/kg)	
	ATA-Positive Animals (n=8)	ATA-Negative Animals (n=2)[a]	ATA-Positive Animals (n=8)	ATA-Negative Animals (n=2)[b]
AUC_{0-7} (day • µg/mL)	7210±782	6130	3570±551	3810
AUC_{0-56} (day • µg/mL)	104000±24900	103000	57300±22600	77800
AUC_{0-140}[c] (day • µg/mL)	170000±37800	NC	115000 ± 21000	NC
AUC_{last} (day • µg/mL)	138000±48100	110000	81800±42300	83300
AUC_{0-7}/Dose (day • µg/mL/mg/kg)	144	123	71.4	76.2
AUC_{0-56}/Dose (day • µg/mL/mg/kg)	2090	2050	1150	1560
AUC_{0-140}/Dose (day • µg/mL/mg/kg)	3390	NC	2290	NC
AUC_{last}/Dose (day • µg/mL/mg/kg)	2770	2200	1640	1670
C_{max}[c] (µg/mL)	3360±719	3130	1560±516	1960
t_{max}[c] (day)	NA	NA	49.0±19.8	42.2

ATA=anti-therapeutic antibody; AUC_{0-7}=area under the serum concentration–time curve from time=0 to Study Day 8 (TK Day 7); AUC_{0-56}=area under the serum concentration–time curve from time=0 to time of the last measurable concentration just before terminal necropsy on Study Day 57 (TK Day 56); AUC_{0-140}=area under the serum concentration–time curve from time=0 to time of the last measurable concentration just before terminal necropsy on Study Day 141 (TK Day 140); AUC/Dose=area under the serum concentration–time curve divided by the respective dose level; AUC_{last}=area under the serum concentration–time curve from time=0 to the last measurable concentration; C_{max}=maximum observed concentration; IV=intravenous; NA=not applicable; NC=not calculated; PK=pharmacokinetic; SC=subcutaneous; t_{max}=time (days) to maximum observed concentration (SC only).

Note: All animals in Groups 2 (5 mg/kg IV), 3 (15 mg/kg IV), and 5 (15 mg/kg SC) were ATA positive.

[a] Animals that were ATA negative for Group 4: 4003-MF10574M and 4502-MF14706F.

[b] Animals that were ATA negative for Group 6: 6001-MF25338M and 6505-MF17529F.

[c] n=2 (recovery animals only).

In study 13-3278, ATAs were detected in 9 of 10 animals in the 5 mg/kg dose group, in 9 of 10 animals in the 15 mg/kg dose group, and in 6 of 10 animals in the 50 mg/kg dose group (overall incidence of 80%). In general, there was a decrease in serum concentrations following detection of ATAs more particularly in the low dose group of 5 mg/kg.

2.3.5. Ecotoxicity/environmental risk assessment

Atezolizumab is a protein, which is expected to biodegrade in the environment and not be 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 preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

2.3.6. Discussion on non-clinical aspects

Non-clinical *in vitro* data were submitted to describe the pharmacological mode of action of atezolizumab. The studies provide information on binding affinity of atezolizumab to its target PD-L1 and on the inhibition of the PD-L1/PD-1 interaction. Atezolizumab did not bind to recombinant PD-L2-Fc, while clear binding was detected with recombinant PD-L1-Fc. The lack of Fc functionality due to removal of the N-glycosylation site was demonstrated, except for the effect on CDC.

The *in vivo* effect of blocking PD-L1 was adequately evaluated in murine syngeneic tumour models using chimeric anti-PD-L1 mAbs. These studies demonstrate that treatment with anti-PD-L1 mediates an effective anti-tumour response and provide sufficient proof-of-concept.

Secondary pharmacology studies and pharmacodynamic drug interaction studies were not performed which is considered acceptable.

The pharmacokinetics of atezolizumab was evaluated in a single-dose PK study in *Cynomolgus* monkeys. Repeat-dose toxicokinetics were assessed from the toxicity studies in *Cynomolgus* monkeys (8 and 26-weeks) and the exploratory toxicity study in mice (15 days). In addition, PK/PD of the chimeric anti-PD-L1 mAb PRO304397 was studied after single-dose administration in mice.

Indirect antigen ELISAs were used for detection of atezolizumab or a chimeric anti-PD-L1 mAb in mouse and *Cynomolgus* serum. Bridging ELISAs were used for detection of anti-atezolizumab antibodies in mouse and *Cynomolgus* serum. All assays used in the pivotal *Cynomolgus* toxicity studies were adequately validated.

In a PK/PD study in BALB/c mice, the PK of a chimeric anti-PD-L1 mAb and saturation of PD-L1 on peripheral blood T cells was evaluated after single IV doses from 1 to 30 mg/kg. The duration of PD-L1 saturation on CD8+ and CD4+ T cells was dose-dependent and correlated with the amount of anti-PD-L1 mAb in serum.

PK of atezolizumab in mice (C57BL/6 and CD1) was evaluated after 3 weekly IV doses of 10 and 50 mg/kg. There was a dose-dependent increase in exposure after the first dose. However, atezolizumab serum concentrations dropped rapidly after the 3rd dose, which correlated with the presence of ATA in all mice after the 3rd dose. Therefore, complete TK characteristics could not be determined.

PK of atezolizumab in *Cynomolgus* monkeys were evaluated after single IV doses (up to 20 mg/kg) and repeated IV and SC doses (up to 50 mg/kg). In all studies, a bi-phasic disposition was observed, with a rapid initial distribution phase followed by a slower elimination phase. The exposure was dose-proportional after the first dose in all dose groups, and in the mid- and high-dose group after the last dose. In the chronic toxicity study, after repeated once weekly administration, there was moderate accumulation of atezolizumab consistent with a half-life of 11.8 – 23.5 days. Bioavailability after SC administration ranged from 51.8 to 54.3%. In all studies the majority of *Cynomolgus* monkeys developed ATA, with a greater incidence in the low-dose group than in the high-dose group. In a number of animals, a decrease in atezolizumab serum concentration was evident after detection of ATA; this was most evident in the low-dose group.

In accordance with ICH S6 (R1), studies on distribution, metabolism and excretion were not conducted.

Non-clinical PK drug interaction studies were not performed. This is acceptable, as monoclonal antibodies are not substrates for by cytochrome P450 enzymes or drug transporters. Furthermore, a cytokine-CYP-based drug-drug interaction between atezolizumab and small molecules is not expected given that atezolizumab by itself did not induce cytokine-release *in vitro*.

To support the safety of atezolizumab, toxicity was evaluated in mice and *Cynomolgus* monkeys. Both species can be considered relevant for testing of atezolizumab. The toxicology programme is in accordance with current guidance and is considered appropriate.

Atezolizumab-related findings in the repeated dose toxicity studies were sciatic neuropathy in C57BL/6 mice and arteritis/periarteritis in *Cynomolgus* monkeys. Both findings may be due to enhancement of an autoreactive immune-response in pre-disposed animals. The toxicity studies provide no margin to the exposure at the proposed clinical dose of atezolizumab.

Genotoxicity studies have not been conducted, which is in accordance with ICH S6(R1).

Carcinogenicity studies have not been conducted in accordance with ICH S6(R1) and ICH S9. Furthermore, due to its mechanism of action, atezolizumab is not expected to be associated with an increased carcinogenic risk.

Reproductive and developmental toxicity studies have not been conducted with atezolizumab. However, in the chronic toxicity study in sexually mature monkeys, atezolizumab treatment at the high-dose resulted in irregular menstrual cycles and a lack of newly formed corpora lutea in the ovaries. The finding was reversible after termination of atezolizumab. Inhibition of the PD-L1/PD-1 pathway, which is intended to modulate the immune system by increasing T cell responses and pro-inflammatory signals, may disrupt the delicate balance between the normal endocrine-immune axis required for maintaining normal ovarian cycling.

Animal studies have demonstrated that inhibition of the PD L1/PD 1 pathway can lead to immune related rejection of the developing foetus resulting in foetal death. Administration of atezolizumab could cause foetal harm, including embryo foetal lethality (see section 5.3 of the SmPC).

A weight-of-evidence approach in accordance to ICH S6(R1) was applied to describe the potential risk of atezolizumab to human pregnancy, which is acceptable. Given the role of the PD-L1/PD-1 pathway in maintaining materno-foetal tolerance, treatment with atezolizumab during pregnancy may lead to abortion or still births. This risk is reflected in section 4.6 of the SmPC: "Women of childbearing potential have to use effective contraception during and for 5 months after treatment with atezolizumab" and "Embryofetal toxicity" has been added as an important potential risk.

Local tolerance was evaluated as part of the 8-week the repeat-dose toxicity studies in *Cynomolgus* monkeys. Microscopic changes at the SC injections sites were reversible and are considered consistent with administration of a heterologous protein.

Atezolizumab does not pose a significant risk to the environment considering that it is a protein which is expected to biodegrade in the environment. According to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), atezolizumab is exempt from preparation of an Environmental Risk Assessment which is considered acceptable.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data submitted are considered appropriate and supportive of the MA for atezolizumab.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

Table 11 Tabular overview of clinical studies

Protocol No.	Location of SynopsisLocation 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
5.3.3 Human PK Studies								
GO27831 (PCD4989g)	**Interim CSR** Report No. 1064914 Synopsis and Interim CSR Data cutoff: 2 December 2014 Supplemental Results Report Report No. 1068014 Data cutoff: 7 August 2015	To evaluate safety, tolerability, and PK	Multicenter, first-in-human, 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 = 483 NSCLC Cohort n = 88 UC Cohort n = 92	Patients with locally advanced or metastatic solid tumors (including NSCLC) and hematologic malignancies	Up to 1 year or until loss of clinical benefit	Ongoing Interim CSR: Full report Supplemental Results Report: Abbreviated report
JO28944	**Primary CSR** Report No. 1067192 Synopsis and Primary CSR Data cutoff: 15 November 2014	To evaluate safety, tolerability, and pharmacokinetics (PK)	Multicenter, dose-escalation, open-label study	atezolizumab 10 mg/kg IV every 3 weeks (q3w) atezolizumab 20 mg/kg IV q3w	n = 6	Patients with advanced or metastatic solid tumors	Two treatment cycles, and then until withdrawal criteria were met	Ongoing Primary CSR Full report
5.3.5 Efficacy and Safety Studies (UC)								
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication								
GO29294 (IMvigor211)	**Results Report** Report No. 11076559 Data cutoff: 13 March 2017	To evaluate the efficacy and safety of atezolizumab compared with chemotherapy in patients with locally advanced or metastatic UC who have progressed during or following a platinum-containing regimen	Global, multicenter, open-label, randomized, controlled study	atezolizumab 1200 mg IV q3w vinflunine 320 mg/m2 q3w or paclitaxel 175 mg/m2 q3w, or docetaxel 75 mg/m2 q3w	Total randomized n = 931 atezolizumab arm n =467 chemotherapy arm n=464 (vinflunine n=250 paclitaxel or docetaxel n =214)	Patients with locally advanced or metastatic urothelial carcinoma who have progressed during or following a platinum-containing regimen	Atezolizumab arm: Until loss of clinical benefit or unacceptable toxicity Chemotherapy arm: Until disease progression or unacceptable toxicity	Ongoing Results report
5.3.5.2 Study Reports of Uncontrolled Clinical Studies								

Protocol No.	Location of SynopsisLocation 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
GO29293 (IMvigor210)	**Primary CSR** Report No. 1065272: Synopsis and Primary CSR Data cutoff: 5 May 2015 **Update CSR** Report No. 1067870 Synopsis and Update CSR Data cutoff: 14 September 2015 Supplemental Results Report Report No. 1067871. Data cutoff: 27 November 2015 Supplemental Results Report Report No. 1073475. Data cutoff: 4 July 2016	To evaluate IRF-assessed ORR per RECIST 1.1, INV-assessed ORR per modified RECIST (primary efficacy endpoints), PFS, DOR, OS, 1-year OS (secondary efficacy endpoints), safety and tolerability, PK	Global, multicenter, monotherapy, single arm trial	atezolizumab 1200 mg IV q 3 weeks	Cohort 1 (1L) = 118 Cohort 2 (2L+) = 311	Patients with locally advanced or 1L metastatic (ineligible for cisplatin-based chemotherapy) and 2L+ UC patients (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 in each cohort was required to be PD-L1-selected (IC2/3).	Cohort 1: Until disease progression Cohort 2: Until loss of clinical benefit	Ongoing Primary and update CSRs: Full reports Supplemental Results Reports Abbreviated reports
5.3.5 Efficacy and Safety Studies (NSCLC)								
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication								
GO28915 (OAK)	**Primary CSR** Report No. 1070445 Synopsis and Primary CSR Data cutoff: 7 July 2016	To evaluate the efficacy and safety of atezolizumab compared with docetaxel in patients with previously treated locally advanced or metastatic NSCLC, in an all-comer population, as well as in subgroups defined by PD-L1 expression.	Global, multicenter, open-label, randomized, controlled study	atezolizumab 1200 mg IV q3w docetaxel 75 mg/m^2 IV q3w	Total randomized n = 1225 atezolizumab arm n = 612 docetaxel arm n = 613 First 850 randomized intent-to-treat patients n = 850 atezolizumab arm n = 425 docetaxel arm n = 425	Patients with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen	Atezolizumab arm: Until loss of clinical benefit or unacceptable toxicity Docetaxel arm: Until disease progression or unacceptable toxicity	Ongoing Primary CSR Full report
GO28753 (POPLAR)	**Primary CSR** Report No. 1065672 Synopsis and Primary CSR Data cutoff: Primary analysis: 8 May 2015 Third interim analysis: 30 January 2015	To evaluate the efficacy of atezolizumab compared with docetaxel as measured by overall survival (OS) (primary efficacy endpoint), overall response rate (ORR), duration of	Global, multicenter, open-label, randomized, controlled study	atezolizumab 1200 mg IV q3w docetaxel 75 mg/m^2 IV q3w	Total randomized n = 287 atezolizumab arm n = 144 docetaxel arm n = 143	Patients with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen	Atezolizumab arm: Until loss of clinical benefit or unacceptable toxicity Docetaxel arm: Until disease progression	Ongoing Primary CSR Full report

Protocol No.	Location of SynopsisLocation 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
	Supplemental Results Report Report No. 1069440 Data cutoff: 1 December 2015	response (DOR), progression free survival (PFS) (secondary efficacy endpoints), as well as safety and tolerability, and PK					or unacceptable toxicity	Supplemental Results Report Abbreviated report
5.3.5.2 Study Reports of Uncontrolled Clinical Studies								
GO28754 (BIRCH)	**Primary CSR** Report No. 1066811 Synopsis and Primary CSR Data cutoff: 28 May 2015 Supplemental Results Report Report No. 1068549 Data cutoff 1 October 2015	To evaluate efficacy of atezolizumab as measured by independent review facility (IRF)-assessed ORR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, (primary efficacy endpoint), PFS, DOR, time in response (TIR), OS, 1-year OS (secondary efficacy endpoints), as well as safety and tolerability, and PK	Global, multicenter, single arm study	atezolizumab 1200 mg IV q3w	Total enrolled n = 667 Cohort 1 (1L) n = 142 Cohort 2 (2L) n = 271 Cohort 3 (3L+) n = 254	PD-L1-selected (TC2/3 or IC2/3) patients with locally advanced or metastatic NSCLC who were either treatment-naive in the metastatic setting (1L) or who had experienced disease progression during or following treatment with one platinum-based regimen (2L) or more than 2 regimens (3L+), one of which had to have been a platinum-containing regimen for advanced disease	Cohort 1: Until disease progression or unacceptable toxicity Cohort 2: Until loss of clinical benefit or unacceptable toxicity Cohort 3: Until loss of clinical benefit or unacceptable toxicity	Ongoing Primary CSR Full report Supplemental Results Report Abbreviated report
GO28625 (FIR).	**Primary CSR** Report No. 1064438 Synopsis and Primary CSR Data cutoff: 7 January 2015	To evaluate the efficacy of atezolizumab as measured by investigator-assessed ORR per modified RECIST (primary efficacy endpoint), PFS, DOR, OS (secondary efficacy endpoints), as well as safety and tolerability, and PK	Global, multicenter, single-arm study	atezolizumab 1200 mg IV q3w	Total enrolled n = 138 Cohort 1 (1L) n = 31 Cohort 2 (2L+) n = 94 Cohort 3 (2L+ w/ previously treated brain metastases) n = 13	PD-L1-selected (TC2/3 or IC2/3) patients with locally advanced or metastatic NSCLC who had not received prior chemotherapy (Cohort 1), who had progressed during or following a prior platinum-based chemotherapy regimen without restriction to the maximum number of prior therapies (Cohort 2), and 2L+ patients with previously treated brain metastases (Cohort 3)	Cohort 1: Until disease progression or unacceptable toxicity Cohort 2: Until loss of clinical benefit or unacceptable toxicity Cohort 3: Until loss of clinical benefit or unacceptable toxicity	Ongoing Primary CSR Full report

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

2.4.2. Pharmacokinetics

Pharmacokinetic data was collected from adult cancer patients only. The clinical pharmacology data is based on data from six clinical studies in cancer patients - two Phase I Studies (PCD4989g and JO28944, various cancer types), two Phase II Studies BIRCH and POPLAR (NSCLC) one Phase II Study IMvigor 210 (UC) and one supporting Phase II study FIR (NSCLC). The dose proposed for atezolizumab monotherapy is 1200 mg 3qw administered intravenously.

During the course of atezolizumab development, several manufacturing changes were introduced. Two formulations of atezolizumab (identified as F01 and F03) have been developed and used in clinical trials. *In vitro* results and atezolizumab population PK analysis support comparability of the atezolizumab drug substance and drug product materials. No patients have been exposed to the commercial drug product.

Table 12: Drug substance manufacturing process versions and drug product formulation

Drug Substance Process Version	Drug Product Formulation[a]	Drug Substance Manufacturing Site	Use
v0.1	F01	South San Francisco	Toxicology and v0.1 Reference Standard
v0.2		South San Francisco	Clinical studies (Phase I/II)
v0.3	F03	South San Francisco	Clinical studies (Phase I/II and Phase III) and v0.3 Reference Standard
v1.0		Basel Biotech Manufacturing Building 95	Clinical and commercial supply

[a] Formulation designation "F02" was not used.

Bioanalytical methods

An indirect sandwich ELISA method has been used for the determination of atezolizumab levels in human serum. The assay was validated and run at two different sites. Cross-validation met criteria for equivalence.

The ATA analysis strategy used a tiered approach. ATAs to atezolizumab in human serum were detected using a validated screening assay.

The Nab assay uses a ligand binding assay format based on the ability of ATA to block the inhibition between PD-1 and PD-L1 by added atezolizumab. The drug tolerance reported is extremely low.

PK of atezolizumab

Non-compartmental (NCA) and population pharmacokinetic (popPK) analyses were conducted to quantitatively describe the pharmacokinetics of atezolizumab in patients and to evaluate the effects of relevant covariates.

Absorption

Atezolizumab is administered intravenously. There have been no studies performed with other routes of administration. Bioequivalence between the different versions or formulations has not been investigated.

Distribution

The mean volume of distribution after a single dose administration is small as observed for other IgG mAbs with large molecular weight.

The population PK analysis describes a linear 2-compartiment PK model with first order elimination. Body weight and gender are significant covariates. A flat dose regimen is suggested, as exposure-efficacy and exposure-safety did not demonstrate expectedly clinically meaningful changes. This should be further justified.

PopPK analysis indicates that V1 is 3.28 L and Vss is 6.91 L in the typical patient.

Elimination

Atezolizumab is supposedly - as other therapeutic proteins - cleared through receptor mediated endocytosis and/or non-specific endocytosis followed by catabolism. No renal elimination is expected given the large molecular weight of monoclonal antibodies. No classical studies regarding metabolism or elimination have been performed.

A population pharmacokinetic analysis indicates that the typical clearance of atezolizumab was 0.200 L/day and the typical terminal $t_{1/2}$ was 27 days. Atezolizumab pharmacokinetics was consistent with linear pharmacokinetics over a dose range of 1 to 20 mg/kg of atezolizumab, including the fixed 1200 mg dose of atezolizumab.

Dose proportionality and time dependencies

- Dose proportionality

The geometric mean dose-normalized $AUC_{0\text{-}21}$, C_{max} and C_{min}, respectively appeared similar across the dose range 1 mg/kg – 20 mg/kg including the 1200 mg fixed dose (equivalent to ~15 mg/kg), indicating dose proportional PK for cycle 1 = single dose. Atezolizumab exposure data at steady state are also dose proportional.

Geometric mean accumulation ratios for C_{min} and C_{max} ranged from 2.07 to 2.39 and 1.21 to 1.41, respectively. This extent of accumulation is line with predictions for a drug with this range of estimated $t_{1/2}$ dosed q3w.

Table 13: Summary statistics (geometric mean(geometric mean CV%)) of atezolizumab exposure metrics at cycle 1 by study and dose levels

Study	Dose Level , N patients	Cmax (µg/mL)	Cmin (µg/mL)	AUC (µg.day/mL)	$t_{1/2}$ beta (day)*
PCD4989g	1 mg/kg , N=3	23.6 (7.9)	3.8 (8.1)	180.1 (3.3)	20.8 (4.69)
	3 mg/kg, N=3	69.8 (30.0)	11.1 (29.3)	569.3 (33.0)	26.5 (3.47)
	10 mg/kg, N=35	259 (14.1)	41.6 (16.2)	2072 (13.5)	22.4 (6.74)
	15 mg/kg, N=233	360 (19.8)	53.6 (29.4)	2717 (23.8)	20.7 (8.83)
	20 mg/kg, N=147	488 (19.5)	75.0 (23.5)	3749 (22.2)	21.5 (8.01)
	1200 mg, N=45	432 (19.1)	87.4 (27.2)	3334 (19.9)	21.7 (5.80)
JO28944	10 mg/kg, N=3	207 (8.4)	32.1 (8.6)	1548 (2.9)	24.2 (5.47)
	20 mg/kg, N=3	509 (5.4)	82.7 (9.6)	4068 (4.1)	27.0 (3.12)

N=Number of patients; Cmax=Cmax at Cycle 1; Cmin=Cmin at Cycle 1; AUC=AUC at Cycle 1; CV=coefficient of variation
**t1/2 beta is the terminal half-life based on post-hoc parameter estimates; for this parameter harmonic mean and pseudo-standard deviation are reported*

Table 14: Summary statistics (geometric mean(geometric mean CV%)) of atezolizumab exposure metrics at steady state by study and dose levels

Study	Dose Level , N patients	Cmax,ss (µg/mL)	Cmin,ss (µg/mL)	AUC,ss (µg.day/mL)	Accumulation ratio
PCD4989g	1 mg/kg , N=3	33.3 (3.2)	9.5 (21.0)	326.5 (11.6)	1.8 (14.6)
	3 mg/kg, N=3	106 (32.3)	35.8 (40.0)	1152 (35.2)	2.0 (9.8)
	10 mg/kg, N=35	384 (16.0)	120 (33.8)	3993 (23.6)	1.9 (17.1)
	15 mg/kg, N=233	522 (25.0)	148 (62.5)	5141 (40.7)	1.9 (23.1)
	20 mg/kg, N=147	715 (21.7)	213 (48.5)	7206 (32.9)	1.9 (21.1)
	1200 mg, N=45	634 (24.0)	193 (45.7)	6409 (33.7)	1.9 (18.1)
JO28944	10 mg/kg, N=3	307 (4.5)	97.3 (22.6)	3114 (13.6)	2.0 (16.5)
	20 mg/kg, N=3	799 (9.5)	288 (17.0)	8787 (12.1)	2.2 (9.6)

N=Number of patients; Cmax,ss=Cmax at steady-state; Cmin,ss=Cmin at steady-state; AUC,ss=AUC at steady-state; Accumulation ratio is derived as the ratio between AUC at Cycle1 and AUC,ss; CV=coefficient of variation

- Time dependency

Geometric mean accumulation ratios for C_{min} and C_{max} ranged from 2.07 to 2.39 and 1.21 to 1.41, respectively, for Cycles 4-8.

Table 15: Atezolizumab accumulation ratio based on C_{min} and C_{max} at each treatment cycle (patients receiving 1mg/kg or higher)

	C_{min} (GM, %CV)	C_{max} (GM, %CV)
Cycle 2	1.52 (42) n=333	1.15 (38) n=384
Cycle 3	1.82 (42) n=290	1.29 (34) n=307
Cycle 4	2.07 (42) n=165	1.32 (44) n=277
Cycle 5	2.04 (61) n=81	1.41 (56) n=55
Cycle 6	2.39 (52) n=133	1.38 (43) n=70
Cycle 7	2.39 (68) n=100	1.36 (58) n=34
Cycle 8	NA	1.21 (70) n=15

Cmax = maximum serum concentration; Cmin = trough or minimum serum concentration; CV = coefficient of variation; GM = geometric mean. NA = pharmacokinetic data at the end of cycle 8 is not available.

NA = PK data at the end of Cycle 8 is not available

The reference concentration for Cmin is Cycle 1 Day 21 (predose for Cycle 2).

The reference concentration for Cmax is Cycle 1 Day 1, 30-minute postdose.

Inter-Individual and Intra-Individual variability

The inter-individual variability is moderate. The results from the popPK analysis suggest the unexplained inter-individual variability is moderate for CL (i.e., 29%), V1 (i.e., 18%), and V2 (i.e., 34%). Of note, these values are based on Phase I study data from cancer patients characterized by a wide tumour type range including data from 20% of each UC and NSCLC patients. Unexplained IIV for CL decreased from 41% to 29%, for V1 from 27% to 18%, V2 was lowered only by 2% by introducing covariates.

Pharmacokinetics in target population

The population pharmacokinetics (popPK) of atezolizumab was assessed based on Phase I data from two clinical studies PCD4989g and JO28944. From these studies, pharmacokinetics of atezolizumab in serum was evaluated in 472 patients with 4563 samples including 88 NSCLC and 92 UC patients. A 2-compartment model was established and evaluated on this data base. From these patients, 88 NSCLC and 92 UC patients were included in the analysis population.

PK in UC and NSCLC Patients

The Phase I population PK model was subsequently subject to external validation for each indication separately, with the use of PK data collected in the NSCLC Phase II Studies BIRCH, POPLAR, and FIR (from 920 patients (out of 938 treated, 98.1%) with 3894 samples) and the UC Phase II Study IMvigor 210 (PK samples from 423 patients (out of 429 treated, 98.6%) with 1248 samples). In total, 5142 samples for external validation were collected from 1393 patients (UC and NSCLC) that received 1200 mg of atezolizumab q3w IV in Phase II studies. Diagnostic plots and model-based simulation up to 10 cycles of PK exposure metrics for each patient group showed deviations from observed data (sparse sampling) and thus will lead to biased exposure-response-relationships. The target patient population (UC and NSCLC patients receiving 1200 mg fix) is weakly represented.

PopPK analysis

The popPK of atezolizumab was assessed based on Phase I data from two clinical studies PCD4989g and JO28944. From these studies, pharmacokinetics of atezolizumab in serum was evaluated in 472 patients with 4563 samples including 88 NSCLC and 92 UC patients. A 2-compartment model was established and evaluated on this data base. From these patients, 88 NSCLC and 92 UC patients were included in the analysis population. Only patients receiving doses of 1-20 mg/kg atezolizumab q3w, or the 1200 mg q3w fixed dose by receiving the Phase III formulation F03 (N=45), were included in the evaluation.

The PopPK model described the PK of atezolizumab by a linear two-compartment model with first-order elimination.

Overall, females have a moderately higher exposure compared to males. Patients with low albumin tend to have a lower exposure with a larger effect on $C_{min,ss}$. Baseline tumour burden and positive ATA have a minor impact on exposure over the dose range investigated in this analysis (i.e., 1 to 20 mg/kg of atezolizumab q3w, or the fixed 1200 mg dose q3w). Overall no covariate effect induces more than 30% change in exposure from the typical patient (the typical patient is a male without positive ATA, weighing 77 kg, with an albumin level of 40 g/L and a tumour burden of 63 mm) except for body weight when evaluated at the lowest extreme of weight (i.e., 10th percentile). Patients with body weight lower than 54 kg would have up to a 32%, 28%, 40% higher $AUC_{,ss}$, $C_{max,ss}$ or $C_{min,ss}$, respectively, than the typical patient. None of these covariate effects would be expected to result in a $C_{min,ss}$ that would be lower than a targeted serum concentration of 6 µg/mL.

The following statistically significant parameter-covariate relationships were identified (i denotes a specific patient):

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

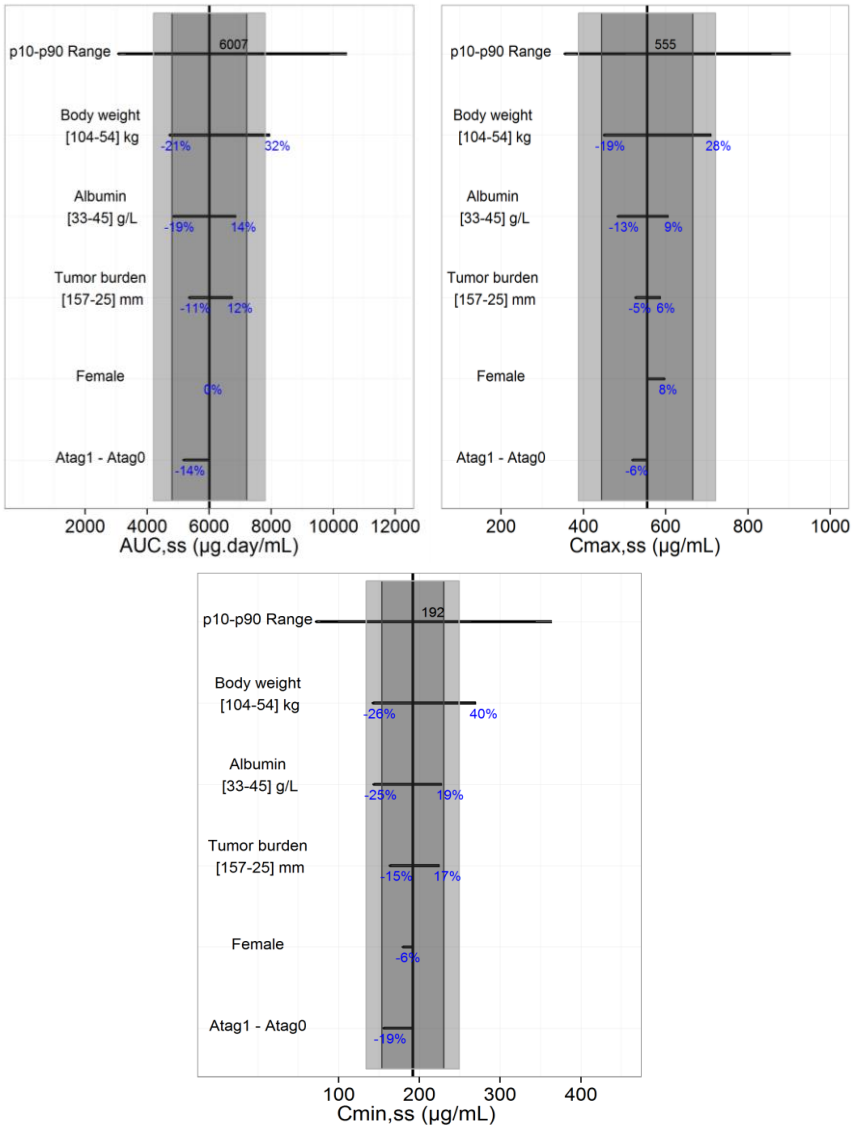
$$V1_i = \left(3.28 \cdot \left(\frac{BWT_i}{77}\right)^{0.559} \cdot \left(\frac{ALBU_i}{40}\right)^{-0.350}\right) \cdot (0.871\ if\ female)$$

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

BWT = body weight (kg); ALBU = albumin (g/L); tumour burden (mm); ATAG = anti-therapeutic antibody.

Special populations

Based on population PK and exposure-response analyses age (21-89 years), region, ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG performance status have no effect on atezolizumab pharmacokinetics. Body weight, gender, positive ATA status, albumin levels and tumour burden have a statistically significant, effect on atezolizumab pharmacokinetics. A sensitivity analysis was performed to examine the influence of the statistically significant covariates on steady-state exposure (AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$) of atezolizumab (see below).



ATAG = post-baseline status of anti-therapeutic antibodies; $AUC_{,ss}$ = area under the serum concentration time curve at steady-state; $C_{max,ss}$ = maximum observed serum concentration at steady-state; $C_{min,ss}$ = minimum observed serum concentration at steady-state.

Figure 4: Sensitivity Plot Comparing the Effect of Covariates on Atezolizumab Steady-State Exposure ($AUC_{,ss}$, $C_{max,ss}$, and $C_{min,ss}$)

- Renal impairment

No dedicated studies of atezolizumab have been conducted in patients with renal impairment. In the population pharmacokinetic analysis, the impact of the degree of renal impairment on atezolizumab CL was further assessed by categorizing patients with varying degrees of renal impairment into 4 categories based on their estimated eGFR (Normal: eGFR ≥ 90 mL/min/1.73 m2, Mild: eGFR ≥ 60 and < 90 mL/min/1.73 m2, Moderate: eGFR ≥ 30 and <60 mL/min/1.73 m2, and Severe: eGFR <30 mL/min/1.73 m2).

Table 16: Comparison of Bayesian post-hoc atezolizumab covariate-normalised CL for renal function categories (mean, 90% CI of the mean)

	RENAL FUNCTION			
Characteristics	**Normal N=140**	**Mild N=208**	**Moderate N=116**	**Severe N=8**
eGFR (mL/min/1.73 m^2)	112 (109; 115)	75.1 (74.1; 76.1)	48.8 (47.7; 50.0)	25.7 (20.4; 31.1)
Normalized CL (L/day)	0.212 (0.204; 0.220)	0.210 (0.203; 0.217)	0.202 (0.194; 0.210)	0.202 (0.169; 0.235)

CL=clearance; eGFR: estimated Glomerular Filtration Rate; N=Number of patients, Normal=eGFR ≥ 90 mL/min/1.73 m^2, Mild=eGFR ≥ 60 and < 90 mL/min/1.73 m^2, Moderate:=eGFR ≥ 30 and <60 mL/min/1.73 m^2, and Severe=eGFR <30 mL/min/1.73 m^2 ; ATAG=Post-baseline status of anti-therapeutic antibodies; BWT=body weight (normalized to a 77-kg body weight); Albumin=normalized to 40 g/L; Tumor burden normalized to 63 mm;
e.g. for NMID 4, Individual CL=0.19 L/day, Albumin =45 g/L, BWT=59.4 kg, tumor burden=43 mm, ATAG=1;
Normalized CL=0.192/((((45/40)^-1.12)((59.4/77)^0.808)*((43/63)^0.125))*(1+1*0.159))=0.245 L/day.*

Only a few patients had severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2; n=8). The effect of severe renal impairment on the pharmacokinetics of atezolizumab is unknown.

- Hepatic impairment

No dedicated studies of atezolizumab have been conducted in patients with hepatic impairment. In the population pharmacokinetic analysis, 401 patients (85%) had normal hepatic function and 71 patients (15%) mild hepatic impairment. No data are available in patients with either moderate or severe hepatic impairment. The comparison of atezolizumab CL normalised on other covariates significant in the model in the patients with different hepatic functions is presented in the table below.

Table 17: Comparison of Bayesian post-hoc atezolizumab covariate-normalised CL for hepatic function categories (mean, 90% CI of the mean)

	HEPATIC FUNCTION	
Characteristics	**Normal N=401**	**Mild N=71**
Normalized CL (L/day)	0.208 (0.203; 0.213)	0.210 (0.200; 0.221)

CL=clearance; N=Number of patients; normal hepatic function=bilirubin ≤ ULN, AST ≤ ULN, mild = bilirubin between 1–1.5 × ULN or (AST > ULN and bilirubin ≤ ULN), moderate=bilirubin between 1.5–3 × ULN, any AST, and severe=bilirubin > 3 × ULN, any AST
ATAG=Post-baseline status of anti-therapeutic antibodies; BWT=body weight (normalized to a 77-kg body weight); Albumin=normalized to 40 g/L; Tumor burden normalized to 63 mm;
e.g. for NMID 4, Individual CL=0.19 L/day, Albumin =45 g/L, BWT=59.4 kg, tumor burden=43 mm, ATAG=1;
Normalized CL=0.192/((((45/40)^-1.12)((59.4/77)^0.808)*((43/63)^0.125))*(1+1*0.159))=0.245 L/day.*

- Elderly

No dedicated studies of atezolizumab have been conducted in elderly patients. The effect of age on the pharmacokinetics of atezolizumab was assessed in a population pharmacokinetic analysis. Age was not identified as a significant covariate influencing atezolizumab pharmacokinetics based on patients of age range of 21-89 years (n=472), and median of 62 years of age. No clinically important difference was observed in the pharmacokinetics of atezolizumab among patients <65 years (n=274), patients between 65-75 years (n=152) and patients > 75 years (n=46)

Study	< 65 Years	65–74 Years	75–84 Years	85 + Years
PCD4989g	271/472	152/472	45/472	4/472
FIR	54/128	47/128	25/128	2/128
POPLAR	85/140	43/140	12/140	—

BIRCH	329/652	223/652	91/652	9/652
OAK	327/596	194/596	74/596	1/596
JO28944	5/6	1/6	—	—
IMvigor 210	145/425	174/425	94/425	12/425
IMvigor210, Cohort1	20/119	50/119	45/119	4/119

- Gender

In the popPK analysis, gender was identified as a statistically significant covariate on both V1 and V2, but not CL, based upon a dataset including 276 men (58.5%) and 196 women (41.5%). The extent of the effect of gender on AUCss, Cmax,ss, and Cmin,ss was determined by a sensitivity analysis and compared to a typical patient with other covariates kept fixed with median values. Tumor type /patient population was not a significant covariate.

- Race

After adjusting for covariate effects in the final popPK model, race (Asian n = 17, Black n = 15, and White n = 375) was not a significant covariate on the pharmacokinetics of atezolizumab and had no clinical relevance to atezolizumab CL.

- Weight

Covariate analysis identified body weight as most statistically significant covariate on CL resulting in a deviation in AUC of + 32% or -21% at the 10%- and 90%-percentiles compared to the typical patient (77 kg). The analysis dataset included patients of weight range from 36.5 to 168 kg. Body weight ranges for the target patent populations were similarly wide (UC: 39.6-161.8 kg, NSCLC: 34.9-175.8 kg). The popPK modelling suggests an exponent of 0.8 indicating that body-weight adjusted dosing would be more appropriate regarding similar exposure in all patients (Wang et al, 2009).

- Immunogenicity

In patients who were positive for ATA, CL is estimated to be 16% higher than in patients without ATA. Positive ATAG did not result in more than a 19% change in $AUC_{,ss}$, $C_{max,ss}$ or $C_{min,ss}$ from the typical patient.

The effect of NAbs is unknown due to limited performance of the NAb assay.

- Albumin and tumour burden

Albumin and baseline tumour burden were also identified as statistically significant covariates on CL. None of these covariates resulted in more than 28% change in $AUC_{,ss}$, $C_{max,ss}$ or $C_{min,ss}$, when evaluated at extreme values compared to the typical patient.

- PD-L1 status and tumour type

Atezolizumab PK was not affected by PD-L1 status (IC score or TC score) or tumour type.

Pharmacokinetic interaction studies

No formal drug-drug interaction studies have been conducted.

2.4.3. Pharmacodynamics

Mechanism of action

See section 2.3.2 non-clinical pharmacology.

Primary and Secondary pharmacology

Atezolizumab (MPDL3280A) is a humanised immunoglobulin G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese Hamster Ovary (CHO) cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and, consequently, eliminates detectable Fc-effector function and depletion of cells expressing programmed death ligand 1 (PD-L1) in humans. Atezolizumab targets human PD-L1 on tumor-infiltrating immune cells (ICs) and tumor cells (TCs), and inhibits its interaction with its receptors programmed death 1 (PD-1) and B7.1, both of which can provide inhibitory signals to T cells. Atezolizumab is being investigated as a potential therapy against various solid tumors and hematologic malignancies.

No studies with biomarkers have been submitted.

Atezolizumab is moderately immunogenic with overall treatment-emergent incidence of ATA to atezolizumab ranged from 16.7 to 54.1%. The ATAs do not seem to impact on efficacy, but the confidence intervals are wide and no firm conclusion can be drawn. Especially, data to evaluate the duration of response in patients positive and negative for ATAs are immature.

Table 18: Objective Response Rate per IRF-Assessed RECIST v1.1 by ATA Positivity (Treated Patients with Urothelial Carcinoma)

	PCD4989g (urothelial carcinoma cohort), Efficacy Evaluable Patients with 12-Weeks Follow-Up		IMvigor 210 Cohort 2, Objective Response Evaluable Patients	
All Treated Patients	ATA-Negative (n = 38)	ATA-Positive (n = 42)	ATA-Negative (n = 161)	ATA-Positive (n = 114)
Responders	15	7	25	22
Non-responders	23	35	136	92
% ORR Responders	39.5%	16.7%	15.5%	19.3%
95% CI for Response Rates	(24.04, 56.61)	(6.97, 31.36)	(10.31, 22.06)	(12.51, 27.75)

ATA = anti-therapeutic antibody; CI = confidence interval; ORR = overall response rate; q3w = every three weeks.
Note: Patients with urothelial carcinoma in Study PCD4989g received doses 15 mg/kg (n □ 82) and 1200 mg (n = 6) q3w.
Results are based on the data cutoff date of 5 May 2015. Refer to the updated IMvigor 210 CSR for results based on the data cutoff date of14 September 2015.

Table 19: POPLAR - Impact of ATA on OS, PFS and best confirmed response (Atezolizumab arm)

	ATA-Negative (n = 62)	ATA-Positive (n = 73)
OS		
Patients with event (%)	28 (45.2%)	41 (56.2%)
Median duration of Survival (months)	NE	13.0
95% CI	(11.0, NE)	(8.5, 16.4)
PFS		
Patients with event (%)	52 (83.9%)	63 (86.3%)
Median duration of PFS (months)	2.7	4.1
95% CI	(1.5, 4.2)	(2.7, 5.7)
Best confirmed response [a]		
Responders (n)	6	15
Non-responders (n)	56	58
ORR	9.7%	20.5%

95% CI for ORR	(3.6, 19.9)	(12.0, 31.6)

ATA = anti-therapeutic antibody; CI = confidence interval; OS = overall survival; NE = not evaluable; PFS = progression free survival.

[a] Based on objective response evaluable population where an ATA sample was available. Best confirmed response rate was the objective response rate.

Table 20: FIR - Impact of ATA on Objective Response as Assessed by Investigator per RECIST V1.1 and Modified RECIST (Treated Population)

	Cohort 1		Cohort 2		Cohort 3	
	ATA-Negative	ATA-Positive	ATA-Negative	ATA-Positive	ATA-Negative	ATA-Positive
ORR per modified RECIST Responders (%) 95% CI of response rate	n = 15 3 (20.0%) 4.33, 48.09	n = 16 6 (37.5%) 15.20, 64.57	n = 40 7 (17.5%) 7.34, 32.78	n = 45 9 (20.0%) 9.58, 34.60	n = 8 2 (25.0%) 3.19, 65.09	n = 5 1 (20.0%) 0.51, 71.64
ORR per RECIST v1.1 Responders (%) 95% CI	n = 15 3 (20.0%) 4.33, 48.09	n = 16 5 (31.3%) 11.02, 58.66	n = 40 7 (17.5%) 7.34, 32.78	n = 45 8 (17.8%) 8.00, 32.05	n = 8 2 (25.0%) 3.19, 65.09	n = 5 1 (20.0%) 0.51, 71.64

ATA = anti-therapeutic antibody; CI = confidence interval; RECIST = Response Evaluation Criteria in Solid

No conclusion can be drawn about the effect of Nabs due to a high proportion of indeterminate samples evaluable for NAbs.

Table 21: Post-treatment number and percentage of positive or negative samples

	PCD4989g	IMvigor 210
Total number of ATA positive samples tested	276	56
Number of NAb Positive Samples	11	0
Number of NAb Negative Samples	13	6
Number of NAb Indeterminate Samples	252	50
Number of NAb Positive or Negative Samples that were from Post-treatment Visits	12	0
% of Nab Positive or Negative Samples that were from Post-treatment Visits	4.40%	0%

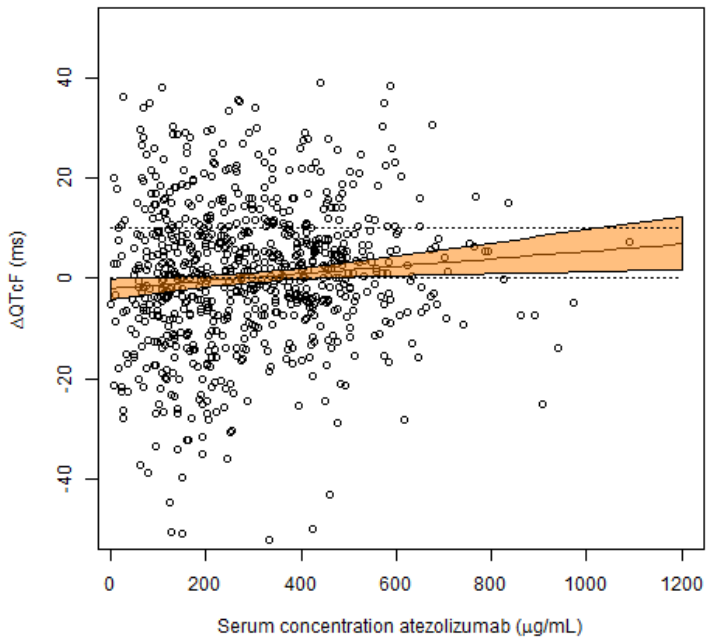
ATA = anti-therapeutic antibody; NAb = neutralizing antibody.

Table 22: Post-treatment number of positive or negative samples

	PCD4989g	BIRCH	POPLAR	FIR
Total number of ATA positive samples tested	276	506	182	127
Number of NAb Positive Samples	11	0	0	1
Number of NAb Negative Samples	13	28	11	2
Number of NAb-Indeterminate Samples	252	478	171	124
Number of NAb Positive or Negative Samples that were from Post-treatment Visits	12	0	0	2
% of Nab Positive or Negative Samples that were from Post-treatment Visits	4.4%	0%	0%	1.6%

ATA = anti-therapeutic antibody; NAb = neutralizing antibody.

An analysis of the relationship between atezolizumab concentration and change from baseline QTc interval (ΔQTcF) was conducted in the open-label Phase Ia Study PCD4989g. A total of 811 ΔQTcF, 858 ΔQTcB, and 593 ΔRR observations with time matched PK samples from 417 patients exposed to atezolizumab of 10 (n=29), 15 (n=227), 20 (n=129) mg/kg or 1200 mg (n=32) were included in the analysis set. It is agreed that by interpolation, no clinically meaningful change in ΔQTcF for the proposed 1200 mg fixed-dose (equivalent to 15 mg/kg) q3w dosing regimen will occur.



CI = confidence interval.
Note: solid line = predicted population mean; orange shaded area = 90% CI.
Note: The dotted horizontal lines were plotted at 0 and 10 milliseconds.

Figure 5: **PCD4989g: Scatter Plot of Observed ΔQTcF versus Serum Concentration of Atezolizumab with the Predicted Population Mean and Associated 90% CI Based on the Final Model.**

No formal DDI studies have been conducted.

A flat dose of atezolizumab 1200 mg 3qw is proposed and has been the administered dose in the clinical studies.

For UC and NSCLC patients, PK exposure Cmax, Cmin and AUC at cycle 1 and AUC at steady-state (AUC,ss) was estimated with the Phase I population PK model. They were compared with the objective response rate (ORR) for exposure-efficacy analyses.

Albeit not shown constantly statistically significant, there is a trend in higher ORR vs. higher AUCss for UC and NSCLC patients. AUC,ss was identified to be most sensitive to body weight. PK exposure was only moderately well predicted (external validation).

Data collected in POPLAR Study (not PD-L1 selected) from NSCLC patients were analysed regarding efficacy endpoint Overall Survival (OS). A constantly increasing trend of OS with atezolizumab exposure AUC was observed with the lowest AUC,ss-tertile showed efficacy that was comparable to docetaxel therapy.

For urothelial carcinoma, no statistically significant ER relationships were identified with objective response rate (ORR) following atezolizumab 1200 mg q3w. In conclusion, disease modelling suggested an increasing trend of overall survival (OS) with atezolizumab exposure following administration of atezolizumab 1200 mg q3w.

The atezolizumab exposure-safety analysis was performed on all treated NSCLC patients in the Phase 1 Study PCD4989g and in the Phase 2 Studies BIRCH, FIR and POPLAR. The data set comprised a total of 1007 patients with exposure data (out of 1026 treated patients in the four studies, 98.1%). Those patients received atezolizumab 1, 10, 15 or 20 mg/kg q3w or 1200 mg q3w. Most of these patients received atezolizumab 1200 mg q3w (N = 920, 91.4%). Two main adverse events (AE) were

investigated: Grade ≥3 AE (AEG35) and AE of special interest (AESI; potential immune related AEs) with respective incidences of 123 (12.5%) and 187 (18.6%).

A statistically significant exposure-safety relationship was identified for AESIs. It was a slight increase in the probability of AESIs (estimate [95% prediction interval]) from 0.18 (0.16, 0.21) to 0.22 (0.18, 0.26) for patients with the median and 90th percentile of AUC_{ss}, respectively. This change in probability of AESIs is not expected to be clinically meaningful. No statistically significant increasing trends of AEG35 with atezolizumab exposure were identified.

Overall, as exposure-response analysis indicated more benefit for patients with higher AUC,ss level while no exposure-safety relationship could be detected, a dose adjustment for patients with high body weight or being characterised by other AUC-predictive factors might result in an improved benefit-risk-ratio for those patients.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics of atezolizumab has been characterised in cancer patients mainly by a population PK model. The popPK model is primarily based on the Phase 1a dose escalation study PCD4989g, but validated and found against PK data from the clinical phase II studies. PK characteristics are consistent in patients with urothelial carcinoma and patients with NSCLC.

The formulation of atezolizumab finished product as presented in this application is not the same as the one which has been used in the clinical studies. Comparability has been demonstrated at the quality level and the differences appear to be minor and does not impact the safety and efficacy of the product. No clinical relevance in PK, efficacy or safety is expected.

The ATA screening assay appears to be capable of measuring only free ATA molecules in the sample, and not those already bound to atezolizumab. Drug tolerance level of 200 µg/mL relates to a relatively high detection level of ATA positive control antibody (500 ng/mL). Thus, the sensitivity of the screening assay in the presence of 200 µg/mL of atezolizumab is only moderate. Furthermore, Cmin,ss levels in cancer patients are not far below this drug tolerance level (e.g. 170 ± 52 µg/mL in BIRCH study). The Nab assay does not have sufficient drug tolerance. This allows the conclusion that the clinical results concerning neutralising ADA occurrence are at least in part invalid and incidence is considered underestimated.

The applicant is currently developing a more tolerant assay and is expected to provide validation results of the improved Nab assay as soon as available. The CHMP recommends providing validation results for the improved NAb assay by Q2 2018.

No dedicated clinical pharmacology studies have been conducted, which is acceptable.

Pop PK analyses suggested a linear two-compartment disposition model with first-order elimination over a dose range of 1 mg/kg to 20 mg/kg of atezolizumab, including the fixed 1200 mg dose (45 patients). The popPK model is well-described and externally validated for each indication showing consistent PK.

The pharmacokinetic parameters of atezolizumab are as expected for an IgG monoclonal antibody; elimination is linear within the therapeutic dose range and though some degree of target mediated elimination is likely as tumour burden is a significant covariate for clearance, no saturation of elimination pathways is observed.

Body weight was identified as a statistically significant covariate on both clearance and distribution with impact at extreme values on AUCss, Cmax and Cmin of up to 32 %, 28 % and 40 % respectively.

The impact of the other statistically significant covariates (gender, positive ATA, albumin, tumour burden) is limited. Body weight, gender, positive ATA status, albumin levels and tumour burden have a statistically significant, but not clinically relevant effect on atezolizumab pharmacokinetics. No dose adjustments are recommended, this has been reflected in Section 4.2 of the SmPC.

The limited and lacking experience in patient with renal and hepatic impairment has been reflected in section 5.2 of the SmPC. No clinically important differences in CL were found for patients with mild and moderate renal impairment, but only few patients with severe renal impairment has been investigated. Mild hepatic function impairment (bilirubin between 1–1.5 × ULN or AST > ULN and bilirubin ≤ ULN) did not affect CL compared to normal hepatic function, but no patients with moderate or severe hepatic impairment has been investigated. Hence, no dose adjustment is required in patients with mild or moderate renal impairment or for patients with mild hepatic impairment Section 4.2 of the SmPC).

Based on a population pharmacokinetic analysis, no dose adjustment of Tecentriq is required in patients ≥ 65 years of age (see section 4.2 of the SmPC).

No drug-drug-interaction studies have been conducted, and no DDIs related to drug metabolising enzymes are expected. There is, however, a risk of pharmacodynamics DDIs, especially with immune-modulating drugs. These were also restricted as concomitant medication in the clinical studies. Hence, the following recommendation has been made in section 4.5 of the SmPC: "The use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of atezolizumab. However, systemic corticosteroids or other immunosuppressants can be used to treat immune-related adverse reactions after starting atezolizumab (see section 4.4)".

A dedicated dose-finding study has not been conducted. Exposure-efficacy and exposure-safety were assessed with data from the clinical studies, dosing: atezolizumab 1200 mg 3qw. There is an increasing trend for better efficacy for patients with UC (not significant) NSCLC (significant), but a statistically significant (but unlikely clinically relevant) increasing trend with Adverse Event of Special Interest (AESIs) was also seen for patients with NSCLC.

The Phase I population PK model was subsequently subject to external validation for each indication separately, with the use of PK data collected in the NSCLC Phase II Studies BIRCH, POPLAR, and FIR (from 920 patients (out of 938 treated, 98.1%) with 3894 samples) and the UC Phase II Study IMvigor 210 (PK samples from 423 patients (out of 429 treated, 98.6%) with 1248 samples). Diagnostic plots and model-based simulation up to 10 cycles of PK exposure metrics for each patient group showed deviations from observed data (sparse sampling) and thus will lead to biased exposure-response-relationships.

The incidence of ATA to atezolizumab ranged from 16.7-54.1 % and atezolizumab is moderately immunogenic. Results of additional investigations requested during the procedure are plausible with decreasing recovery as the ATA concentration is increased relative to the atezolizumab concentration. ATA interference was becoming visible at ATA surrogate concentrations > 50 µg/mL in samples containing 50 µg/mL atezolizumab.

It is agreed that the surrogate ATA might not reflect the concentration, neutralising ability, and affinity of ATA in each ATA-positive patient sample. However, as the geometric mean of C_{min} values of atezolizumab at steady state were > 160 µg/mL in the UC and NSCLC patient groups, the results are ensuring that for the majority of PK trough samples, no relevant ATA interference is expected. Hence, the applicant is expected to provide validation results for the improved NAb assay.

2.4.5. Conclusions on clinical pharmacology

In conclusion, pharmacokinetics of atezolizumab has been characterised in cancer patients by means of a popPK model and PK parameters are as observed for other IgG monoclonal antibodies.

Atezolizumab is moderately immunogenic. The impact of ATAs and NAbs on efficacy and safety is inconclusive.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

The CHMP recommends providing validation results for the improved NAb assay by Q2 2018.

2.5. Clinical efficacy Non-Small Cell Lung Cancer (NSCLC)

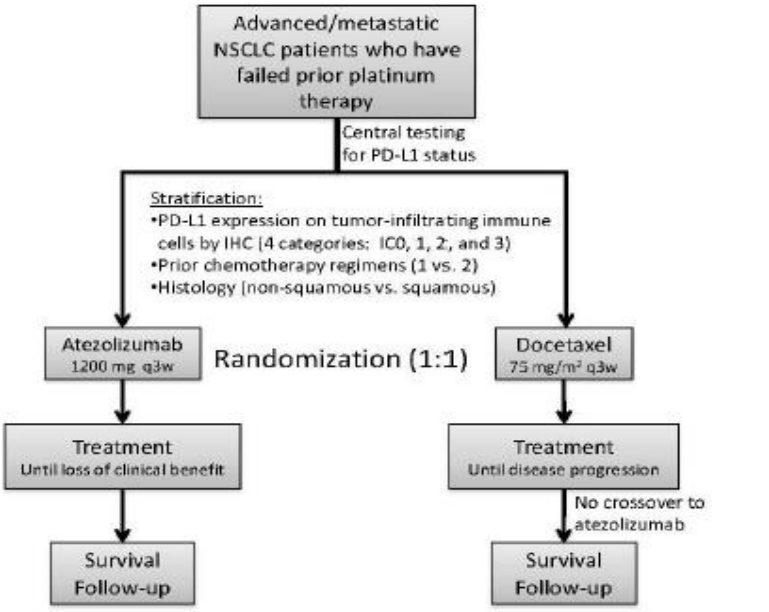
2.5.1. Dose response study(ies)

The atezolizumab fixed dose of 1200 mg was selected on the basis of both nonclinical studies and available clinical data from Study PCD4989g as described below. The target exposure for atezolizumab was projected on the basis of nonclinical tissue distribution data in tumour-bearing mice, target-receptor occupancy in the tumour, the observed atezolizumab interim PK in humans, and other factors. The target trough concentration (Ctrough) was projected to be 6 µg/mL on the basis of several assumptions, including: 1) 95% tumour-receptor saturation needed for efficacy and 2) the tumour-interstitial concentration to plasma ratio of 0.30 based on tissue distribution data in tumour-bearing mice.

The atezolizumab dose was also informed by available clinical activity, safety, PK, and immunogenicity (ATA) data. Anti-tumour activity has been observed across doses from 1 mg/kg to 20 mg/kg. The maximum tolerated dose (MTD) of atezolizumab was not reached, and no dose limiting toxicities (DLTs) were observed at any dose in Study PCD4989g. Available preliminary PK data (0.03-20 mg/kg) from Study PCD4989g suggested that for doses ≥1 mg/kg, overall atezolizumab exhibits PK that were both linear and consistent with typical IgG1 antibodies. ATAs were observed in patients at all dose levels but were associated with changes in pharmacokinetics for several patients in only the lower dose cohorts (0.3, 1, and 3 mg/kg). No clear relationship between the development of ATAs and safety or efficacy has been observed. Available data suggested that the development of detectable ATAs did not appear to have a significant impact on the pharmacokinetics for doses from 10 to 20 mg/kg in most patients. Accordingly, patients dosed at the 10-, 15-, and 20-mg/kg dose levels maintained target trough levels of drug despite the detection of ATAs. Currently available PK and ATA data suggest that the 15-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent) for Phase II and Phase III studies would be sufficient to maintain Cmin ≥6 µg/mL. This dose level was also considered appropriate to safeguard against both inter-patient variability and the possibility that development of ATAs could lead to sub-therapeutic levels of atezolizumab relative to the 10-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent). Simulations did not suggest any clinically meaningful differences in exposure following a fixed dose or a dose adjusted for weight. On the basis of this analysis, a fixed dose of 1200 mg was selected (equivalent to an average body weight-based dose of 15 mg/kg). Selection of an every-21-day dosing interval was supported by this preliminary PK evaluation and allowed for a convenient integration with common chemotherapeutic regimens.

2.5.2. Main studies

OAK (GO28915): 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



IHC = immunohistochemistry; IC = tumor-infiltrating immune cell; NSCLC = non−small cell lung cancer; PD-L1 = programmed death−ligand 1; q3w = every 3 weeks.

Figure 6: Overview of study design (GO28915)

Methods

Study Participants

Table 23: **Efficacy-Related Key Eligibility Criteria in Studies OAK, POPLAR, BIRCH, FIR, and PCD4989g**

	OAK	POPLAR	BIRCH	FIR	PCD4989g
Inclusion Criteria					
Age ≥ 18 years	√	√	√	√	√ [a]
Life expectancy≥ 12 weeks	√	√	√	√	–
ECOG performance status 0 or 1	√	√	√	√	√ [b]
Stage IIIB/IV, or recurrent NSCLC (per UICC/AJCC)	√	√	√	√	√ [c]
Pathological characterization defining either squamous or non-squamous histology	√	√	√	–	–
PD following chemoradiotherapy must be outside the prior radiotherapy port	–	–	√	√	–
Tissue evaluable for tumor PD-L1 expression by a central laboratory prior to study enrollment	√	√	√	√	√
Prospective selection by tumor PD-L1 status	–	–	√	√	–
Investigator-assessed measurable disease per RECIST v1.1	√	√	√	√	√
Sensitizing mutation in the *EGFR* gene and PD or intolerance to treatment with an EGFR TKI [d, e]	√	√	√	√	–
ALK fusion oncogene and PD or intolerance to treatment with an ALK inhibitor [d, e]	√	√	√	√	–
No prior chemotherapy for advanced disease (1L)	–	–	√	√	–
PD during/after one or two chemotherapy regimens (including platinum-based chemotherapy) for advanced disease [2L/3L]	√	√	√	√	√
PD during/after a platinum-based chemotherapy regimen and at least two additional chemotherapy regimens for advance disease	–	–	√	√	√

	OAK	POPLAR	BIRCH	FIR	PCD4989g
Exclusion Criteria					
CNS disease (exception: treated supratentorial brain mets not requiring corticosteroids allowed)	–[f]	–[f]	√	–	–[f]
Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti-PD-1, and anti–PD-L1 therapeutic antibodies	√	√	√ [g]	√	√ [g]

ALK = anaplastic lymphoma kinase CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; IC = tumor-infiltrating immune cell; NSCLC = non–small cell lung cancer; PD = progressive disease; PD-L1 = programmed death–ligand 1; RECIST = Response Evaluation Criteria in Solid Tumors; TC = tumor cell; TKI = tyrosine kinase inhibitor UICC/AJCC = Union Internationale contre le Cancer/American Joint Committee on Cancer staging system

[a] Patients 16 to 17 years old (body weight ≥ 40 kg) (if approved by the Medical Monitor).

[b] Patients with ECOG performance status of 2, secondary to the underlying disease, could be enrolled after consultation with the Medical Monitor.

[c] Histologically or cytologically documented, incurable or metastatic solid tumor or hematologic malignancy that was advanced (non-resectable) or recurrent and progressing since the last anti-tumor therapy and for which no recognized standard curative therapy existed.

[d] Patients who have received an investigational inhibitor may be eligible following discussion with the Medical Monitor.

[e] Testing for gene mutation status was not mandatory at enrollment and data are therefore only available for a subset of patients.

[f] Patients with a history of treated asymptomatic CNS metastases were eligible, provided they met all of certain criteria (see individual CSRs for details)

[g] Patients who have had prior anti-CTLA-4 treatment may have been enrolled, provided the protocol requirements were met.

Treatments

OAK:

Atezolizumab

The dose level of atezolizumab tested was 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) administered by IV infusion q3w (21 [±3] days) until loss of clinical benefit or unacceptable toxicity.

Docetaxel

The starting dose of docetaxel was 75 mg/m2 q3w. Dose modifications were performed according to the locally approved label. Treatment continued until disease progression or unacceptable toxicity.

Objectives

Primary objective:

To determine if atezolizumab treatment results in an improved overall survival (OS) compared with docetaxel treatment in patients with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen.

Secondary objectives:

• To evaluate efficacy of atezolizumab compared with docetaxel with respect to anti-tumour effects as measured by progression free survival (PFS) per investigator using RECIST v1.1

• To evaluate efficacy of atezolizumab compared with docetaxel with respect to anti-tumour effects as measured by objective response rate (ORR) per investigator using RECIST v1.1

• To evaluate efficacy of atezolizumab compared with docetaxel with respect to anti-tumour effects as measured by duration of response (DOR) per RECIST v1.1 for responding patients

Outcomes/endpoints

Primary Endpoint: OS

Secondary Endpoints: PFS, ORR and DOR, assessed by investigators using RECIST v1.1

PD-L1 assessment

An IUO-labelled assay was used to assess PD-L1 expression status at baseline in tissue from patients. The PD-L1 IHC assay and scoring system was developed to measure PD-L1-specific signals on both TCs and ICs using the SP142 IHC assay. Four levels of IC expression (IC0, IC1, IC2, IC3) and four levels of TC expression (TC0, TC1, TC2, TC3) were determined. Any cut-off references are to a single TC or IC score (e.g., TC2 or IC2) whereas patient population references include all IHC subgroups captured by a particular cut-off (e.g., TC2/3 population is captured by selection at the TC2 cut-off and include patients with TC expression level of TC2 or TC3).

Table 24: Criteria for PD-L1 expression assessment in atezolizumab NSCLC studies

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

IC = tumor-infiltrating immune cell; IHC = immunohistochemistry; NSCLC = non–small cell lung cancer; PD-L1 = programmed death–ligand 1; TC = tumor cell.

Tumour Measurements

Table 25: Schedule of tumour assessments across studies OAK, BIRCH, POPLAR, FIR and PCD4989g

	OAK	POPLAR	BIRCH	FIR	PCD4989g
0-24 weeks	Every 6 weeks	Every 6 weeks	Every 6 weeks	Every 6 weeks	Every 6 weeks
24-36 weeks	Every 6 weeks	Every 6 weeks	Every 6 weeks	Every 6 weeks	Every 12 weeks
37-52 weeks	Every 9 weeks	Every 9 weeks	Every 6 weeks	Every 6 weeks	Every 12 weeks
> 52 weeks	Every 9 weeks	Every 9 weeks	Every 9 weeks	Every 9 weeks	Every 12 weeks

Tumour response was evaluated by radiologic imaging (CT scans or MRI) according to RECIST v1.1 and modified RECIST in OAK, BIRCH, POPLAR and FIR. The same radiographic procedure was used to assess disease sites at screening and throughout the study. The same evaluator performed the assessments if possible to ensure internal consistency across visits. At the investigator's discretion, CT scans were repeated at any time if PD was suspected. For subsequent tumour assessments, procedures for tumour assessment were performed as clinically indicated. Specifically in BIRCH, scans were submitted for central review to an IRF.

Tumour Response Criteria

All studies used RECIST v.1.1 criteria to assess tumour response. In addition, Modified RECIST criteria were used in studies OAK, BIRCH, POPLAR, and FIR to further characterize response patterns that may

result from cancer immunotherapies, such as atezolizumab, which can produce delayed responses even after apparent radiological progression.

In PCD4989g, immune-related response criteria (irRC) were used in addition to RECIST v.1.1.

Table 26: Definition of immune-related response criteria (irRC)

Overall Response	Criterion
irCR	Complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmed by a repeat, consecutive assessment ≥4 weeks from the date first documented
irPR	Decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment ≥4 weeks from the date first documented
irSD	Criteria for irCR, irPR, and irPD are not met; does not require confirmation
irPD	Increase in tumor burden ≥25% relative to nadir confirmed by a consecutive assessment ≥4 weeks from the date first documented

irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

Determination of irBOR

Once a patient has completed all tumor assessments, his/her irBOR may be determined:

Condition	irBOR
At least one irCR	irCR
At least one irPR and no irCR	irPR
At least one irSD and no irCR and no irPR	irSD
At least one irPD and no irCR, no irPR, and no irSD	irPD

irBOR = immune-related best overall response; irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

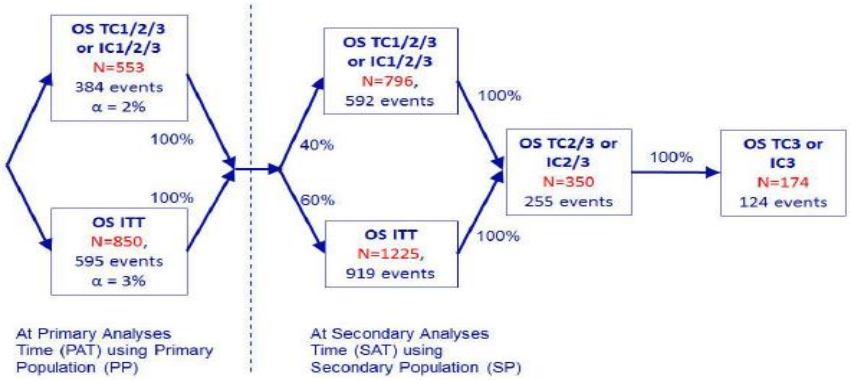
Sample size

OAK

Study OAK initially planned to enroll 850 patients in an Intent-to-Treat (ITT) population in order to have approximately 255 PD-L1 IC2/3 patients and 425 PD-L1 tumour-Infiltrating Immune Cell (IC1)/2/3 patients. Based on the interim analysis of POPLAR (randomized Phase II study) and additional data from PCD4989 and FIR studies, the Sponsor subsequently modified the statistical analysis plans according to the pre-specified Modification Plan (see the SAP and the study protocol Version 4). As a result, the sample size of OAK was increased to approximately 1100 patients (up to a maximum of 1300) in order to ensure at least

220 patients with PD-L1 TC3 or IC3 status, assuming a 20% prevalence of the TC3 or IC3 subgroup. The final enrollment in OAK was 1225 randomized patients. Later, the primary analysis of POPLAR showed that OS treatment benefit extended beyond the TC3 or IC3 subgroup to broader subgroups. Study design assumptions in OAK based on these POPLAR results led to a fully powered study for OS evaluation in an ITT population with fewer than 1225 patients. Therefore, as outlined in the study protocol and prior to unblinding of the data, the planned primary OS analysis in OAK was modified to be conducted on the Primary Population (PP) of the first randomized 850 ITT patients at the Primary Analysis Time. The OS secondary analysis for the Secondary Population of all 1225 randomized ITT patients will be conducted at the Secondary Analyses Time To control the type I error rate in the evaluation of OS in the primary and secondary populations, alpha was split between the ITT population

and the TC1/2/3 or IC1/2/3 subgroup of the PP first. The OS testing in the PP started with a 3% alpha (two-sided) in the ITT population and a 2% alpha (two-sided) in the TC1/2/3 or IC1/2/3 subgroup of the PP (i.e., first 850randomized ITT patients). If either of these two hypotheses was rejected, then the remaining alpha would be split between the ITT population and the TC1/2/3 or IC1/2/3 subgroup of the SP first; subsequently, the further remaining alpha would be spent on the TC2/3 or IC2/3 subgroup in the SP of the 1225 ITT patients, and lastly, passed down to the TC3 or IC3 subgroup in the SP of the 1225 ITT patients.



IC = tumor-infiltrating immune cell; OS = overall survival; TC = tumor cell.

Figure 7: Type I error control plan (two-sided)

Randomisation

Patients were randomised to one of the two treatment arms occurred in a 1:1 ratio. Permuted-block randomization was applied to ensure a balanced assignment to each treatment arm. Randomization was stratified by the following factors:

- PD-L1 expression on ICs by IHC (four categories of expression: IC0, IC1, IC2, and IC3
- Number of prior chemotherapy regimens (1, 2)
- Histology (non-squamous, squamous)

If possible, patients received their first dose of study treatment on the day of randomization. If this was not possible, the first dose was administered no later than 3 business days after randomization.

Blinding (masking)

OAK study was open-label.

Statistical methods

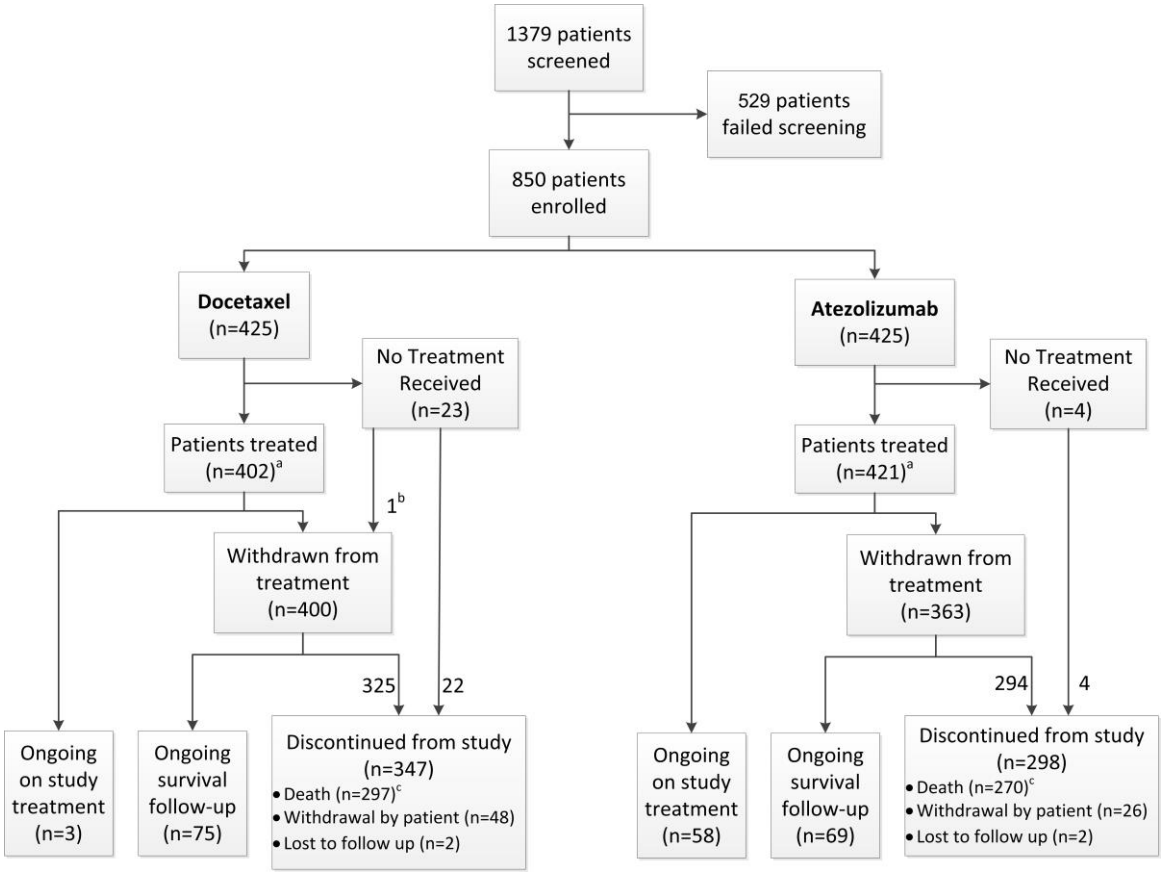
The primary efficacy endpoint is the duration (in months) of OS defined as the difference in time from the date of randomization to the date of death due to any cause. Data for patients who were not reported as having died at the time of analysis were censored at the date they were last known to be alive. Patients who did not have post-baseline information were censored at the date of randomization plus 1 day. The OS analyses were performed for the PP at the PAT and results are presented in this primary CSR. OS analyses will be performed for the SP at the SAT and results will be presented in a separate report.

For the PP of the first 850 randomized ITT patients, the two treatment comparisons with respect to OS were based on a stratified log-rank test at the two-sided level of significance, which was determined from the testing procedure described in Figure 2. The stratification factors were those used during randomization (i.e., tumor PD-L1 status [four categories of PD-L1 IC expression] per IxRS, the number of prior lines of therapy [1, 2] per IxRS, and histology [non-squamous, squamous] per eCRFs). An unstratified analysis was performed for the IHC subpopulations with the exception of the co-primary IHC subpopulation.

The null and alternative hypotheses for the OS analysis in the ITT population, as well as in the TC1/2/3 or IC1/2/3 subgroup, can be phrased in terms of the survival functions SA(t) and SB(t) in Arm A (atezolizumab) and Arm B (docetaxel), respectively: H0: $SA_{(t)} = SB_{(t)}$ versus H1: $SA_{(t)} \neq SB_{(t)}$ Kaplan-Meier methodology was used to estimate the median OS for each treatment arm and to construct survival curves for the visual description of the difference between the treatment arms. The Brookmeyer-Crowley methodology was used to construct the 95% CI for the median OS for each treatment arm (Brookmeyer and Crowley 1982). The HR, $\lambda A/\lambda B$, where λA and λB represent the hazard of death in Arm A (atezolizumab) and Arm B (docetaxel), respectively, was estimated using a stratified Cox regression model with the same stratification variables used in the stratified log-rank test, including 95% CIs.

Results

Participant flow



[a] One patient randomized to docetaxel received atezolizumab.

[b] One patient withdrew from treatment before receiving any dose of study drug, but did not withdraw from the study at the time of the clinical cutoff date.

[c] Two additional deaths (1 docetaxel, 1 atezolizumab) were collected from public record for a total of 298 deaths in the docetaxel arm and 271 deaths in the atezolizumab arm. These 2 patients are captured in the study discontinuation eCRF as "withdrawal by patient", but were included as deaths (i.e., not censored) in the efficacy analyses.

Source: t_dst01v1_IT850 and l_rnott_IT850_NTRT

Figure 8: Patient disposition (primary population) - OAK

Recruitment

First patient randomized: 11 March 2014. Last patient randomized in the Primary Population (PP; first 850 randomized Intent-to-Treat [ITT] patients): 28 November 2014. Last patient randomized in the Secondary Population (SP; all 1225 randomized ITT patients): 29 April 2015. The data cutoff date for the CSR submitted as part of this application is 7 July 2016 (at the primary analysis time [PAT])

Conduct of the study

The protocol was amended five times. The key changes to the protocol are summarized below.

Protocol Amendment 2 (Version 3) – 5 August 2014.

In this amendment, the treatment duration for atezolizumab was modified to allow patients to be treated until patients are no longer experiencing clinical benefit; accordingly, the 16-cycle or 12-month initial treatment, follow-up, and re-treatment periods no longer apply.

An exclusion criterion regarding known tumor PD-L1 expression status from other clinical trials was added to ensure a natural distribution of the prevalence of PD-L1 expression levels.

Protocol Amendment 3 (Version 4) – 2 December 2014.

Planned PD-L1 expression subgroups for analysis were amended to include PD-L1 expression on TCs in addition to ICs. The sample size was increased from 850 to 1100 patients to allow for testing patients with TC3 or IC3 as first step in the hierarchy.

Protocol Amendment 4 (Version 5) – 6 October 2015.

Implementation of more stringent approaches for the management of immune-mediated toxicity; therefore, the management of gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, potential pancreatic or eye toxicity and other immune-mediated adverse events was updated.

Protocol Amendment 5 (Version 6) – 28 January 2016.

The study was resized to fully power for testing OS benefit in this TC3 or IC3 patients (1100 patients, up to 1300).

Changes to Planned Analyses

The primary analysis population for ORR was changed to include all randomized patients regardless of whether they had measureable disease at baseline. For exploratory purposes, additional descriptive statistics were produced to summarize study drug exposure and efficacy after PD in patients who received at least one dose of atezolizumab after their first PD. The incidence of AEs before and after PD was also examined in patients who received at least one dose of atezolizumab after their first PD.

Protocol violations OAK

A major study conduct deviation was reported in 16.5% of patients in the docetaxel arm vs. 19.8% of patients in the atezolizumab arm. The most common on-study protocol deviation was "other procedural deviation significant for safety and/or efficacy" (i.e., not related to prohibited medication or incorrect dose received), with similar incidence between the arms.

The category of "other procedural deviation significant for safety and/or efficacy" specifically included: missing lab or tumor assessment, tumor assessment performed out of window, failure to report SAE within 24 hours, delay in obtaining signature for informed consent form amendment or to allow continuation of treatment after disease progression. In addition, 3 patients (0.7%) in the docetaxel arm versus 19 patients (4.5%) in the atezolizumab arm received "treatment beyond discontinuation criteria"; 2 patients in the docetaxel arm and 1 patient in the atezolizumab arm received a prohibited concomitant medication; 2 patients in the docetaxel arm had deviations in the category of "incorrect study treatment or wrong dose" and of these 1 patient who was randomized to the docetaxel arm received atezolizumab.

Baseline data

Table 27: Summary of key demographic characteristics across studies

	OAK All-comer		POPLAR All-comer		BIRCH PD-L1 selected	FIR PD-L1 selected	PCD4989g NSCLC Cohort All-comer
	docetaxel N=425	atezo N=425	docetaxel N=143	atezo N=144	atezo N=520	atezo N=93	atezo N=88
Age (years)							
mean (SD)	63.3 (9.3)	63.1 (9.4)	61.8 (9.4)	61.5 (9.2)	63.0 (9.8)	65.2 (9.3)	60.8 (11.9)
median (range)	64.0 (34-85)	63.0 (33-82)	62.0 (36-84)	62.0 (42-82)	63.0 (28-84)	65.0 (44-85)	60.5 (24-84)
Sex							
Male	259 (60.9%)	261 (61.4%)	76 (53.1%)	93 (64.6%)	317 (61.0%)	59 (63.4%)	50 (56.8%)
Female	166 (39.1%)	164 (38.6%)	67 (46.9%)	51 (35.4%)	203 (39.0%)	34 (36.6%)	38 (43.2%)
Race							
White	296 (69.6%)	302 (71.1%)	116 (81.1%)	110 (76.4%)	428 (82.3%)	82 (88.2%)	70 (79.5%)
Asian	95 (22.4%)	85 (20.0%)	13 (9.1%)	23 (16.0%)	66 (12.7%)	5 (5.4%)	1 (1.1%)
Black or African American	11 (2.6%)	5 (1.2%)	4 (2.8%)	3 (2.1%)	8 (1.5%)	5 (5.4%)	3 (3.4%)
Other/unknown	23 (5.4%)	33 (7.8%)	10 (7.0%)	8 (5.5%)	18 (3.5%)	1 (1.1%)	14 (15.9%)
Smoking history							
never	72 (16.9%)	84 (19.8%)	29 (20.3%)	27 (18.8%)	91 (17.5%)	15 (16.1%)	17 (19.3%)
current	67 (15.8%)	59 (13.9%)	21 (14.7%)	25 (17.4%)	54 (10.4%)	13 (14.0%)	10 (11.4%)
previous	286 (67.3%)	282 (66.4%)	93 (65.0%)	92 (63.9%)	375 (72.1%)	65 (69.9%)	61 (69.3%)

Sources: OAK Table 16, POPLAR Table 18, BIRCH Table 15, FIR Tables 11 and 12, PCD Table 23

Table 28: Summary of key baseline disease characteristics across studies

	OAK All comer		POPLAR All comer		BIRCH PD-L1 selected	FIR PD-L1 selected	PCD4989g NSCLC Cohort All comer[a]
	docetaxel N=425	atezo N=425	docetaxel N=143	atezo N=144	atezo N=520	atezo N=93[b]	atezo N=88[b]
Line of Therapy							
n	425	425	143	144	520	93	88
3L+	105 (24.7%)	105 (24.7%)	47 (32.9%)	51 (35.4%)	253 (48.7%)	44 (47.3%)	50 (56.8%)
ECOG Performance Status							
n	425	425	142	142	520	92	88
0	160 (37.6%)	155 (36.5%)	45 (31.7%)	46 (32.4%)	173 (33.3%)	24 (26.1%)	25 (28.4%)
1	265 (62.4%)	270 (63.5%)	97 (68.3%)	96 (67.6%)	342 (65.8%)	68 (73.9%)	63 (71.6%)
2	-	-	0	0	5 (1.0%)	0	0
Histology Type							
n	425	425	143	144	520	93	88
Non-squamous	315 (74.1%)	313 (73.6%)	95 (66.4%)	95 (66.0%)	368 (70.8%)	67 (72.0%)	67 (76.1%)
Squamous	110 (25.9%)	112 (26.4%)	48 (33.6%)	49 (34.0%)	152 (29.2%)	26 (28.0%)	21 (23.9%)
Current disease status							
n	425	425	143	144	520	93	88
locally advanced	19 (4.5%)	29 (6.8%)	5 (3.5%)	8 (5.6%)	18 (3.5%)	2 (2.2%)	ND
metastatic disease	406 (95.5%)	396 (93.2%)	138 (96.5%)	136 (94.4%)	502 (96.5%)	91 (97.8%)	ND
EGFR Mutation							
n	425	425	83	83	254	51	64
positive	43 (10.1%)	42 (9.9%)	8 (9.6%)	10 (12.0%)	29 (11.4%)	5 (9.8%)	10 (11.4%)
negative	310 (72.9%)	318 (74.8%)	75 (90.4%)	72 (86.7%)	224 (88.2%)	44 (86.3%)	54 (61.4%)
T790M	-	-	0	1 (1.2%)	1 (0.4%)	2 (3.9%)	0
unknown[c]	72 (16.9%)	65 (15.3%)	-	-	-	-	-
EML4-ALK Mutation							
n	425	425	58	61	297	65	46
positive	0	2 (0.5%)	3 (5.2%)	0	6 (2.0%)	1 (1.5%)	2 (4.3%)
negative	201 (47.3%)	223 (52.5%)	55 (94.8%)	61 (100%)	291 (98.0%)	64 (98.5%)	44 (95.7%)
KRAS Mutation							
n	425	425	30	42	137	44	51
positive	33 (7.8%)	26 (6.1%)	13 (43.3%)	14 (33.3%)	45 (32.8%)	15 (34.1%)	14 (27.5%)
negative	104 (24.5%)	99 (23.3%)	17 (56.7%)	28 (66.7%)	92 (67.2%)	29 (65.9%)	37 (72.5%)
Brain Metastases							
n	425	425	143	144	520	93	88
Yes	47 (11.1%)	38 (8.9%)	15 (10.5%)	8 (5.6%)	2 (0.4%)	1 (1.1%)	5 (5.7%)

ND = not done. Data based on Primary analysis for each study

[a] patients were initially enrolled as an all-comer population, followed by selective enrollment on the basis of PD-L1 expression.

[b] 1/93 patients in FIR and 15/88 patients in PCD4989g had no prior lines of therapy for metastatic disease (1L)

[c] The 'Unknown' category for EGFR mutation status, ALK-rearrangement status, and KRAS mutation status included patients whose test results were not done, not evaluable, invalid or missing.

Sources: OAK CSR Table 16 and 20; POPLAR CSR Tables 18 and 19; BIRCH CSR Tables 15 and 16, and t_lhis_SE; FIR CSR Table 11, 12, and 13; PCD4989g CSR Table 23 and t_dm_NSCLC_SE.

Table 29: Baseline demographic characteristics (primary population - ITT) - OAK

	Docetaxel (Randomized) (N=425)	Atezolizumab (Randomized) (N=425)	All Patients (N=850)
Age (years)			
n	425	425	850
Mean (SD)	63.3 (9.3)	63.1 (9.4)	63.2 (9.3)
Median	64.0	63.0	64.0
Min - Max	34 - 85	33 - 82	33 - 85
Age group (years)			
n	425	425	850
< 65	218 (51.3%)	235 (55.3%)	453 (53.3%)
>= 65	207 (48.7%)	190 (44.7%)	397 (46.7%)
Age Group 4 Categories (years)			
n	425	425	850
<65	218 (51.3%)	235 (55.3%)	453 (53.3%)
65 to 74	170 (40.0%)	137 (32.2%)	307 (36.1%)
75 to 84	35 (8.2%)	53 (12.5%)	88 (10.4%)
>=85	2 (0.5%)	0	2 (0.2%)
Sex			
n	425	425	850
Male	259 (60.9%)	261 (61.4%)	520 (61.2%)
Female	166 (39.1%)	164 (38.6%)	330 (38.8%)
Ethnicity			
n	425	425	850
Hispanic or Latino	25 (5.9%)	28 (6.6%)	53 (6.2%)
Not Hispanic or Latino	382 (89.9%)	377 (88.7%)	759 (89.3%)
Not reported	13 (3.1%)	10 (2.4%)	23 (2.7%)
Unknown	5 (1.2%)	10 (2.4%)	15 (1.8%)
Race			
n	425	425	850
American Indian or Alaska Native	2 (0.5%)	1 (0.2%)	3 (0.4%)
Asian	95 (22.4%)	85 (20.0%)	180 (21.2%)
Black or African American	11 (2.6%)	5 (1.2%)	16 (1.9%)
Native Hawaiian or other Pacific Islander	2 (0.5%)	2 (0.5%)	4 (0.5%)
White	296 (69.6%)	302 (71.1%)	598 (70.4%)
Other	5 (1.2%)	8 (1.9%)	13 (1.5%)
Multiple	0	2 (0.5%)	2 (0.2%)
Unknown	14 (3.3%)	20 (4.7%)	34 (4.0%)
Weight (kg) at baseline			
n	398	408	806
Mean (SD)	70.61 (16.08)	72.89 (17.79)	71.77 (17.00)
Median	68.55	73.00	70.00
Min - Max	40.2 - 144.9	35.4 - 163.2	35.4 - 163.2
Tobacco Use History			
n	425	425	850
Never	72 (16.9%)	84 (19.8%)	156 (18.4%)
Current	67 (15.8%)	59 (13.9%)	126 (14.8%)
Previous	286 (67.3%)	282 (66.4%)	568 (66.8%)
ECOG Performance Status Score			
n	425	425	850
0	160 (37.6%)	155 (36.5%)	315 (37.1%)
1	265 (62.4%)	270 (63.5%)	535 (62.9%)

Data Cut-off: 7 Jul 2016; RAVE Data Extracted: 19 Aug 2016.

Table 30: Baseline PD-L1 expression status (primary population) - OAK

Baseline PDL-1 Expression Status
First 850 Randomized Intent-to-Treat Patients
Protocol: GO28915 (Data Cut: 7JUL2016)

	Docetaxel (Randomized) (N=425)	Atezolizumab (Randomized) (N=425)	All Patients (N=850)
IC Score (0 to 3) per TC1IC1 Reread			
n	425	425	850
0	219 (51.5%)	210 (49.4%)	429 (50.5%)
1	142 (33.4%)	158 (37.2%)	300 (35.3%)
2	44 (10.4%)	35 (8.2%)	79 (9.3%)
3	16 (3.8%)	18 (4.2%)	34 (4.0%)
Unknown	4 (0.9%)	4 (0.9%)	8 (0.9%)
TC Score (0 to 3) per TC1IC1 Reread			
n	425	425	850
0	296 (69.6%)	294 (69.2%)	590 (69.4%)
1	38 (8.9%)	41 (9.6%)	79 (9.3%)
2	48 (11.3%)	46 (10.8%)	94 (11.1%)
3	39 (9.2%)	40 (9.4%)	79 (9.3%)
Unknown	4 (0.9%)	4 (0.9%)	8 (0.9%)
TC3IC3 vs TC012IC012 per TC3IC3 Reread			
n	425	425	850
TC3 or IC3	65 (15.3%)	72 (16.9%)	137 (16.1%)
TC0/1/2 and IC0/1/2	356 (83.8%)	348 (81.9%)	704 (82.8%)
Unknown	4 (0.9%)	5 (1.2%)	9 (1.1%)
TC23IC23 vs TC01IC01 per TC2IC2 Reread			
n	425	425	850
TC2/3 or IC2/3	136 (32.0%)	129 (30.4%)	265 (31.2%)
TC0/1 and IC0/1	284 (66.8%)	290 (68.2%)	574 (67.5%)
Unknown	5 (1.2%)	6 (1.4%)	11 (1.3%)
TC123IC123 vs TC0IC0 per TC1IC1 Reread			
n	425	425	850
TC1/2/3 or IC1/2/3	222 (52.2%)	241 (56.7%)	463 (54.5%)
TC0 and IC0	199 (46.8%)	180 (42.4%)	379 (44.6%)
Unknown	4 (0.9%)	4 (0.9%)	8 (0.9%)
TC/IC 4 Incremental Subgroups			
n	425	425	850
TC3 or IC3	65 (15.3%)	72 (16.9%)	137 (16.1%)
TC2/3 or IC2/3 exclude TC3 or IC3	70 (16.5%)	59 (13.9%)	129 (15.2%)
TC1/2/3 or IC1/2/3 exclude TC2/3 or IC2/3	87 (20.5%)	111 (26.1%)	198 (23.3%)
TC0 and IC0	199 (46.8%)	180 (42.4%)	379 (44.6%)
Unknown	4 (0.9%)	3 (0.7%)	7 (0.8%)

Data Cut-off: 7 Jul 2016; RAVE Data Extracted: 19 Aug 2016.

Table 31: Prior cancer therapies reported by ≥10% of patients in either treatment arm (primary population) - OAK

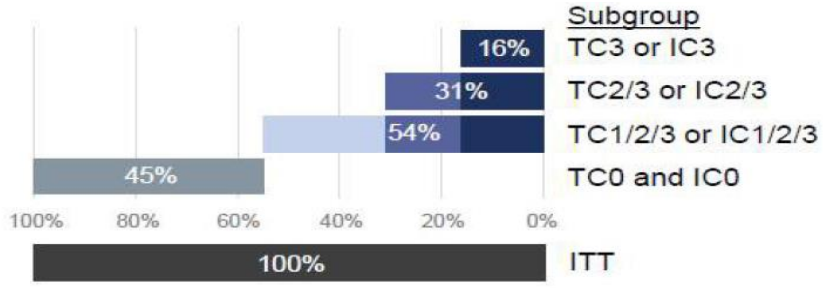
Prior Cancer Therapy
First 850 Randomized Intent-to-Treat Patients
Protocol: GO28915 (Data Cut: 7JUL2016)

Therapy Setting Regiment/Agent	Docetaxel (Randomized) (N=425)	Atezolizumab (Randomized) (N=425)	All Patients (N=850)
Total number of patients with at least one treatment	424 (99.8%)	425 (100.0%)	849 (99.9%)
Overall total number of treatments	1355	1419	2774
METASTATIC			
Total number of patients with at least one treatment	370 (87.1%)	385 (90.6%)	755 (88.8%)
Total number of treatments	1019	1091	2110
CARBOPLATIN	224 (52.7%)	229 (53.9%)	453 (53.3%)
PEMETREXED	195 (45.9%)	210 (49.4%)	405 (47.6%)
CISPLATIN	153 (36.0%)	167 (39.3%)	320 (37.6%)
PACLITAXEL	85 (20.0%)	110 (25.9%)	195 (22.9%)
GEMCITABINE	90 (21.2%)	77 (18.1%)	167 (19.6%)
BEVACIZUMAB	56 (13.2%)	69 (16.2%)	125 (14.7%)
ERLOTINIB	44 (10.4%)	41 (9.6%)	85 (10.0%)
ADJUVANT/NEO-ADJUVANT			
Total number of patients with at least one treatment	103 (24.2%)	97 (22.8%)	200 (23.5%)
Total number of treatments	248	226	474
CISPLATIN	72 (16.9%)	67 (15.8%)	139 (16.4%)
MAINTENANCE			
Total number of patients with at least one treatment	67 (15.8%)	80 (18.8%)	147 (17.3%)
Total number of treatments	86	100	186
PEMETREXED	51 (12.0%)	49 (11.5%)	100 (11.8%)

Multiple uses of a specific medication for a patient were counted once in frequency for the medication. Likewise, multiple uses within a specific medication class for a patient were counted once in frequency for the medication class.
Data Cut-off: 7 Jul 2016; RAVE Data Extracted: 19 Aug 2016.

PD-L1 Expression Status

The majority of patients were IC0 (51.5% docetaxel vs. 49.4% atezolizumab) or IC1 (33.4% vs. 37.2%). TC levels were also balanced between treatment arms across all expression levels with the majority of patients being TC0 (69.6% vs. 69.2%). The combination of TC and IC PD-L1 expression levels showed that all subgroups were balanced between treatment arms, except the atezolizumab arm had a higher proportion of patients in the mutually exclusive subgroup of TC1/2/3 or IC1/2/3 excluding TC2/3 or IC2/3 (20.5% vs. 26.1%).



Data cutoff: 7 July 2016

Figure 9: Baseline PD-L1 expression status (primary population) - OAK

Numbers analysed

Table 32: Summary of analysis populations in OAK study

Patient Populations
All Patients
Protocol: GO28915 (Data Cut: 7JUL2016)

	Docetaxel	Atezolizumab	All Patients
All Randomized Intent-to-Treat Patients	612	613	1225
All Safety Evaluable Patients	578	609	1187
First 850 Randomized Intent-to-Treat Patients	425	425	850
First 850 Randomized Patients with Measurable Disease	425	424	849
Safety Evaluable Patients Among the First 850 Randomized Patients	401	422	823
PRO Evaluable Patients for EORTC QLQ-C30 Among the First 850 Randomized Patients	364	382	746
PRO Evaluable Patients for EORTC QLQ-LC13 Among the First 850 Randomized Patients	361	377	738
All PK Evaluable Atezolizumab Treated Patients	0	606	606
All ATA Evaluable Atezolizumab Treated Patients	0	565	565
PK Evaluable Atezolizumab Treated Patients Among the First 850 Randomized Patients	0	420	420
ATA Evaluable Atezolizumab Treated Patients Among the First 850 Randomized Patients	0	394	394

ATA = anti-therapeutic antibodies; PRO = patient reported outcome, PK=Pharmacokinetic.
Safety, ATA and PK Evaluable populations are actual treatment received.
All other populations are randomized treatment. Data Cut-off: 7 Jul 2016; RAVE Data Extracted: 19 Aug 2016.

Outcomes and estimation

Primary endpoint (OS)

All-comers

The Primary analysis of the study was performed as of the clinical cutoff date of 7 July 2016, at which time 569 deaths had occurred in the ITT population (event/patient ratio 66.9%).

Atezolizumab treatment resulted in prolongation in OS as compared to docetaxel. The stratified HR was 0.73 (95% CI: 0.62, 0.87; stratified log-rank p-value = 0.0003). Patients in the ITT population had a median OS that was 4.2 months longer in the atezolizumab arm: 9.6 months (95% CI: 8.6, 11.2) in the docetaxel arm versus 13.8 months (95% CI: 11.8, 15.7) in the atezolizumab arm.

Table 33: **Duration of OS (Primary Analysis-ITT Population) - OAK**

	Docetaxel (Randomized) (N=425)	Atezolizumab (Randomized) (N=425)
Patients with event (%)	298 (70.1%)	271 (63.8%)
Earliest contributing event		
Death	298	271
Patients without event (%)	127 (29.9%)	154 (36.2%)
Time to Event (Months)		
Median	9.6	13.8
95% CI	(8.6, 11.2)	(11.8, 15.7)
25% and 75%-ile	4.8, 19.5	6.0, NE
Range	0.0^ to 26.9	0.0* to 27.0*
Unstratified Analysis		
Hazard Ratio	0.73	
95% CI	(0.62, 0.86)	
p-value (log-rank)	0.0002	
Stratified Analysis		
Hazard Ratio	0.73	
95% CI	(0.62, 0.87)	
p-value (log-rank)	0.0003	

* Censored, ^ Censored and event, NE = Not estimable.
Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Strata are: IC levels per IxRS, the number of prior chemotherapy regimens per IxRS, and histology per eCRF.
Data Cut-off: 7 Jul 2016; RAVE Data Extracted: 19 Aug 2016.

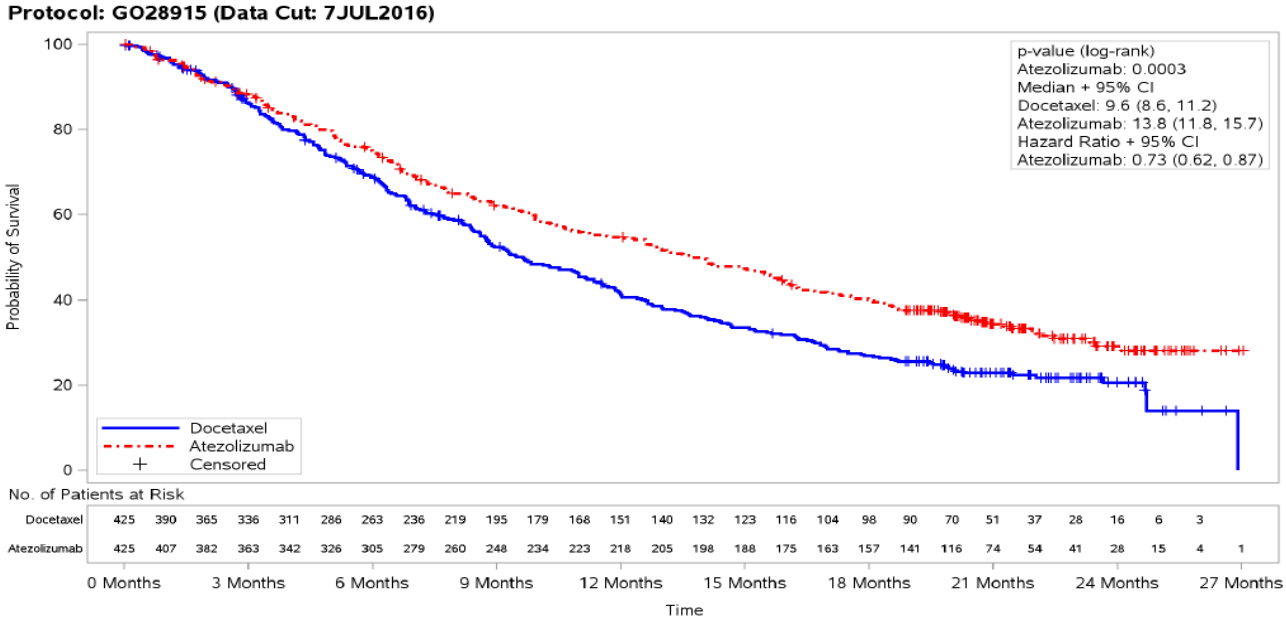


Figure 10: KM plot of OS (primary population) – OAK

Treatment with atezolizumab resulted in prolonged survival. The HR is 0.73 (95% CI; 0.62, 0.87), p-value = 0.0003. Median OS was prolonged 4.2 months in the atezolizumab. These results are not only statistically significant, but also clinically highly relevant in a patient population with a dismal prognosis. The data are considered mature, as more than 66% of the events had occurred at the time of the clinical cut-off date.

Secondary endpoint: PFS

Table 34: Duration of PFS (primary population) – OAK

	Docetaxel (Randomized) (N=425)	Atezolizumab (Randomized) (N=425)
Patients with event (%)	375 (88.2%)	380 (89.4%)
Earliest contributing event		
Death	85	48
Disease Progression	290	332
Patients without event (%)	50 (11.8%)	45 (10.6%)
Time to Event (Months)		
Median	4.0	2.8
95% CI	(3.3, 4.2)	(2.6, 3.0)
25% and 75%-ile	1.6, 7.0	1.4, 8.3
Range	0.0^ to 26.9	0.0* to 24.9*
Unstratified Analysis		
p-value (log-rank)	0.3596	
Hazard Ratio	0.93	
95% CI	(0.81, 1.08)	
Stratified Analysis		
p-value (log-rank)	0.4928	
Hazard Ratio	0.95	
95% CI	(0.82, 1.10)	

* Censored, ^ Censored and event, NE = Not estimable.
Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Strata are: IC levels per IxRS, the number of prior chemotherapy regimens per IxRS, and histology per eCRF.
Data Cut-off: 7 Jul 2016; RAVE Data Extracted: 19 Aug 2016.

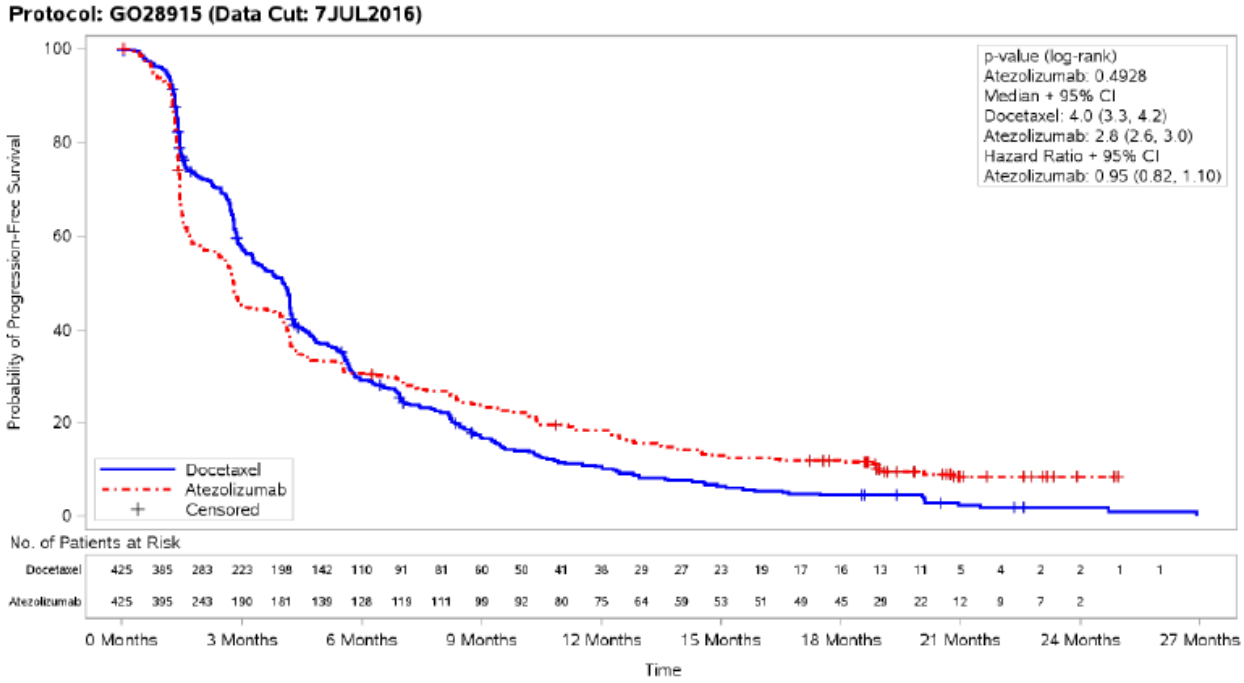


Figure 11: KM plot for PFS (primary population) - OAK

Table 35: Overview of efficacy results (primary population) - OAK

Parameter	Docetaxel	Atezolizumab
Primary Efficacy Parameter: Overall Survival		
ITT Population	n=425	n=425
Patients with event (%)	298 (70.1%)	271 (63.8%)
Median duration of Survival (months)	9.6	13.8
95% CI	(8.6, 11.2)	(11.8, 15.7)
Stratified Analysis		
Hazard Ratio (95% CI)	0.73 (0.62, 0.87)	
p–value (log-rank)	0.0003	
TC1/2/3 or IC1/2/3	n=222	n=241
Patients with event (%)	149 (67.1%)	151 (62.7%)
Median duration of Survival (months)	10.3	15.7
95% CI	(8.8, 12.0)	(12.6, 18.0)
Stratified Analysis		
Hazard Ratio (95% CI)	0.74 (0.58, 0.93)	
p–value (log-rank)	0.0102	
Secondary Efficacy Parameters		
Progression-free survival		
ITT Population	n=425	n=425
Patients with event (%)	375 (88.2%)	380 (89.4%)
Median duration of PFS (months)	4.0	2.8
95% CI	(3.3, 4.2)	(2.6, 3.0)
Stratified Hazard Ratio (95% CI)	0.95 (0.82, 1.10)	
TC1/2/3 or IC1/2/3	n=222	n=241
Patients with event (%)	193 (86.9%)	216 (89.6%)
Median duration of PFS (months)	4.1	2.8
95% CI	(2.9, 4.3)	(2.6, 4.0)
Stratified Hazard Ratio (95% CI)	0.91 (0.74, 1.12)	
Objective Response Rate		
ITT Population	n=425	n=425
Responders (%)	57 (13.4%)	58 (13.6%)
95% CI (Clopper-Pearson)	(10.32, 17.02)	(10.53, 17.28)
TC1/2/3 or IC1/2/3	n=222	n=241
Responders (%)	36 (16.2%)	43 (17.8%)
95% CI (Clopper-Pearson)	(11.62, 21.74)	(13.22, 23.27)

Parameter	Docetaxel	Atezolizumab
Duration of Response		
ITT Population	n=57	n=58
Median DOR (months)	6.2	16.3
95% CI	(4.9, 7.6)	(10.0, NE)
Unstratified Hazard Ratio (95% CI)	0.34 (0.21, 0.55)	
TC1/2/3 or IC1/2/3	n=36	n=43
Median DOR (months)	6.2	16.0
95% CI	(4.9, 9.2)	(9.7, NE)
Unstratified Hazard Ratio (95% CI)	0.38 (0.22, 0.65)	

CI=confidence interval; DOR=duration of response; IC=immune cell; ITT=intent-to-treat; TC=tumor cell; NE=not estimable; PFS=progression-free survival.

Secondary endpoint: ORR

Table 36: Summary of ORR (Primary Population) - OAK

	Docetaxel (Randomized) (N=425)		Atezolizumab (Randomized) (N=425)
Responders	57 (13.4%)		58 (13.6%)
Non-Responders	368 (86.6%)		367 (86.4%)
95% CI for Response Rates (Clopper-Pearson)	(10.32, 17.02)		(10.53, 17.28)
Difference in Response Rates		0.24	
95% CI (Wald)		(-4.36, 4.83)	
p-value (Cochran-Mantel-Haenszel)		0.9202	
Odds Ratio		1.02	
95% CI		(0.69, 1.51)	
Complete Response (CR)	1 (0.2%)		6 (1.4%)
95% CI	(0.01, 1.30)		(0.52, 3.05)
Partial Response (PR)	56 (13.2%)		52 (12.2%)
95% CI	(10.11, 16.77)		(9.27, 15.73)
Stable Disease (SD)	177 (41.6%)		150 (35.3%)
95% CI	(36.92, 46.50)		(30.75, 40.05)
Progressive Disease (PD)	117 (27.5%)		187 (44.0%)
95% CI	(23.33, 32.04)		(39.22, 48.86)
Missing or unevaluable	74 (17.4%)		30 (7.1%)

Wald is the normal approximation.
Patients were classified as missing or unevaluable when no post-baseline response assessments were available or all post-baseline response assessments were unevaluable.
Data Cut-off: 7 Jul 2016; RAVE Data Extracted: 19 Aug 2016.

Secondary endpoint: DOR

Table 37: Summary of DOR (Primary Population Patients with a Confirmed Response per RECIST v1.1) - OAK

	Docetaxel (Randomized) (N=57)		Atezolizumab (Randomized) (N=58)
Patients with event (%)	47 (82.5%)		28 (48.3%)
Earliest contributing event			
Death	7		2
Disease Progression	40		26
Patients without event (%)	10 (17.5%)		30 (51.7%)
Time to Event (Months)			
Median	6.2		16.3
95% CI	(4.9, 7.6)		(10.0, NE)
25% and 75%-ile	4.1, 10.1		6.2, NE
Range	1.4* to 21.3*		1.6* to 21.7*
Unstratified Analysis			
Hazard Ratio		0.34	
95% CI		(0.21, 0.55)	
Stratified Analysis			
Hazard Ratio		0.31	
95% CI		(0.18, 0.55)	

* Censored, ^ Censored and event, NE = Not estimable.
Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. The hazard ratio were estimated by Cox regression. Strata are: IC levels per IxRS, the number of prior chemotherapy regimens per IxRS, and histology per eCRF.
Data Cut-off: 7 Jul 2016; RAVE Data Extracted: 19 Aug 2016.

Ancillary analyses

PD-L1 expression

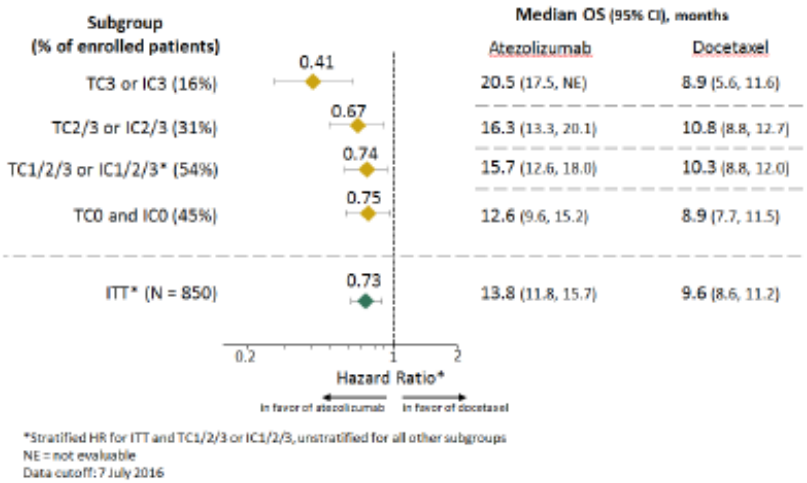


Figure 12: Forest plot of OS by PD-L1 expression subgroups (primary population) – OAK

Table 38: Duration of OS – PD-L1 expression subgroups (primary population) – OAK

	Docetaxel	Atezolizumab
TC3 or IC3	n = 65	n = 72
Patients with event (%)	49 (75.4%)	37 (51.4%)
Median duration of Survival (months; 95% CI)	8.9 (5.6, 11.6)	20.5 (17.5, NE)
Unstratified Hazard Ratio (95% CI)	0.41 (0.27, 0.64)	
TC2/3 or IC2/3	n = 136	n = 129
Patients with event (%)	92 (67.6%)	79 (61.2%)
Median duration of Survival (months; 95% CI)	10.8 (8.8, 12.7)	16.3 (13.3, 20.1)
Unstratified Hazard Ratio (95% CI)	0.67 (0.49, 0.90)	
TC0 and IC0	n = 199	n = 180
Patients with event (%)	146 (73.4%)	116 (64.4%)
Median duration of Survival (months; 95% CI)	8.9 (7.7, 11.5)	12.6 (9.6, 15.2)
Unstratified Hazard Ratio (95% CI)	0.75 (0.59, 0.96)	

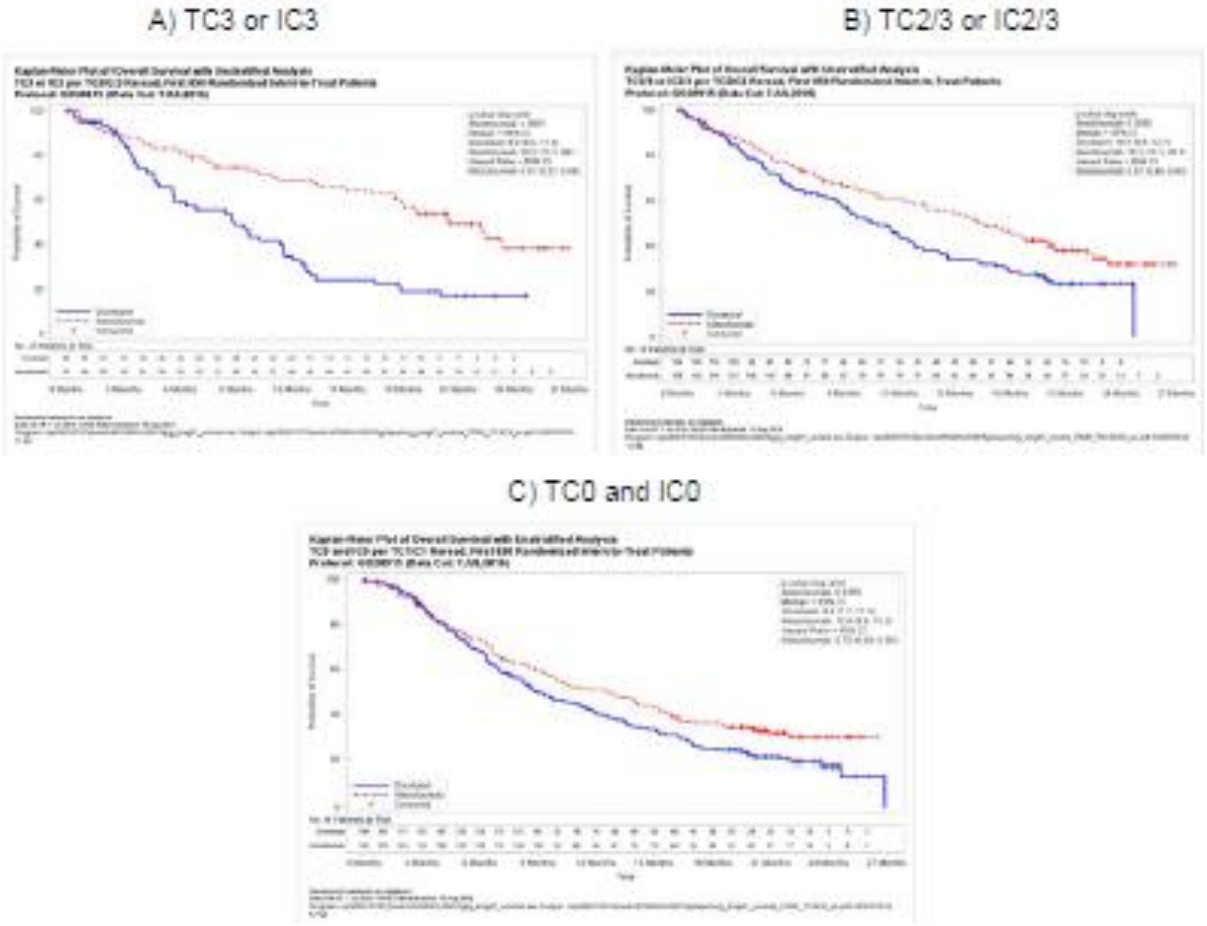


Figure 13: KM plot of OS by PD-L1 expression subgroups (primary population) – OAK

Histology

Across all PD-L1 expression subgroups defined by different TC or IC cutoffs, the point estimates of the HRs for OS were equal to or below 0.82**.**

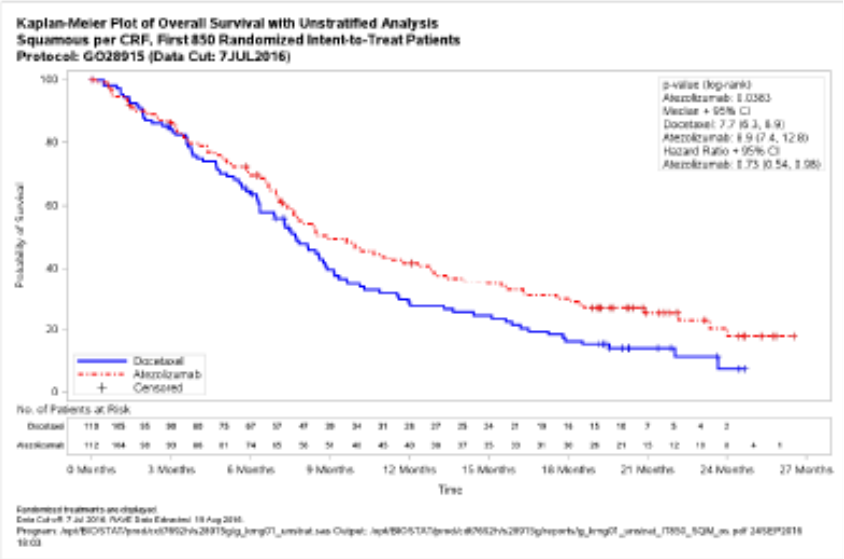
Table 39: Hazard Ratio for OS in patients with squamous or non-squamous disease – PD-L1 expression subgroups (primary population) – OAK

Number of patients (n) Hazard Ratio (95% CI)	Squamous	Non-Squamous
ITT population		
PP	n=222 0.73 (0.54, 0.98)	n=628 0.73 (0.60, 0.89)
PD-L1 expression subgroups		
TC1/2/3 or IC1/2/3	n=130 0.71 (0.48, 1.06)	n=333 0.72 (0.55, 0.95)
TC2/3 or IC2/3	n=77 0.76 (0.45, 1.29)	n=188 0.61 (0.42, 0.88)
TC3 or IC3	n=41 0.57 (0.27, 1.20)	n=96 0.35 (0.21, 0.61)
TC0 and IC0	n=89 0.82 (0.51, 1.32)	n=290 0.75 (0.57, 1.00)
Mutually exclusive subgroups		
TC1/2/3 or IC1/2/3 excluding TC2/3 or IC2/3	n=53 0.68 (0.36, 1.26)	n=145 0.88 (0.58, 1.35)
TC2/3 or IC2/3 excluding TC3 or IC3	n=36 1.03 (0.48, 2.20)	n=93 1.14 (0.68, 1.90)

Source:

- ITT: Table 35.
- TC3 or IC3: squamous and non-squamous.
- TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3: squamous and non-squamous.
- mutually exclusive subgroups: squamous and non-squamous.

A. Squamous



B. Non-Squamous

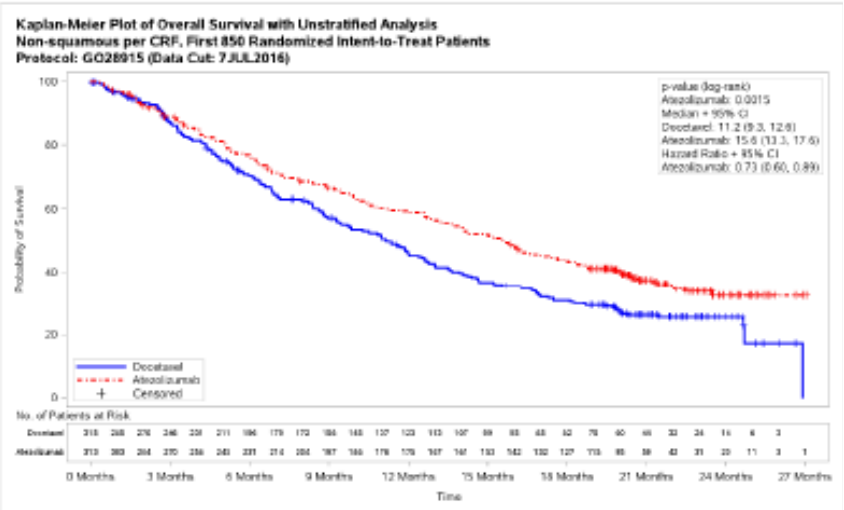


Figure 14: KM plot of OS by histology (primary population) – OAK

EORTC QLQ-LC13 - Time to deterioration (TTD) of lung cancer symptoms

Prolonged time to deterioration of patient-reported pain in chest as measured by the EORTC QLQ-LC13 was observed with atezolizumab compared to docetaxel (HR of 0.71, 95% CI: 0.49, 1.05; median not reached in either arm). The time to deterioration in other lung cancer symptoms (i.e. cough, dyspnoea, and arm/shoulder pain) as measured by the EORTC QLQ-LC13 was similar between atezolizumab and docetaxel.

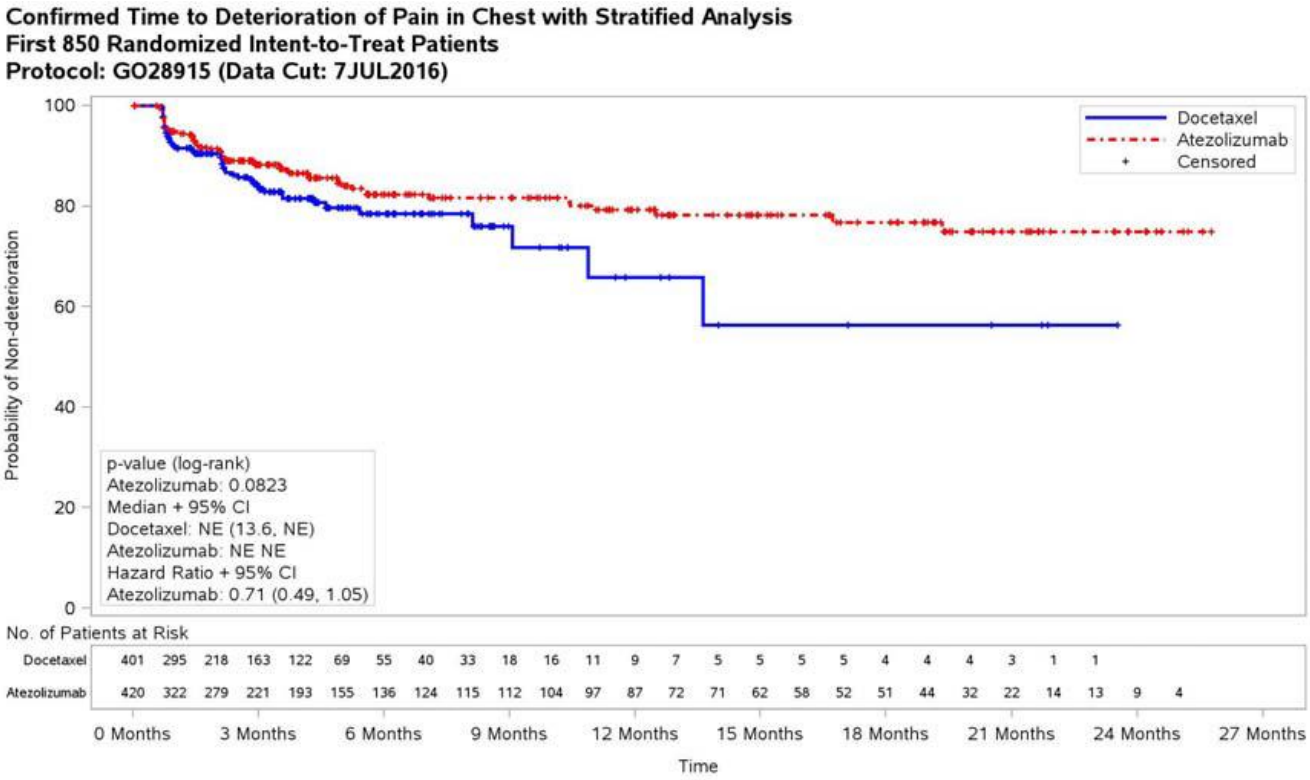
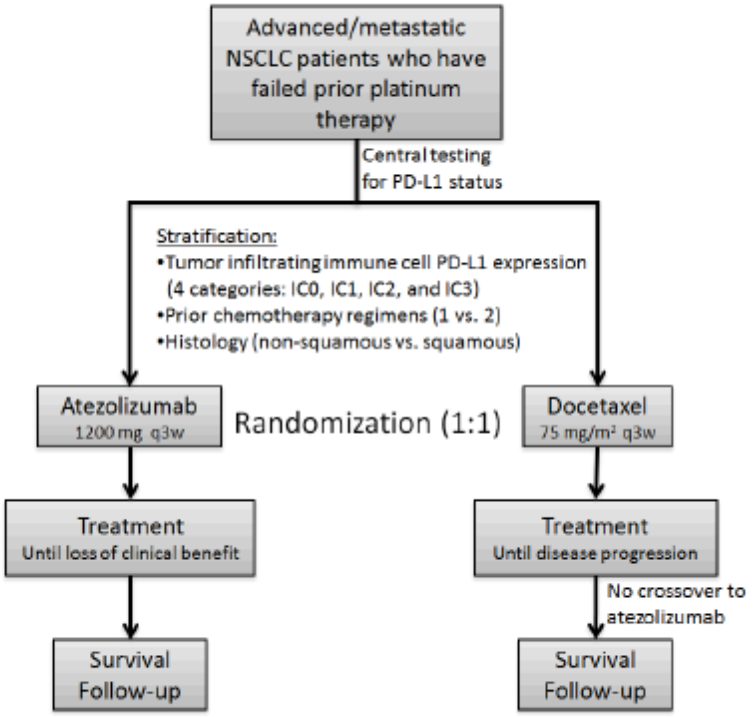


Figure 15: **Time to Deterioration of Chest Pain (Primary Population) - OAK POPLAR**

POPLAR (GO28753): A Phase II, open-label, multicenter, randomized study to investigate the efficacy and safety of MPDL3280A (anti−PD-L1 antibody) compared with docetaxel in patients with non−small cell lung cancer after platinum failure.



IHC=immunohistochemistry; NSCLC=non−small cell lung cancer; PD-L1=programmed death−ligand 1; q3w=every 3 weeks.

Figure 16: Overview of study design (GO28753 - POPLAR)

Methods

Study Participants

Please refer to Figure 17: Patient disposition (3rd interim analysis – ITT population) - POPLAR.

Treatments

POPLAR:

Atezolizumab

The dose level of atezolizumab tested was 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) administered by IV infusion q3w (21 [±2] days) until loss of clinical benefit or unacceptable toxicity.

Docetaxel

The starting dose of docetaxel was 75 mg/m2 q3w. Dose modifications were performed according to the locally approved label. Treatment continued until disease progression or unacceptable toxicity.

Objectives

Primary objective:

To estimate the efficacy of atezolizumab compared with docetaxel as measured by OS

Secondary objectives:

To evaluate the efficacy of atezolizumab compared with docetaxel with respect to anti-tumour effects measured by overall response, DOR, and PFS per RECIST v1.1

To evaluate the efficacy of atezolizumab with respect to anti-tumour effects measured by overall response, DOR, and PFS per modified RECIST

Outcomes/endpoints

Primary Endpoint: OS.

Secondary Endpoints: PFS, ORR, DOR: by RECIST v1.1 and mRECIST.

Please refer to "Outcome/endpoints" of OAK study for further information regarding PD-L1 assessment, tumour measurements and tumour response criteria.

Sample size

This Phase II study was designed to provide an assessment of the efficacy and safety of atezolizumab and the primary purpose was the estimation of the OS and PFS hazard ratios in the PD-L1 expression subgroups and in the ITT population. The study was designed to enrol a minimum of approximately 54

PD-L1 IC2 or IC3 patients. In the case that the PD-L1 IC2 or IC3 prevalence was lower than 18%, up to a maximum of 300 total patients could be enrolled.

The study was expected to enrol 285 total patients and 55 PD-L1 IC2 or IC3 patients. These numbers were used for the statistical calculations described below.

The power and 95% CIs for OS and PFS in the PD-L1 IC2 or IC3 subset were based on the following assumptions: Event times are exponentially distributed, median PFS in the control arm is 3 months, median OS in the control arm is 8 months, and patients are enrolled over 8 months.

The power and 95% CIs for OS and PFS in the ITT population are based on the following assumptions: Event times are exponentially distributed, median PFS in the control arm is 3 months, median OS in the control arm is 8 months, and patients are enrolled over 8 months. Patients were followed until approximately 180 patient deaths in the ITT population occurred.

Randomisation

Randomization was stratified by tumour tissue PD-L1 expression on tumour-infiltrating immune cells (IC0, IC1, IC2, and IC3), number of prior lines of chemotherapy (1 versus 2) and histology (non-squamous versus squamous). Randomization was conducted using an Interactive Web Response System (IWRS).

Blinding (masking)

POPLAR study was open-label.

Statistical methods

Three interim OS analyses were conducted when approximately 30, 100, and 150 events in the ITT population occurred. An α of 0.0001, 0.0001, and 0.001 was spent for the first, second, and third planned interim analysis of OS, respectively. The primary OS analysis was conducted at the 4.88% level of significance when approximately 180 events were observed in the ITT population. The testing hierarchy for OS started with the subgroup of TC2/3 or IC2/3 at the two-sided alfa-level of 4.88% and in the event that the null hypothesis was rejected, the test continued to the next subgroup at the same 4.88% level of significance.

Table 40: Hierarchical statistical considerations for primary endpoint (primary analysis only) in POPLAR

	2-sided α = 4.88%	target HR	minimum detectable HR
1.	TC2/3 or IC2/3	0.5	0.616
2.	TC1/2/3 or IC1/2/3	0.6	0.699
3.	ITT	0.65	0.746
4.	TC3 or IC3	0.35	0.48

Results

Participant flow

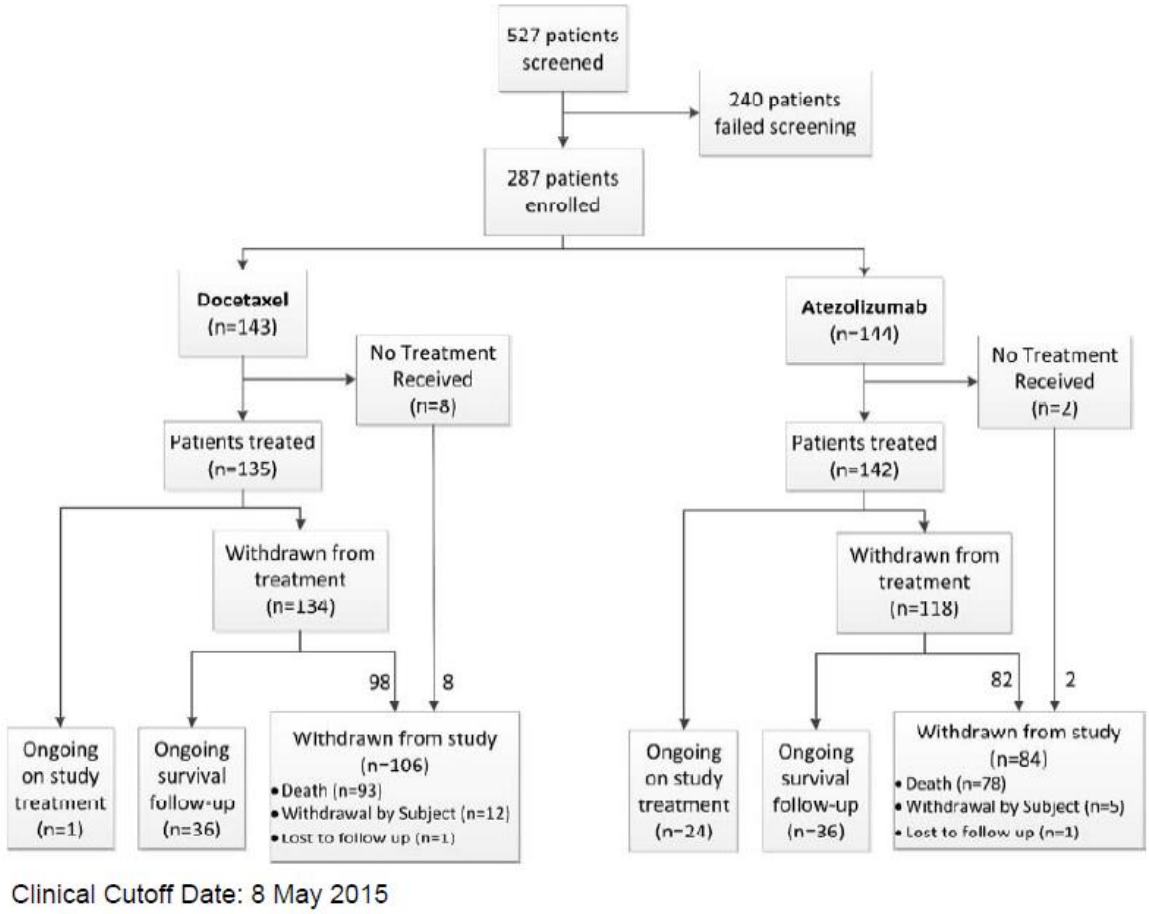


Figure 17: Patient disposition (3rd interim analysis – ITT population) - POPLAR

Of the 240 patients that failed screening, there were 130 patients who failed to meet protocol-defined inclusion criteria, 90 patients who met conditions for exclusion, and 20 patients who failed screening for other reasons unrelated to inclusion and exclusion criteria. This was primarily driven by insufficient tumour sample for pathology (47 patients); Inadequate hematologic and end organ function (31 patients); and 56 patients with known active or untreated CNS metastases.

Recruitment

First patient randomized: 5 August 2013. Last patient randomized: 31 March 2014.

61 centers in 13 countries: USA (26 centers), Poland (4), Germany (4), Spain (4), France (5), Korea (3), Thailand (3), Great Britain (4), Belgium (1), Turkey (2), Canada (2), Italy (2), Sweden (1).

Conduct of the study

The protocol was amended five times. The key changes to the protocol are summarized below.

Protocol Amendment 2 (Version 3) – 30 January 2014.

Protocol revised to reflect the continuation of enrollment of patients until a minimum of approximately 54 patients PD-L1−positive were accrued. In the case that the prevalence of PD-L1−positive patients was lower than 18%, up to a maximum of approximately 300 total patients could be enrolled.

Protocol Amendment 3 (Version 4) – 21 May 2014.

Treatment duration for atezolizumab was modified to allow patients to be treated until clinical benefit was no longer being experienced; accordingly, the 16-cycle or 12-month initial treatment, follow-up, and re-treatment periods no longer applied. The timing of the interim safety and efficacy data evaluation by the Internal Monitoring Committee changed from when 30 and 60 deaths were observed to when approximately 30 and 100 deaths had occurred.

Protocol Amendment 5 (Version 6) – 24 February 2015.

Adjusted the event threshold for the primary analysis to approximately 180 death events and converted the originally planned analysis at approximately 150 death events to an interim analysis. Clarified that stratification by PD-L1 IHC status was based on PD-L1 expression on tumor-infiltrating immune cells. In addition to the primary analyses on the ITT population and the subgroup of patients with PD-L1 IHC 2 or IHC 3 expression status in ICs, the protocol was amended to allow for subgroup analyses based on other categories of PD-L1 expression (e.g., including expression on tumor cells [TCs]).

Protocol violations

Table 41: Major protocol violations, enrolled patients

Summary of Major Protocol Deviations and Violations
Intent-to-Treat Patients
Protocol: GO28753 (Data Cut: 8May2015)

Deviation Category Types of Deviations	Docetaxel (N=143)	Atezolizumab (N=144)	All Patients (N=287)
Total number of patients with at least one deviation	20 (14.0%)	17 (11.8%)	37 (12.9%)
Overall total number of deviations	22	20	42
Eligibility Violations			
Total number of patients with at least one deviation	7 (4.9%)	7 (4.9%)	14 (4.9%)
Total number of events	8	8	16
Untreated and/or excluded CNS metastases	3 (2.1%)	1 (0.7%)	4 (1.4%)
Did not meet Laboratory requirements	1 (0.7%)	2 (1.4%)	3 (1.0%)
Excluded concurrent illness	2 (1.4%)	1 (0.7%)	3 (1.0%)
Treatment with prohibited medication within excluded window relative to randomization	0	3 (2.1%)	3 (1.0%)
Did not meet Prior NSCLC treatment requirements	1 (0.7%)	1 (0.7%)	2 (0.7%)
Prior excluded immunotherapy	1 (0.7%)	0	1 (0.3%)
Study Procedures Violations			
Total number of patients with at least one deviation	13 (9.1%)	11 (7.6%)	24 (8.4%)
Total number of events	14	12	26
Other procedural deviation significant for safety and/or efficacy	12 (8.4%)	10 (6.9%)	22 (7.7%)
Prohibited medication	0	2 (1.4%)	2 (0.7%)
Incorrect treatment or wrong dose	1 (0.7%)	0	1 (0.3%)

A patient will be only counted once if received more than one deviation of the same type.
A patient will be counted more than once if received more than one type of the deviation.
Atezolizumab patient 200005 reported receiving prohibited concomitant therapy/medication and this is reported as a Eligibility Violation and a Study Prodeccured Violation.
Data Cut-off: 8 May 2015; SDTM Data Extracted: 16 Jul 2015.

Baseline data

For further information on the baseline characteristics of POPLAR study, please also refer to Table 42 and Table 43.

Table 42: Baseline PD-L1 expression status (ITT population) - POPLAR

PD-L1 Status	Docetaxel	Atezolizumab	All patients
All Patients	**n=143**	**n=144**	**n=287**
IC Levels			
0	63 (44.1%)	62 (43.1%)	125 (43.6%)
1	54 (37.8%)	53 (36.8%)	107 (37.3%)
2	18 (12.6%)	19 (13.2%)	37 (12.9%)
3	8 (5.6%)	10 (6.9%)	18 (6.3%)
TC Levels			
0	82 (57.3%)	96 (66.7%)	178 (62.0%)
1	21 (14.7%)	19 (13.2%)	40 (13.9%)
2	25 (17.5%)	14 (9.7%)	39 (13.6%)
3	15 (10.5%)	15 (10.4%)	30 (10.5%)
IC3 or TC3			
TC3 or IC3	23 (16.1%)	24 (16.7%)	47 (16.4%)
TC0/1/2 and IC0/1/2	120 (83.9%)	120 (83.3%)	240 (83.6%)
IC2/3 or TC2/3			
TC2/3 or IC2/3	55 (38.5%)	50 (34.7%)	105 (36.6%)
TC0/1 and IC0/1	88 (61.5%)	94 (65.3%)	182 (63.4%)
IC1/2/3 or TC1/2/3			
TC1/2/3 or IC1/2/3	102 (71.3%)	93 (64.6%)	195 (67.9%)
TC0 and IC0	41 (28.7%)	51 (35.4%)	92 (32.1%)
IC/TC Level Mutually Exclusive Subgroups			
TC3 or IC3	23 (16.1%)	24 (16.7%)	47 (16.4%)
TC2/3 or IC2/3 exclude TC3 or IC3	32 (22.4%)	26 (18.1%)	58 (20.2%)
TC-IC1/2/3 exclude TC2/3 or IC2/3	47 (32.9%)	43 (29.9%)	90 (31.4%)
TC0 and IC0	41 (28.7%)	51 (35.4%)	92 (32.1%)
Histology by TC/IC subgroups			
NSQM TC3 or IC3	18 (12.6%)	18 (12.5%)	36 (12.5%)
NSQM TC0/1/2 and IC0/1/2	77 (53.8%)	77 (53.5%)	154 (53.7%)
SQM TC3 or IC3	5 (3.5%)	6 (4.2%)	11 (3.8%)
SQM TC0/1/2 and IC0/1/2	43 (30.1%)	43 (29.9%)	86 (30.0%)
Histology by TC/IC subgroups			
NSQM TC2/3 or IC2/3	36 (25.2%)	34 (23.6%)	70 (24.4%)
NSQM TC0/1 and IC0/1	59 (41.3%)	61 (42.4%)	120 (41.8%)
SQM TC2/3 or IC2/3	19 (13.3%)	16 (11.1%)	35 (12.2%)
SQM TC0/1 and IC0/1	29 (20.3%)	33 (22.9%)	62 (21.6%)
Histology by TC/IC subgroups			
NSQM TC1/2/3 or IC1/2/3	66 (46.2%)	61 (42.4%)	127 (44.3%)
NSQM TC0 and IC0	29 (20.3%)	34 (23.6%)	63 (22.0%)
SQM TC1/2/3 or IC1/2/3	36 (25.2%)	32 (22.2%)	68 (23.7%)
SQM TC0 and IC0	12 (8.4%)	17 (11.8%)	29 (10.1%)

SQM: squamous; NSQM: non-squamous

Table 43: NSCLC History (ITT population) - POPLAR

tent-to-Treat Patients
otocol: GO28753 (Data Cut: 8May2015)

	Docetaxel (N=143)	Atezolizumab (N=144)	All Patients (N=287)
Pathology/Histology			
n	143	144	287
Non-squamous	95 (66.4%)	95 (66.0%)	190 (66.2%)
Squamous	48 (33.6%)	49 (34.0%)	97 (33.8%)
Number of Prior Therapies			
n	143	144	287
1	96 (67.1%)	93 (64.6%)	189 (65.9%)
2	47 (32.9%)	51 (35.4%)	98 (34.1%)
Measurable Disease at Baseline			
n	143	144	287
Yes	143 (100.0%)	144 (100.0%)	287 (100.0%)
Stage of initial diagnosis			
n	143	144	287
IA	4 (2.8%)	4 (2.8%)	8 (2.8%)
IB	4 (2.8%)	1 (0.7%)	5 (1.7%)
IIA	5 (3.5%)	4 (2.8%)	9 (3.1%)
IIB	7 (4.9%)	7 (4.9%)	14 (4.9%)
IIIA	16 (11.2%)	13 (9.0%)	29 (10.1%)
IIIB	14 (9.8%)	25 (17.4%)	39 (13.6%)
IVA	37 (25.9%)	45 (31.3%)	82 (28.6%)
IVB	53 (37.1%)	43 (29.9%)	96 (33.4%)
Unknown	3 (2.1%)	2 (1.4%)	5 (1.7%)
Current disease status			
n	143	144	287
Locally Advanced	5 (3.5%)	8 (5.6%)	13 (4.5%)
Metastatic Disease	138 (96.5%)	136 (94.4%)	274 (95.5%)

Data Cut-off: 8 May 2015; SDTM Data Extracted: 16 Jul 2015.

There are slightly more patients with TC 2 status in the docetaxel arm. However, the majority of patients are TC0 or IC0.

Numbers analysed

Table 44: Summary of analysis populations in POPLAR study

Patient Populations
All Patients
Protocol: GO28753 (Data Cut: 8May2015)

	Docetaxel (N=143)	Atezolizumab (N=144)	All Patients (N=287)
Intent-to-Treat Patients			
Yes	143 (100.0%)	144 (100.0%)	287 (100.0%)
Safety-Evaluable Patients			
No	8 (5.6%)	2 (1.4%)	10 (3.5%)
Yes	135 (94.4%)	142 (98.6%)	277 (96.5%)
Pharmacokinetics Evaluable Patients			
No	143 (100.0%)	2 (1.4%)	145 (50.5%)
Yes	0	142 (98.6%)	142 (49.5%)

All patients have measurable disease at baseline.
Data Cut-off: 8 May 2015; SDTM Data Extracted: 16 Jul 2015.

Outcomes and estimation

Primary endpoint: OS

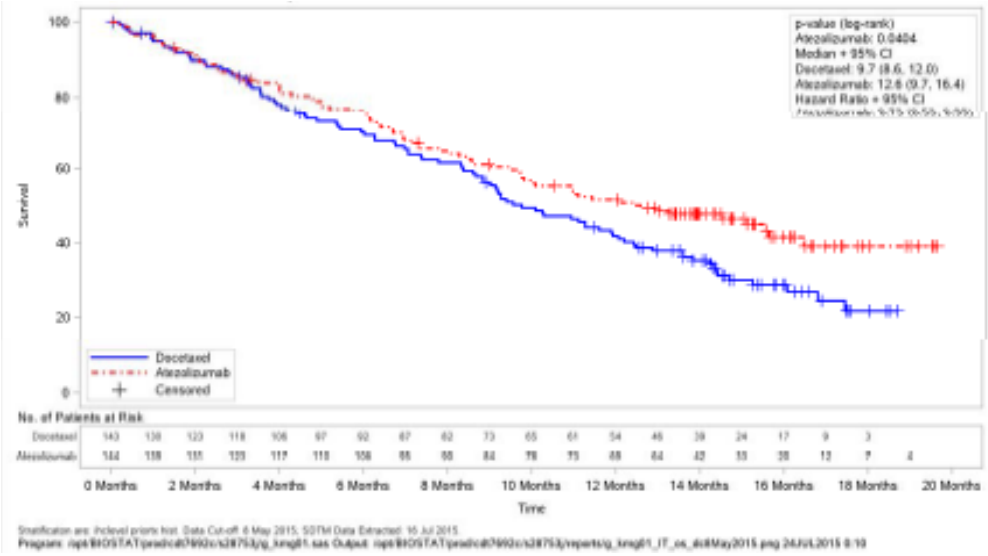


Figure 18: KM plot of OS (primary analysis-ITT population) (cut-off 8 May 2015) – POPLAR

Table 45: Duration of OS(primary analysis-ITT population)– POPLAR

Time to Event Summary for Overall Survival
Intent-to-Treat Patients
Protocol: GO28753 (Data Cut: 8May2015)

Overall Survival

	Docetaxel (N=143)	Atezolizumab (N=144)
Patients with event (%)	95 (66.4%)	78 (54.2%)
Earliest contributing event		
Death	95	78
Patients without event (%)	48 (33.6%)	66 (45.8%)
Time to Event (Months)		
Median	9.7	12.6
95% CI	(8.6, 12.0)	(9.7, 16.4)
25% and 75%-ile	4.6, 16.8	6.0, NE
Range	0.0* to 18.7*	0.2 to 19.6*
Unstratified Analysis		
p-value (log-rank)	0.0342	
Hazard Ratio	0.72	
95% CI	(0.54, 0.98)	
Stratified Analysis		
p-value (log-rank)	0.0404	
Hazard Ratio	0.73	
95% CI	(0.53, 0.99)	

* Censored, ^ Censored and event
Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of
Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.
Data Cut-off: 8 May 2015; SDTM Data Extracted: 16 Jul 2015.

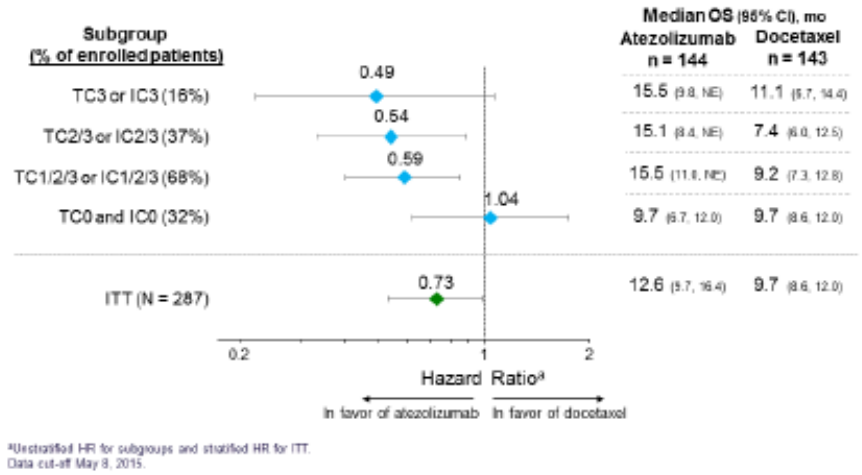


Figure 19: Forest plot of OS by PD-L1 expression subgroup (primary analysis – ITT population) (cut-off 8 May 2015) - POPLAR

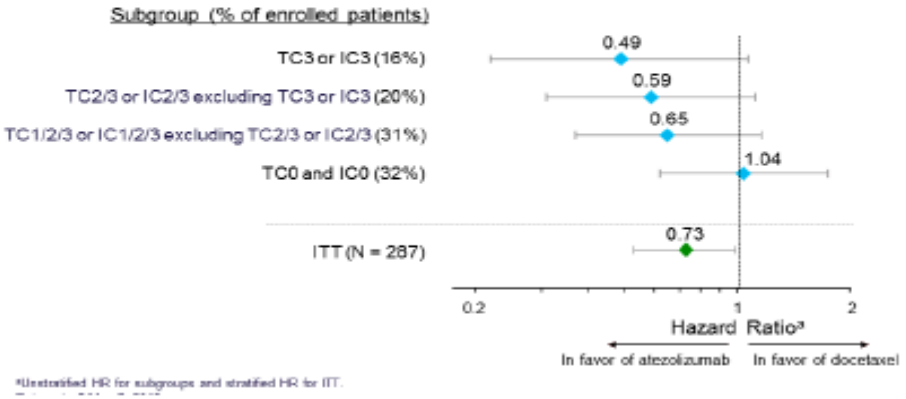


Figure 20: Forest plot –analysis of OS by level of PD-L1 expression (mutually exclusive subgroups) – 8 May 2015 cut-off - POPLAR

Forest plot - Subgroup Analysis of Duration, Overall Survival, Page 4 of 7
Intent-to-Treat Patients
Protocol: GO28753 (Data Cut: 8May2015)

Baseline Risk Factors	Total n	Docetaxel (N=143) n	Events	Median (Months)	Atezolizumab (N=144) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	287	143	95	9.7	144	78	12.6	0.72	(0.54, 0.98)
Ventana TC Levels									
0	178	82	52	10.9	96	55	11.0	0.84	(0.57, 1.22)
1	40	21	12	11.6	19	10	12.4	0.91	(0.39, 2.11)
2	39	25	20	6.2	14	7	13.0	0.48	(0.20, 1.14)
3	30	15	11	10.1	15	6	15.5	0.36	(0.13, 1.00)
Ventana IC Levels									
0	125	63	40	10.2	62	37	10.9	0.89	(0.57, 1.39)
1	107	54	35	11.9	53	25	15.5	0.59	(0.35, 0.99)
2	37	18	15	6.2	19	11	9.0	0.55	(0.25, 1.20)
3	18	8	5	11.8	10	5	NE	0.76	(0.22, 2.62)
Ventana TC3 or IC3 vs. TC0/1/2 and IC0/1/2									
TC3 or IC3	47	23	16	11.1	24	10	15.5	0.49	(0.22, 1.07)
TC0/1/2 and IC0/1/2	240	120	79	9.4	120	68	11.1	0.78	(0.56, 1.08)

NE = Non-Estimable; Median survival was estimated from Kaplan-Meier method. Unstratified Hazard ratio relative to Docetaxel and 95% CI for the hazard ratio were estimated using Cox regression. The vertical dashed line indicates the hazard ratio for all patients. The diameter of a square is proportional to the square root of the total number of events. Data Cut-off: 8 May 2015; SDTM Data Extracted: 16 Jul 2015.

Figure 21: Subgroup analysis of OS by individual TC or IC expression levels (primary analysis- ITT population) – POPLAR

- Updated results cut-off 1 December 2015

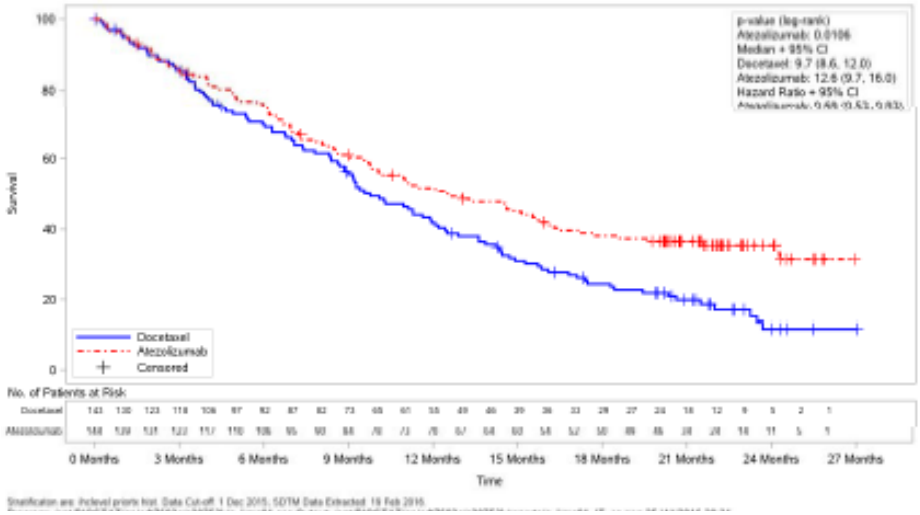


Figure 22: KM curve of OS, stratified analysis (ITT, cut-off 1 December 2015) - POPLAR

Table 46: OS by PD-L1 expression level and histology (cut-off 1 December 2015) - POPLAR

Population	Atezolizumab		docetaxel		HR[a] 95% CI
	n	Median, mo	n	Median, mo	
ITT	144	12.6	143	9.7	0.69 (0.52-0.92)
PD-L1 subgroup					
TC3 or IC3	24	NE	23	11.1	0.45 (0.22-0.95)
TC2/3 or IC2/3	50	15.1	55	7.4	0.50 (0.31-0.80)
TC1/2/3 or IC1/2/3	93	15.1	102	9.2	0.59 (0.41-0.83)
TC0 and IC0	51	9.7	41	9.7	0.88 (0.55-1.42)
Histological subtype					
Squamous	49	10.1	48	8.6	0.66 (0.41-1.05)
Nonsquamous	95	14.8	95	10.9	0.69 (0.49-0.98)

NE = not estimable
[a] Stratified for ITT and unstratified for subgroups.

Secondary endpoints: PFS, ORR and DOR

Table 47: Key efficacy results (primary cutoff – 8 May 2015) - POPLAR

Parameter	docetaxel	atezolizumab
Primary Efficacy Endpoint: Overall Survival (OS)		
ITT Population	n=143	n=144
Patients with event (%)	95 (66.4%)	78 (54.2%)
Median OS (months) (95% CI)	9.7 (8.6, 12.0)	12.6 (9.7, 16.4)
Stratified p–value (log-rank)	0.0404	
Stratified HR (95%CI)	0.73 (0.53, 0.99)	
TC3 or IC3	n=23	n=24
Patients with event (%)	16 (69.6%)	10 (41.7%)
Median OS (months) (95% CI)	11.1 (6.7, 14.4)	15.5 (9.8, NE)
Unstratified p–value (log-rank)	0.0684	
Unstratified HR (95%CI)	0.49 (0.22, 1.07)	
TC2/3 or IC2/3	n=55	n=50
Patients with event (%)	41 (74.5%)	25 (50.0%)
Median OS (months) (95% CI)	7.4 (6.0, 12.5)	15.1 (8.4, NE)
Unstratified p–value (log-rank)	0.0146	
Unstratified HR (95%CI)	0.54 (0.33, 0.89)	
TC1/2/3 or IC1/2/3	n=102	n=93
Patients with event (%)	69 (67.6%)	45 (48.4%)
Median OS (months) (95% CI)	9.2 (7.3, 12.8)	15.5 (11.0, NE)
Unstratified p–value (log-rank)	0.0050	
Unstratified HR (95%CI)	0.59 (0.40, 0.85)	
TC0 and IC0	n=41	n=51
Patients with event (%)	26 (63.4%)	33 (64.7%)
Median OS (months) (95% CI)	9.7 (8.6, 12.0)	9.7 (6.7, 12.0)
Unstratified HR (95%CI)	1.04 (0.62, 1.75)	
Secondary Efficacy Endpoint: Progression-free survival per RECIST v1.1		
ITT Population	n=143	n=144
Patients with event (%)	121 (84.6%)	124 (86.1%)
Median PFS (months) (95% CI)	3.0 (2.8, 4.1)	2.7 (2.0, 4.1)
Stratified HR (95%CI)	0.94 (0.72, 1.23)	
TC3 or IC3	n=23	n=24
Patients with event (%)	20 (87.0%)	20 (83.3%)
Median PFS (months) (95% CI)	3.9 (1.9, 5.7)	7.8 (2.7, 12.3)
Unstratified HR (95%CI)	0.60 (0.31, 1.16)	
TC2/3 or IC2/3	n=55	n=50
Patients with event (%)	50 (90.9%)	43 (86.0%)
Median PFS (months) (95% CI)	2.8 (1.9, 3.9)	3.4 (1.4, 6.9)
Unstratified HR (95%CI)	0.72 (0.47, 1.10)	
TC1/2/3 or IC1/2/3	n=102	n=93
Patients with event (%)	87 (85.3%)	80 (86.0%)
Median PFS (months) (95% CI)	3.0 (2.8, 4.1)	2.8 (2.6, 5.5)
Unstratified HR (95%CI)	0.85 (0.63, 1.16)	
TC0 and IC0	n=41	n=51
Patients with event (%)	34 (82.9%)	44 (86.3%)
Median PFS (months) (95% CI)	4.1 (2.7, 5.6)	1.7 (1.4, 4.2)
Unstratified Hazard Ratio (95%CI)	1.12 (0.72, 1.77)	

Table 47 ctd.

Secondary Efficacy Endpoint: Objective Response Rate per RECIST v1.1		
ITT	n=143	n=144
Responders (%)	21 (14.7%)	21 (14.6%)
95% CI (Clopper-Pearson)	(9.33, 21.57)	(9.26, 21.42)
TC3 or IC3	n=23	n=24
Responders (%)	3 (13.0%)	9 (37.5%)
95% CI (Clopper-Pearson)	(2.78, 33.59)	(18.80, 59.41)
TC2/3 or IC2/3	n=55	n=50
Responders (%)	8 (14.5%)	11 (22.0%)
95% CI (Clopper-Pearson)	(6.50, 26.66)	(11.53, 35.96)
TC1/2/3 or IC1/2/3	n=102	n=93
Responders (%)	17 (16.7%)	17 (18.3%)
95% CI (Clopper-Pearson)	(10.02, 25.34)	(11.02, 27.65)
TC0 and IC0	n=41	n=51
Responders (%)	4 (9.8%)	4 (7.8%)
95% CI (Clopper-Pearson)	(2.72, 23.13)	(2.18, 18.88)
Secondary Efficacy Endpoint: Duration of Response per RECIST v1.1		
ITT	n=21	n=21
Patients with events (PD/death)	16 (76.2%)	9 (42.9%)
Median DOR (months) (95% CI)	7.2 (5.6, 12.5)	14.3 (11.6, NE)
TC3 or IC3	n=3	n=9
Patients with events (PD/death)	2 (66.7%)	6 (66.7%)
Median DOR (months) (95% CI)	13.1 (12.5, 13.8)	11.6 (4.1, 14.3)
TC2/3 or IC2/3	n=8	n=11
Patients with events (PD/death)	6 (75.0%)	6 (54.5%)
Median DOR (months) (95% CI)	12.0 (8.5, 13.8)	11.6 (4.1, NE)
TC1/2/3 or IC1/2/3	n=17	n=17
Patients with events (PD/death)	13 (76.5%)	9 (52.9%)
Median DOR (months) 95% CI	7.2 (5.8, 12.5)	11.9 (5.6, NE)
TC0 and IC0		
Patients with events (PD/death)	3 (75%)	0
Median DOR (months) (95% CI)	7.9 (2.8, NE)	NE (NE)

CI = confidence interval, DOR = duration of response; HR = Hazard Ratio ITT = intent-to-treat, NE = not estimable, PFS = progression-free survival.

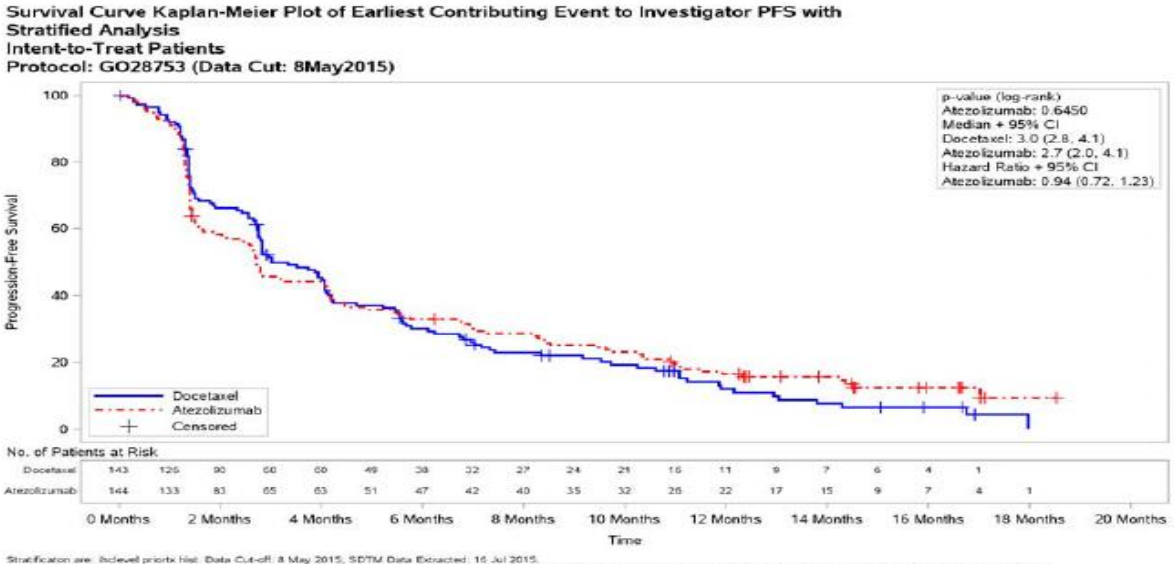
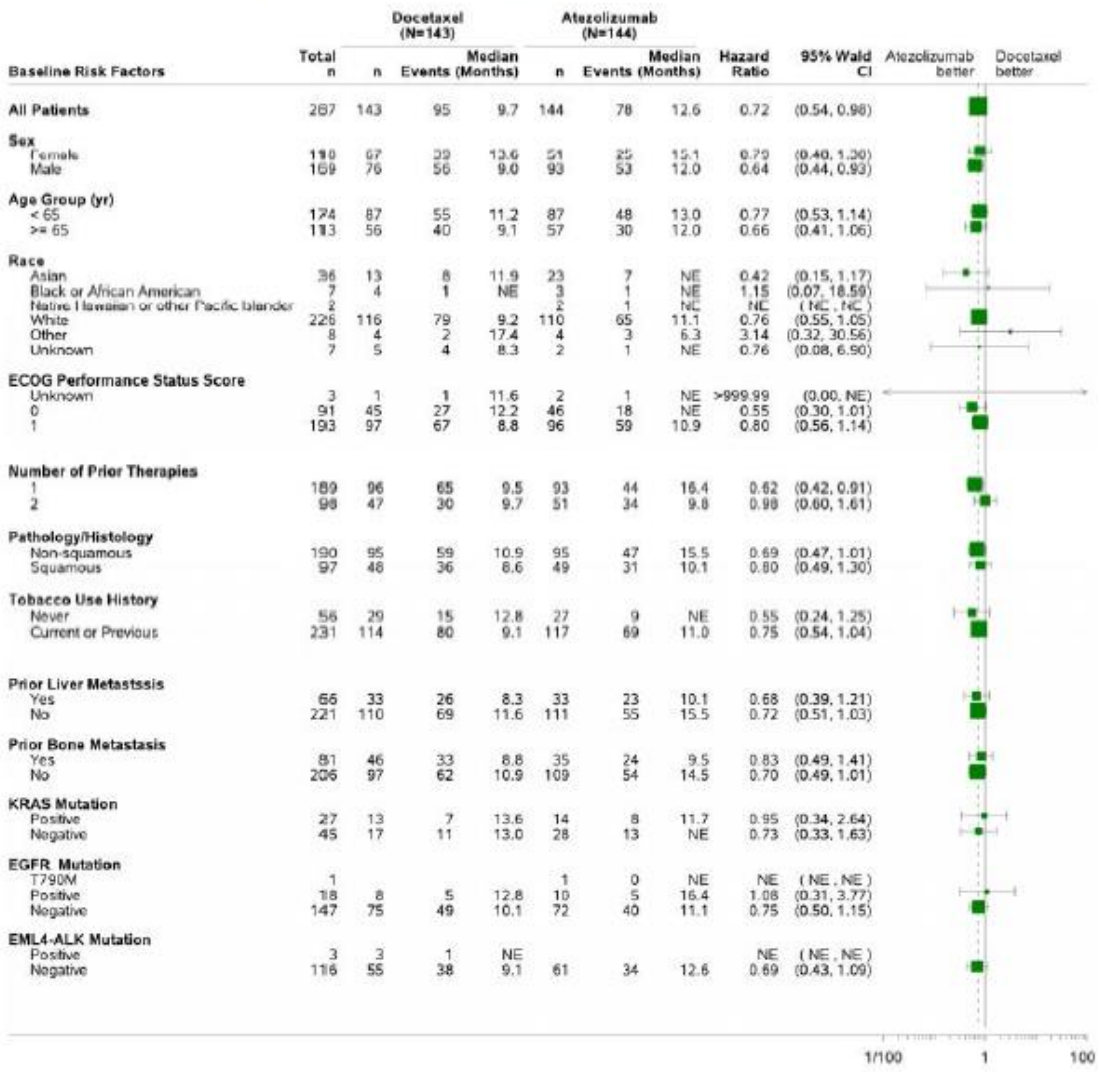


Figure 23: KM plot for PFS (primary analysis – ITT population) – POPLAR

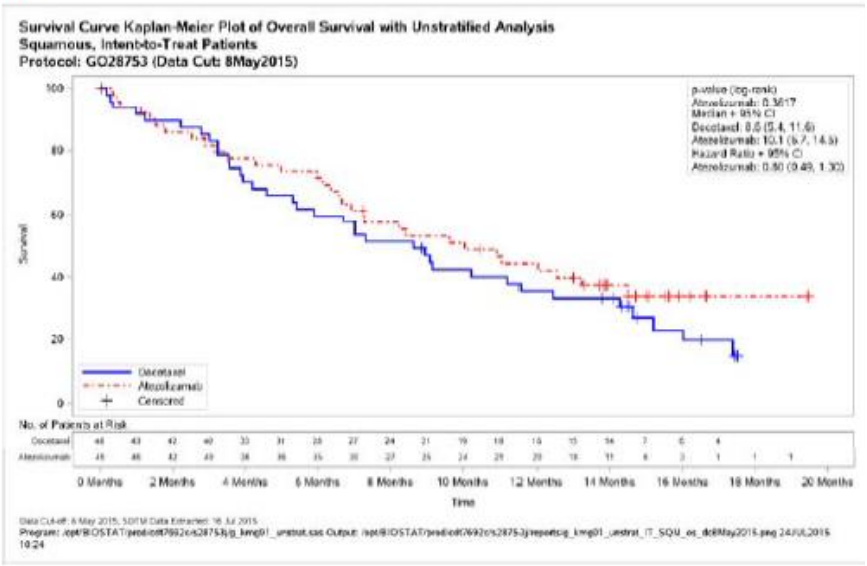
Ancillary analyses



NE = Non-Estimable; Median survival was estimated from Kaplan-Meier method. Unstratified Hazard ratio relative to Docetaxel and 95% CI for the hazard ratio were estimated using Cox regression. The vertical dashed line indicates the hazard ratio for all patients. The diameter of a square is proportional to the square root of the total number of events. Data Cut-off: 8 May 2015; SDTM Data Extracted: 16 Jul 2015.

Figure 24: Forest plot – subgroup analysis of OS (cut-off 8 May 2015) – POPLAR

A. Squamous



B. Non-Squamous

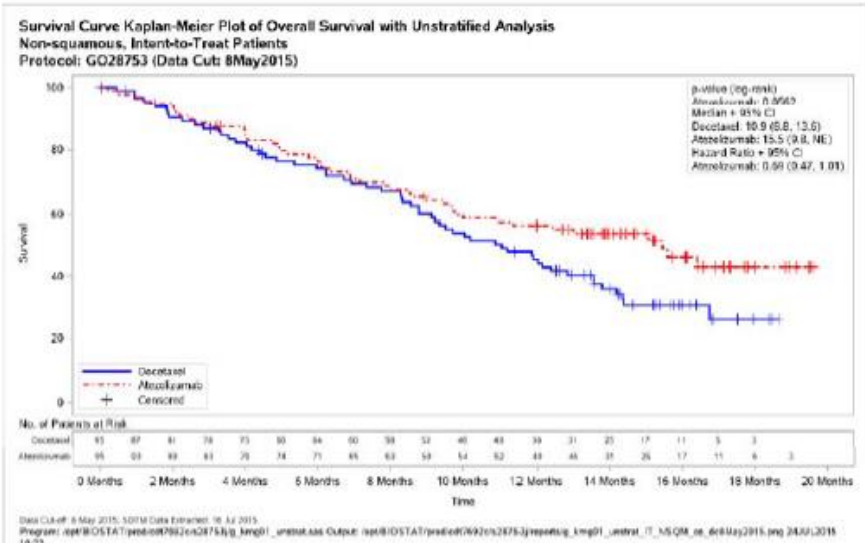


Figure 25: KM plot of OS by histology (primary analysis - ITT population) – POPLAR

Table 48: Duration of OS – squamous vs non-squamous histology (primary analysis - ITT population) - POPLAR

	Docetaxel	Atezolizumab
Squamous	n=48	n=49
Patients with event (%)	36 (75.0%)	31 (63.3%)
Median duration of Survival (months)	8.6	10.1
95% CI	(5.4, 11.6)	(6.7, 14.5)
Unstratified Analysis		
p-value (log-rank)	0.3617	
Hazard Ratio (95%CI)	0.80 (0.49, 1.30)	
Non-Squamous	n=95	n=95
Patients with event (%)	59 (62.1%)	47 (49.5%)
Median duration of Survival (months)	10.9	15.5
95% CI	(8.8, 13.6)	(9.8, NE)
Unstratified Analysis		
p-value (log-rank)	0.0562	
Hazard Ratio (95%CI)	0.69 (0.47, 1.01)	

Table 49: OS by PD-L1 expression level and histology (cut-off 1 Dec 2015) - POPLAR

Population	Atezolizumab		docetaxel		HR[a] 95% CI
	n	Median, mo	n	Median, mo	
ITT	144	12.6	143	9.7	0.69 (0.52-0.92)
PD-L1 subgroup					
TC3 or IC3	24	NE	23	11.1	0.45 (0.22-0.95)
TC2/3 or IC2/3	50	15.1	55	7.4	0.50 (0.31-0.80)
TC1/2/3 or IC1/2/3	93	15.1	102	9.2	0.59 (0.41-0.83)
TC0 and IC0	51	9.7	41	9.7	0.88 (0.55-1.42)
Histological subtype					
Squamous	49	10.1	48	8.6	0.66 (0.41-1.05)
Nonsquamous	95	14.8	95	10.9	0.69 (0.49-0.98)

NE = not estimable
[a] Stratified for ITT and unstratified for subgroups.

Summary of main studies

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 50: Summary of Efficacy for the OAK study

Title: . 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.			
Study identifier	OAK(GO28915)		
Design	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 (OAK)		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	2 years not applicable not applicable	
Hypothesis	Superiority		
Treatments groups	Atezolizumab 1200mg		Treatment IV until loss of benefit, 425 randomized
	Doxetacel 75 mg/m2		Treatment IV until progression or nonacceptable toxicity, 425 randomized
Endpoints and definitions	Primary endpoint	OS	Time from the date of randomization to the date of death due to any cause
	Secondary endpoint	PFS	Interval between date of randomization and date of first documented PD per RECIST v1.1 or death
	Secondary endpoint	ORR per RECIST v1.1	Proportion of patients achieving confirmed best response of CR or PR per RECIST v1.1
	Secondary endpoint	DOR	Interval between first documented objective response (CR or PR) and first documented PD or death
Database lock	19 Aug 2016		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat; TC1/2/3 or IC1/2/3 median follow up: 21.3 months in the docetaxel arm and 21.4 months in the atezolizumab arm		
Descriptive statistics and estimated variability	Treatment group	doxetaxel	atezolizumab
	Number of subject	425	425
	OS (months) median	9.6	13.8
	95% CI	(8.6, 11.2)	(11.8, 15.7)
	PFS (months) median	4.0	2.8
	95% CI	(3.3, 4.2)	(2.6, 3.0)
	ORR (%)	13.4	13.6

	95% CI	(10.32, 17.02)	(10.53, 17.28)
	DOR (time to event, month)	6.2	16.3
	95% CI	(4.9, 7.6)	(10.0, NE)
	Number of subjects	222	241
	OS (TC1/2/3 or IC1/2/3) (months) median	10.3	15.7
	95% CI	(8.8, 12.0)	(12.6, 18.0)
Effect estimate per comparison	Primary endpoint **OS**	Comparison groups	Atezolizumab vs. docetaxel
		HR	0.73
		95% CI	(0.62, 0.87)
		P-value	0.0003
	Secondary endpoint **PFS**	HR	0.95
		95% CI	(0.82, 1.10)
	Secondary endpoint **ORR**	ORR difference (%)	0.24
		95% CI	(-4.36, 4.83)
	Secondary endpoint **DOR**	HR	0.34
		95%CI	(0.21, 0.55)
	Primary endpoint **OS** (TC1/2/3 or IC1/2/3)	Comparison groups	Atezolizumab vs. docetaxel
		HR	0.74
		95% CI	(0.58, 0.93)
		P-value	0.0102
Notes	The co-primary endpoint OS in the ITT population was to be tested on a significance level of 3%, and the second co-primary endpoint OS in the IC/TC 1/2/3 population was to be tested on a significance level of 2%. Secondary endpoints are descriptive only. No error control and hence no confirmation of pre-defined hypothesis was foreseen in the final protocol.		

Table 51: Summary of efficacy for the POPLAR study

Title: A Phase II, open-label, multicenter, randomized study to investigate the efficacy and safety of MPDL3280A (anti−PD-L1 antibody) compared with docetaxel in patients with non−small cell lung cancer after platinum failure.		
Study identifier	POPLAR(GO28753)	
Design	Open-label Phase II trial of intravenous atezolizumab at 1200mg q3w versus docetaxel in subjects with NSCLC who had experienced disease progression after platinum-containing systemic therapy.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	2 years not applicable not applicable
Hypothesis	Superiority	
Treatments groups	Atezolizumab 1200mg	Treatment IV until loss of benefit, 144 randomized
	Doxetacel 75 mg/m2	Treatment IV until progression or nonacceptable toxicity, 143 randomized

Endpoints and definitions	Primary endpoint	OS	Time from the date of randomization to the date of death due to any cause
	Secondary endpoint	PFS	Interval between date of randomization and date of first documented PD per RECIST v1.1 or death
	Secondary endpoint	ORR per RECIST v1.1	Proportion of patients achieving confirmed best response of CR or PR per RECIST v1.1
	Secondary endpoint	ORR per modified RECIST (atezolizumab arm only)	Proportion of patients achieving confirmed or unconfirmed best response of CR or PR per modified RECIST
	Secondary endpoint	DOR	Interval between first documented objective response (CR or PR) and first documented PD or death
Database lock	8 May 2015		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat; median follow up: 15.7 months in the docetaxel arm and 14.8 months in the atezolizumab arm		
Descriptive statistics and estimate variability	Treatment group	doxetaxel	atezolizumab
	Number of subject	143	144
	OS (months) median	9.7	12.6
	95% CI	(8.6, 12.0)	(9.7, 16.4)
	PFS (months) median	3.0	2.7
	95% CI	(2.8, 4.1)	(2.0, 4.1)
	ORR (%) 95% CI	14.7 (9.33, 21.57)	14.6 (9.26, 21.42)
	DOR (time to event, month)	7.2	14.3
	95% CI	(5.6, 12.5)	(11.6, NE)
Effect estimate per comparison	Primary endpoint **OS**	Comparison groups	Atezolizumab vs. docetaxel
		HR	0.73
		95% CI	(0.53, 0.99)
		P-value	0.0404
	Secondary	HR	0.94

	endpoint **PFS**	95% CI	(0.72, 1.23)
		P-value	<P-value>
	Secondary endpoint **ORR**	ORR diference (%)	-0.8
		95% CI	(-8.28, 8.08)
	Secondary endpoint (DOR)	HR	0.41
		95%CI	(0.18, 0.96)

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

In order to evaluate consistency of efficacy across the studies in this application, the following section presents side-by-side comparisons of baseline characteristics and key efficacy results from 2L+ NSCLC patients across all four studies. The populations of these studies are different with respect to patient selection by PD-L1 status, which needs to be taken into consideration when comparing the efficacy data.

Comparison of efficacy results across studies

Table 52: Summary of key efficacy endpoints across studies

	OAK All-comer		POPLAR All-comer		BIRCH PD-L1 selected	FIR PD-L1 selected	PCD4989g NSCLC Cohort All-comer[a]
	docetaxel N=425	atezo N=425	docetaxel N=143	atezo N=144	atezo N=520	atezo N=93	atezo N=88
median survival FU [b] (months, 95% CI)	21.3 (20.6, 21.9)	21.4 (20.8, 21.7)	15.7 (14.6, 16.3)	14.8 (14.0, 15.7)	8.4 (8.2, 8.7)	9.7 (8.1, 12.6)	ND
Overall Survival							
Patients with event (%)	298 (70.1%)	271 (63.8%)	95 (66.4%)	78 (54.2%)	187 (36.0%)	43 (46.2%)	49 (55.7%)
Median OS (months) (95% CI)	9.6 (8.6, 11.2)	13.8 (11.8, 15.7)	9.7 (8.6, 12.0)	12.6 (9.7, 16.4)	NE (11.2, NE)	10.6 (5.7, NE)	16.5 (13.7, 22.0)
HR (95% CI)	0.73 (0.62, 0.87)		0.73 (0.53, 0.99)		N/A	N/A	N/A
6-month OS rate	68.7%	74.9%	69.1%	75.4%	73.4%	58.6%	ND
1-year OS rate (%)	41.1%	54.7%	41.8%	51.6%	55.3%	48.3%	63.1%
ORR per RECIST v1.1							
Responders (%)	57 (13.4%)	58 (13.6%)	21 (14.7%)	21 (14.6%)	90 (17.3%)	15 (16.1%)	20 (22.7%)
95% CI	(10.32, 17.02)	(10.53, 17.28)	(9.33, 21.57)	(9.26, 21.42)	(14.2, 20.8)	(9.3, 25.2)	(14.5, 32.9)
DOR per RECIST v1.1	n=57	n=58	n=21	n=21	n=90	n=15	n=20
Patients with events (PD/death)	47 (82.5%)	28 (48.3%)	16 (76.2%)	9 (42.9%)	33 (36.7%)	2 (13.3%)	12 (60%)
Median DOR (months) (95% CI)	6.2 (4.9, 7.6)	16.3 (10.0, NE)	7.2 (5.6, 12.5)	14.3 (11.6, NE)	8.4 (6.9, NE)	NE (10.4, NE)	17.3 (14.2, 24.7)
PFS per RECIST v1.1							
Patients with event (%)	375 (88.2%)	380 (89.4%)	121 (84.6%)	124 (86.1%)	401 (77.1%)	69 (74.2%)	76 (86.4%)
Median PFS (months) (95% CI)	4.0 (3.3, 4.2)	2.8 (2.6, 3.0)	3.0 (2.8, 4.1)	2.7 (2.0, 4.1)	2.8 (2.7, 2.9)	2.7 (1.5, 3.5)	3.8 (2.6, 10.0)
6-month PFS (%)	29.0%	30.4%	30.1%	33.0%	30.0%	32.3%	45.3%
1-year PFS (%)	10.7%	18.2%	11.9%	16.4%	11.9%	21.5%	30.7%

N/A = not applicable; ND=not done; NE = not estimable.

a patients were initially enrolled as an all-comer population, followed by selective enrollment on the basis of PD-L1 expression.

b Medians of survival FU are Kaplan-Meier estimates (event=date last known to be alive; deaths are censored). 95% CI computed using method of Brookmeyer and Crowley.

ORR, DOR and PFS were IRF-assessed for BIRCH (investigator-assessed for other studies)

Sources: OAK CSR: Table 8, Table 23, Table 37 (Data cutoff: 7 July 2016); POPLAR CSR: Table 10, Table 21 (Data cutoff: 8 May 2015); BIRCH CSR: Table 9, Table 17 (Data cutoff: 28 May 2015); FIR CSR: Table 7, Table 14 (Data cutoff: 7 January 2015);

Table 53: Analysis of ORR by demographic and baseline characteristics in BIRCH and POPLAR studies

	BIRCH			POPLAR					
	n	ORR[b]	95% CI	docetaxel		atezolizumab		Odds ratio	95% CI
				n	ORR[c]	n	ORR[c]		
All	520	90 (17.3)	14.2, 20.8	143	21 (14.7)	144	21 (14.6)	0.99	0.52,1.91
Age, yrs									
< 65	276	44 (15.9)	11.8, 20.8	87	11 (12.6)	87	11 (12.6)	1.00	0.41,2.45
≥ 65	244	46 (18.9)	14.2, 24.3	56	10 (17.9)	57	10 (17.5)	0.98	0.37,2.57
Gender									
Female	203	32 (15.8)	11.0, 21.5	67	14 (20.9)	51	6(11.8)	0.50	0.18,1.42
Male	317	58 (18.3)	14.2, 23.0	76	7 (9.2)	93	15 (16.1)	1.90	0.73,4.92
Race [a]									
White	428	77 (18.0)	14.5, 22.0	116	14 (12.1)	110	19 (17.3)	1.52	0.72,3.21
Asian	66	9 (13.6)	6.4, 24.3	13	2 (15.4)	23	1 (4.3)	0.25	0.02,3.07
ECOG PS									
0	173	40 (23.1)	17.1, 30.1	45	7 (15.6)	46	11 (23.9)	1.71	0.60,4.89
1	342	48 (14.0)	10.5, 18.2	97	14 (14.4)	96	10 (10.4)	0.69	0.29,1.64
Histology									
Non-Squamous	368	73 (19.8)	15.9, 24.3	95	17 (17.9)	95	14 (14.7)	0.79	0.37,1.72
Squamous	152	17 (11.2)	6.7, 17.3	48	4 (8.3)	49	7 (14.3	1.83	0.50,6.72
Smoking status									
Current/ previous	429	81 (18.9)	15,3, 22.9	114	14 (12.3)	117	21 (17.9)	1.56	0.75,3.25
Never	91	9 (9.9)	4.6, 18.0	29	7 (24.1)	27	0	NE<0 .01	0.00, NE

2L+ = second-line and beyond; ECOG PS = Eastern Cooperative Oncology Group performance status; IC = tumor-infiltrating immune cell; ORR = objective response rate; TC = tumor cell.

[a] Other races (Black or African American, Multiple, Unknown) had small numbers of patients and are not included here.

[b] Assessed by Independent Review Facility per RECIST v1.1

[c] Assessed by investigator per RECIST v1.1

Clinical studies in special populations

Atezolizumab has not been investigated in a paediatric patient population or patients with moderate or severe hepatic impairment or patients with severe renal impairment. This is reflected in the SmPC section 4.2.

Table 54: Elderly patients included in the efficacy trials

Study	< 65 Years	65–74 Years	75–84 Years	85 + Years
Uncontrolled studies				
FIR	54/128	47/128	25/128	2/128
BIRCH	329/652	223/652	91/652	9/652
Controlled studies				
POPLAR	85/140	43/140	12/140	—
OAK	327/596	194/596	74/596	1/596

Supportive studies

- **BIRCH (GO28754): A Phase II, Multicenter, Single-Arm Study of MPDL3280A in Patients with PD-L1-Positive Locally Advanced or Metastatic Non-Small Cell Lung Cancer.**

The primary objective was to evaluate the efficacy of atezolizumab in patients with PD-L1 selected patients with locally advanced or metastatic NSCLC as measured by the Independent Review Facility (IRF)-assessed ORR according to RECIST v1.1.

The primary endpoint was IRF-assessed ORR per RECIST v1.1. The key secondary endpoints included investigator (INV)- assessed ORR, DoR, PFS and TIR per RECIST v1.1 and per modified RECIST. IRF-assessed DOR, PFS, TIR per RECIST v1.1; PFS rate at 6 months and 1 year; OS, OS rate at 6 months and 1 year.

In BIRCH, the efficacy analysis of the primary efficacy outcome measure, comparison of ORRs to historic controls (per data available in 2013, Massarelli et al. 2003, Younes et al. 2011, Zietemann and Duell 2011), followed a hierarchical fixed sequence procedure. In each of the seven sub-populations, the IRF-assessed ORR according to RECIST v1.1 was sequentially tested at a two-sided alfa-level of 0.05. The overall type I error rate was controlled at a two-sided alfa-level of 0.05.

Study participants:

For inclusion/exclusion criteria, please refer to Table 23.

Treatment:

The dose level of atezolizumab in this study was 1200 mg every 3 weeks (q3w) administered by IV infusion.

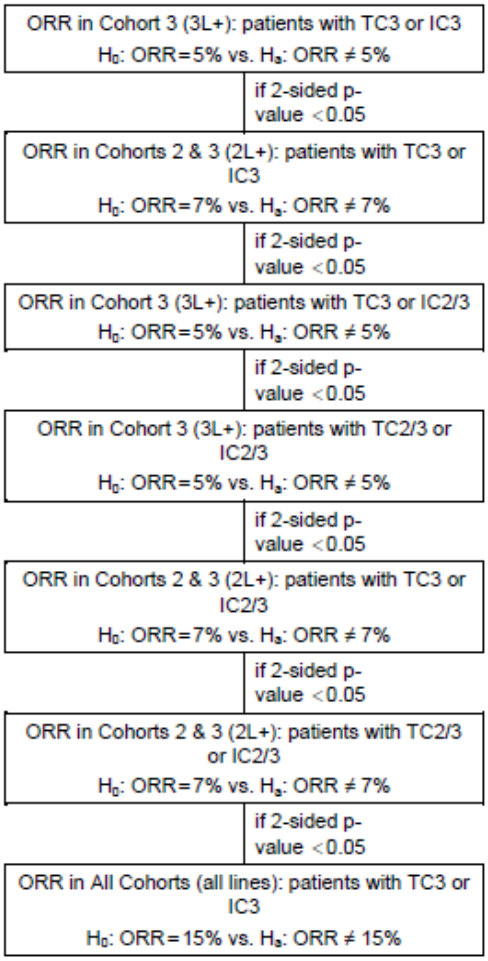
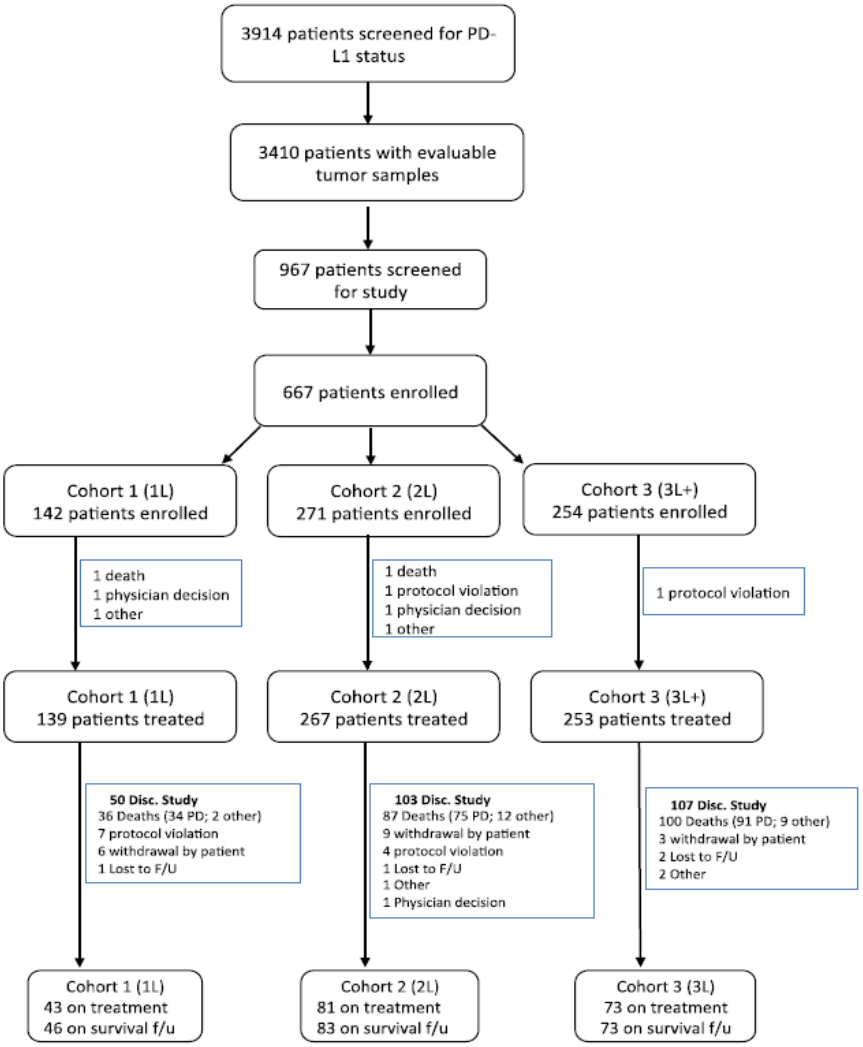


Figure 26: Protocol-specified hierarchical fixed-sequence testing procedure in BIRCH

Patient disposition



1L = first-line; 2L = second line; 3L + = third-line and beyond; F/U = follow up; PD = progressive disease; PD-L1 = programmed death – ligand 1.

Figure 27: Patient disposition in study GO28754 (BIRCH)

Baseline characteristics

Patients in the study were predominantly male (59%) and White (83%). Asians accounted for 12% of the overall population. The median age of the study population was 64 years (range 28-88 years). The majority of patients had a history of tobacco use; 72% were previous smokers and 11% were current smokers. Approximately 64% had a baseline ECOG PS of 1.

With respect to disease characteristics, the predominant histologic type was non-squamous NSCLC (72%), 33% had a *KRAS* mutation, 12% had an *EGFR* mutation, and 2% had EML4-ALK rearrangement

Efficacy results

Table 55: Summary of results for primary and key secondary efficacy endpoints (primary analysis), treated patients - BIRCH

Efficacy Endpoint		Cohort 2 (2L) N=267	Cohort 3 (3L+) N=253	Cohorts 2+3 (2L+) N=520
TC2/3 or IC2/3		n=267	n=253	n=520
IRF ORR [a]	Responders (%)	46 (17.2%)	44 (17.4%)	90 (17.3%)
	95% CI	(12.9, 22.3)	(12.9, 22.6)	(14.2, 20.8)
IRF-DOR [a]	Patients with events (PD or death)	19/46 (41.3%)	14/44 (31.8%)	33/90 (36.7%)
	Median (months) 95% CI	8.4 (6.9, NE)	8.4 (5.7, NE)	8.4 (6.9, NE)
IRF-PFS [a]	Patients with events (PD or death)	201 (75.3%)	200 (79.1%)	401 (77.1%)
	Median (months) (95% CI)	2.8 (1.5, 3.5)	2.8 (2.7, 3.7)	2.8 (2.7, 2.9)
	6-month PFS rate	28.9%	31.2%	30.0%
	12-month PFS rate	15.9%	6.8%	11.9%
OS	Patients with events (death)	87 (32.6%)	100 (39.5%)	187 (36.0%)
	Median (months) (95% CI)	NE (11.2, NE)	NE (8.4, NE)	NE (11.2, NE)
	6-month survival rate	76.2%	70.5%	73.4%
	12-month survival rate	57.2%	54.4%	55.3%
TC3 or IC3		n=122	n=115	n=237
IRF ORR [a]	Responders (%)	29 (23.8%)	31 (27.0%)	60 (25.3%)
	95% CI	(16.5, 32.3)	(19.1, 36.0)	(19.9, 31.4)
IRF-DOR [a]	Patients with events (PD/death)	11/29 (37.9%)	12/31 (38.7%)	23/60 (38.3%)
	Median (months) (95% CI)	NE (4.9, NE)	7.2 (5.6, NE)	7.2 (5.7, NE)
IRF-PFS [a]	Patients with events (PD or death)	83 (68.0%)	84 (73.0%)	167 (70.5%)
	Median (months) (95% CI)	4.1 (1.8, 5.5)	4.2 (2.8, 5.6)	4.1 (2.8, 5.4)
	6-month PFS rate	34.5%	38.9%	36.7%
	12-month PFS rate	24.6%	9.1%	16.8%
OS	Patients with events (death)	36 (29.5%)	38 (33.0%)	74 (31.2%)
	Median (months) (95% CI)	NE (10.6, NE)	NE (NE)	NE (12.1, NE)
	6-month survival rate	79.7%	75.1%	77.4%
	12-month survival rate	61.5%	62.6%	61.3%

DOR = Duration of Response; INV = Investigator; IRF = Independent Review Facility; NE = not estimable; PFS = Progression-Free Survival;
[a] ORR/DOR/PFS as assessed per RECIST v1.1

- **FIR: A phase II, multicentre, single-arm study of atezolizumab in patients with PD-L1 positive locally advanced or metastatic NSCLC.**

The main objective of the study was to assess the clinical activity of atezolizumab, as measured by the investigator-assessed ORR per modified RECIST, in patients with PD-L1-positive locally advanced or metastatic non-small cell lung cancer.

The secondary objectives were to estimate the ORR based on investigator assessment per RECISTv1.1, to assess the DOR, to estimate the PFS and estimate the OS.

Study participants:

Study FIR enrolled patients with locally advanced and metastatic NSCLC with PD-L1 expressing tumors and measurable disease at baseline assessed per RECIST v1.1 and ECOG PS of 0 or 1. Disease was progressing since the last antitumor therapy. Patients had either not received prior chemotherapy for advanced disease (Cohort 1), or had progressed during or following a prior platinum-based chemotherapy regimen for advanced disease (2L+; Cohort 2) or were 2L+ and previously treated for brain metastases.

Treatment:

The dose level of atezolizumab in this study was 1200 mg every 3 weeks (q3w) administered by IV infusion.

Patients remained on study treatment as long as they continued to experience clinical benefit (or occurrence of unacceptable toxicity or symptomatic deterioration attributed to radiographic PD).

Analysis population:

The analyses of ORR, PFS, OS have been performed on all treated patients, i.e., all patients who received any dose of atezolizumab during the study treatment period (efficacy-evaluable population). DOR and TTOR have been assessed in all treated patients with objective response (efficacy-evaluable population with objective response).

Patient disposition:

At the time of the data cutoff (7 January, 2015), a total of 28 patients (7 in Cohort 1, 21 in Cohort 2) were continuing to receive treatment with atezolizumab. All 13 patients in Cohort 3 had withdrawn from study treatment. The primary reason for discontinuation from treatment remained progression of disease (59,8% [82/137 patients]).

Baseline characteristics:

Baseline characteristics of patients enrolled in the study were representative of the general population of patients with advanced NSCLC. Patients in the study were predominantly male (57.7%) and White (89.1%). The median age of the study population was 66 years (range 42-85 years). The majority of patients had a history of tobacco use with 73.0% being previous smokers and 13% current smokers. Approximately 70% had a baseline ECOG PS of 1. The predominant histologic type was non-squamous NSCLC (72.3%).

To support the claimed indication, an interim analysis of FIR study was provided.

Table 56: Summary of Key for Cohort 2 (2L+) Patients by PD-L1 Expression Subgroup, Treated Patients Efficacy Results

	TC3 or IC3	TC2/3 or IC2/3 (i.e., all patients)
ORR (95% CI) By Modified RECIST (95%CI) By RECIST v1.1 (95%CI)	n=38 10 (26.3%) (13.4, 43.1) 9 (23.7%) (11.4, 40.2)	n=93 16 (17.2%) (10.2, 26.4) 15 (16.1%) (9.3, 25.2)
DOR by RECIST v1.1 Patients with events (PD or death) Median DOR (months) (95% CI)	n=9 1 (11.1%) NE (10.4, NE)	n=15 2 (13.3%) NE (10.4, NE)
TTOR by RECIST v1.1 Median TTOR (months) (95% CI)	n=9 1.4 (1.4, 2.6)	n=15 2.6 (1.4, 2.7)
PFS by RECIST v1.1 Patients with events Median PFS (months) (95% CI)	n=38 25 (65.8%) 4.1 (1.5, 12.9)	n=93 69 (74.2%) 2.7 (1.5, 3.5)
6-month OS rate	42.47%	32.29%
12-month OS rate	34.07%	21.45%
Overall Survival (OS) Patients with events Median OS (months) (95% CI) 6-month OS rate 12-month OS rate	n=38 14 (36.8%) NE (5.8, NE) 62.99% 59.99%	n=93 43 (46.2%) 10.6 (5.7, NE) 58.59% 48.28%

In line with above mentioned study results higher PD-L1 expression was associated with higher ORR in the FIR study: the TC3 or IC3 subgroup had the highest ORR (26.3% per modified RECIST and 23.7% per RECIST v1.1 vs. 17.2% per modified RECIST and 16.1% per RECIST v1.1 in TC2/3 or IC2/3). Restrictions are the limited duration of follow-up and immature OS and DOR data.

- **PCD4989G**

Study PCD4989g is an ongoing Phase Ia, multicenter, first-in-human, open-label, dose-escalation study to evaluate the safety, tolerability, and PK of atezolizumab administered as a single agent by IV infusion q3w to patients with locally advanced or metastatic solid malignancies, including NSCLC.

Study participants:

Study PCD4989g NSCLC Cohort enrolled patients with locally advanced and metastatic or recurrent NSCLC, with measurable disease at baseline assessed per RECIST v1.1 and ECOG PS of 0 or 1. Disease was progressing since the last antitumor therapy.

The initial recruitment of patients into this dose expansion cohort was based on high PD-L1 expression as assessed by IHC (i.e., IC2/3) status. Once an efficacy signal was observed, recruitment was expanded to an all IC status population. Later, in order to have a more precise estimate of the ORR in the IC2/3 subset, enrolment was again limited to IC2/3 status. Due to the resultant enrichment of IC2/3 status, the prevalence of PD-L1 IC scores in the study population did not reflect the natural prevalence in patients with NSCLC.

Treatment:

Atezolizumab IV infusion q3w at ≤1mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg. Overall, 88 patients received a weight-based dosing.

Patients remained on study treatment as long as they continued to experience clinical benefit (or occurrence of unacceptable toxicity or symptomatic deterioration attributed to radiographic PD).

Analysis populations:

The primary analysis population identified for the NSCLC indication was the safety-evaluable population, which comprised all enrolled patients who received any amount of atezolizumab (n = 88) as of 2 December 2014. Analyses of ORR were performed on the objective response (OR)-evaluable population (efficacy evaluable population [received dose of ≥ 1 mg/kg] with measurable disease per RECIST v1.1 at baseline for PCD4989g).

Efficacy Endpoints

The primary efficacy endpoint for NSCLC was confirmed ORR assessed by INV-RECIST v1.1. Secondary endpoints comprised BOR (unconfirmed), DOR, 6-month PFS, 1-year PFS per RECIST v1.1; and 1-year OS. Exploratory endpoints comprised PFS, TIR, PFS in responders; TTOR, per RECIST v1.1; and OS.)

Patient disposition:

At the time of the 7 August 2015 clinical data cutoff for the updated efficacy analysis, 89.8% of the patients in the NSCLC cohort (79/88patients) were no longer receiving atezolizumab. The primary reason for discontinuation from treatment remained disease progression (58.0% [51/88 patients], at the 2 December 2014 clinical data cut.

Baseline characteristics:

Baseline characteristics were also representative of patients with poor prognostic factors inclusive of ECOG PS of 1 (71.6% of patients), smokers (81%, current or previous), and heavily pretreated (56.8% had received ≥ 3 prior lines of therapy). Of those patients tested, EGFR mutations were documented in 10 of 64 patients, KRAS in 14 of 51 patients, and EML4-ALK translocations in 2 of 46 patients.

Baseline characteristics are comparable between POPLAR and Study PCD4989g besides the number of prior systemic regimens in the metastatic setting. Patients in the Phase I trial were more heavily pre-treated (98% of ≥2 lines compared to 35.4% in Cohort 2 of POPLAR).

Efficacy results

The NSCLC tumour response results as of 2 December 2014 based on the 88 OR-evaluable patients, inclusive of the primary and sensitivity analyses of the primary efficacy endpoints and secondary efficacy endpoints, are presented in the Table below.

Table 57: Supportive Study PCD4989g: Summary of Efficacy Results in All lines of Therapy (1L, 2L, and 3L+) by PD-L1 Expression Subgroup, Treated Patients) (Data Cutoff of 2 December 2014)

Key Efficacy Endpoints	TC3 or IC3 (n = 22)	TC2/3 or IC2/3 (n = 48)	TC0/1 and IC0/1 (n = 32)	All Patients (n = 88)
ORR (95% CI) [a]	11 (50.0%) (28.2, 71.8)	16 (33.3%) (20.4, 48.4)	4 (12.5%) (3.5, 28.9)	20 (22.7%) (14.5, 32.9)
DOR	n=11	n=16	n=4	n=20
Median DOR (months) (95% CI) [a]	14.6 (8.7, 25.3)	17.3 (14.2, NE)	18.2 (9.9, 24.7)	17.3 (14.2, 24.7)
Patients with ongoing response	5 (45.5%)	8 (50.0%)	0	8 (40%)
PFS				
Patients with events (PD or death)	17 (77.3%)	39 (81.3%)	30 (93.8%)	76 (86.4%)
Median PFS (months) (95% CI) [a]	7.1 (1.4, 17.3)	2.8 (1.9, 10.1)	4.8 (1.4, 11.6)	3.8 (2.6, 10.0)
1-year PFS rate	50.0%	41.6%	46.7%	45.3%
OS				
Patients who died	10 (45.4%)	24 (50.0%)	20 (62.5%)	49 (55.7%)
Median OS (months) (95% CI)	17.9 (14.5, NE)	17.9 (14.1, NE)	14.2 (8.0, 22.0)	16.5 (13.7, 22.0)
I-year OS rate	70.3%	66.2%	56.7%	63.1%

Confirmed and unconfirmed response rates are increasing with the level of PD-L1 expression (TC3/IC3 vs TC2/3/IC2/3 vs TC0/1/IC0)) compared to low PD-L1 expression across all analysis. Response was durable. The median DOR per investigator assessed RECIST v1.1 for the 20 responders was 17.3 months (95% CI: [14.2, 24.7]), and 8 of the 20 responders continued to respond. The median DOR was similar across all PD-L1 expression subgroups: 14.6 months (TC3 or IC3), 17.3 months (TC2/3 or IC2/3).

2.5.3. Discussion on clinical efficacy

Two pivotal (BIRCH and POPLAR) and two supportive studies (FIR and PCD4989G) were initially provided in support of the sought indication (*Atezolizumab is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy).* During the procedure the primary results from the OAK study were also provided and assessed. The proposed posology is 1200 mg administered by IV infusion q3w. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

Design and conduct of clinical studies

The BIRCH and FIR study included PD-L1 selected patients across a range of lines (1L, 2L, 3L+), while the OAK, POPLAR and FIR study enrolled patients with locally advanced or metastatic disease that had progressed during or following a platinum-containing regimen, regardless of their PD-L1 expression. Furthermore, patients with EGFR mutation and ALK oncogene were also included.

The BIRCH and FIR were single-arm studies with ORR as primary endpoint. ORR is a suitable endpoint for single-arm studies, and can be assessed earlier, compared to other endpoint, e.g. OS and PFS. Also, the observed effect is directly associated to the investigated drug.

The OAK and POPLAR studies are a two-arm, open-label, randomised phase III and II studies respectively. Primary endpoint is OS in both studies. Few and clinically meaningful stratification factors have been applied. This is endorsed. Docetaxel is an adequate comparator for second line treatment, the open-label design is considered acceptable with regard to overall survival as primary endpoint.

In the OAK study, it seems that about 50 % of the patients were ALK mutation positive. A proportion of less than 5 % would rather be expected (as observed in POPLAR, BIRCH, FIR and PCD4989g). The Applicant is asked to clarify.

The Applicant has used "permuted-block randomization". Despite large and randomly varied block sizes, this randomization procedure can still lead to bias, if the number of patients is small, thus, leading to imbalance in factors that are not included in the stratification. However, since the most important clinical factors are included in the stratification, there are no major concerns about the use of permuted-block randomization in the POPLAR and OAK studies.

The Applicant has included several secondary and efficacy endpoints in the pivotal studies, including "biomarker analyses" and PRO data.

Immune checkpoint inhibitors may require additional time to confirm a measurable or clinical effects compared with traditional cytotoxic chemotherapy (Chiou et al. 2015, JCO). In order to avoid cases of pseudo-progression, which is a recognized problem with PD-L1 check point inhibitors, the Applicant has implemented modified RECIST criteria. This is endorsed. A consecutive assessment is conducted ≥ 4 weeks from the date first documented. This consecutive assessment should be able to detect cases of pseudo-progression.

The Applicant has based the pre-specified historical control rate (BIRCH study) on previously published studies in 1L and 2L as seen in the below table. The Applicant clarifies that the wording of "5% to 30%" in the study protocol refers to an increase from 5% (assumed historical control rate in the 3L setting which can be as low as 2%) (Massarelli et al. 2003) to 30% (expected ORR with the treatment of atezolizumab) and not to the range of the historical control rate. A large number of patients (3914) were screened for PD-L1 status, but only 967 were screened for study and 667 patients were included and the Applicant was asked to clarify the apparent large difference in patients screened for PD-L1 status and the actual number of patients screened for study. The reason for the large pre-screen failure rate (56%) was mostly due to negative or non-evaluable PD-L1 status and no tissue provided. The screen failure of 300 patients were primarily driven by the following: PD-L1 status not confirmed, brain metastases, in- and exclusion criteria not met. These reasons are understandable and acceptable in the context of the targeted patient population The Applicant changed the planned analyses, and did not generate waterfall plots showing the best change in SLD. However, these data were provided upon request and the waterfall plots show that the treatment of atezolizumab is active in many patients and even a few CRs were observed. The inclusion/excl. criteria and thus the included patient population support the sought indication.

In the OAK study, the primary analysis was planned (according to SAP v2) when in the PP population, 595 deaths have occurred. This is, however, not in line with the actual timing of the analysis which was conducted after 569 events, i.e., 26 events earlier than the pre-planned timing. Additional analysis (based on 595 events) did not indicate a major impact of the early stopping on study results.

Protocol GO28915 (V6) was amended for the final statistical analysis strategy on 28.01.2016 when all patients were already randomized following an amended SAP (V2) dated 10.12.2015. The additional analysis for the ITT population of the first 850 randomized patients with a data cutoff per 10 Dec 2015 did not reveal a relevant difference to the primary analysis provided in the CSR.

Efficacy data and additional analyses

Response rates in the range of 17% to 27% are observed in cohort 2 and 3 (2L and 3L respectively) in the BIRCH study. Compared to historical control rates, the results are statistically highly significant. However, it is not evident, how the Applicant has determined to the historical response rates in the different TC and IC subgroups. The Applicant was asked to clarify.

The pivotal study OAK showed a median OS for atezolizumab of 13.8 months vs. 9.6 months for docetaxel and a HR of 0.73 (95%CI: 0.62, 0.87, p<0.0003) for the overall population.

The study POPLAR showed a median OS for atezolizumab of 12.6 months vs. 9.7 months for docetaxel and a HR of 0.73 (95%CI: 0.56, 0.80, p<0.0404) for the overall population.

In the POPLAR study, the subgroup analysis show consistent results across most subgroups. This is reassuring. It is noted that the effect of atezolizumab seems to be independent of sex, age and ECOG, but the effect seems to be comparable to docetaxel in the subgroup of patients that have received one prior line of therapy compared to patients having received 2 prior lines of therapy. Updated analyses confirm, similar to the primary analysis, that only patients in the atezolizumab arm with one prior therapy had improved survival over those in the docetaxel arm (unstratified HR of 0.56, 95% CI: 0.39, 0.79). OS benefit was not significant for patients with two prior therapies, but the study is not powered for this subgroup analysis, hence, this result may not be valid and should not be reflected in the approved indication. Also, the effect of atezolizumab seems to be higher in non-squamous in the primary analysis. The HR in the squamous subgroup is 0.8, but the 95%CI (0.49, 1.30) is wide as result of low number of patients in this subgroup. However, the updated analyses (cut-off 1. Dec 2015) of OS by histology shows that the HR has improved to 0.66 (95%CI; 0.41, 1.05).

In the OAK study, both squamous and non-squamous histology subgroups, the TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3, and TC0 and IC0 subgroups treated with atezolizumab showed OS improvement compared with patients treated with docetaxel. Across all PD-L1 expression subgroups defined by different TC or IC cutoffs, the point estimates of the HRs for OS were equal to or below 0.82**.**

Nonetheless, when taking into account the TCO/IC0 subgroup the visual inspection of OS survival curves shows a separation of the curves beyond 3 months with a trend to further increased differences at subsequent time points. Thus, it was considered that the data were still immature and the Applicant was asked to present updated data for better understanding of the time dependent effect. The OS results at the update were similar to those from the primary analysis.

Antibodies (ATA)

Key efficacy endpoints, including ORR and DOR in all four studies and OS and PFS in POPLAR, were also analyzed in relation to ATA status (data not shown). Overall, there was no clinically relevant impact of ATA on efficacy**.**

HRQoL

Prolonged time to deterioration of patient reported pain in chest as measured by the EORTC QLQ LC13 was observed with atezolizumab compared to docetaxel in the OAK study. The time to deterioration in

other lung cancer symptoms (i.e. cough, dyspnoea, and arm/shoulder pain) as measured by the EORTC QLQ LC13 was similar between atezolizumab and docetaxel. These results should be interpreted with caution due to the open-label design of the study.

2.5.4. Conclusions on the clinical efficacy (NSCLC)

Taken together the overall results of the OAK and POPLAR studies have demonstrated clinically meaningful improvement of OS compared to docetaxel in adult patients with advanced NSCLC who have disease progression on or after prior chemotherapy. These results are further supported by supportive studies. The effect of atezolizumab appears dependent on PD-L1 expression level, histology and the number of prior therapies.

2.6. Clinical efficacy – Urothelial Carcinoma (UC)

The submission for UC is based on the analysis of the efficacy and safety data from:

- IMvigor 210 (GO29293): a pivotal single-arm phase II study in patients with locally advanced or metastatic urothelial (bladder) cancer (UC) for the metastatic urothelial carcinoma indication;

- IMvigor 211 (Study GO29294): a randomized phase III study comparing atezolizumab monotherapy to chemotherapy [investigator's choice of one of vinflunine or a taxane such as paclitaxel or docetaxel] in second-/third-line patients with UC).

- Supportive data from one phase Ia study PCD4989g (GO27831) conducted in patients with locally advanced or metastatic malignancies (including a cohort of patients with urothelial carcinoma)

The proposed recommended dosage for atezolizumab in the treatment of UC is a fixed flat dose of 1200 mg, every 3 weeks (q3w).

2.6.1. Dose response studies

As described in section 2.5.1., the fixed dose of 1200 mg was selected on the basis of both nonclinical studies and available clinical data from Study PCD4989g. The atezolizumab dose was also informed by available clinical activity, safety, PK, and immunogenicity (ATA) data. No statistically significant Exposure- Response (ER) relationships were identified with ORR as assessed by an IRF using RECIST v1.1 following atezolizumab 1200 mg q3w in IMvigor 210, Cohorts 1 and 2.

- These results suggest no improved efficacy would be expected with atezolizumab doses higher than 1200 mg q3w.
- None of the fold-changes in atezolizumab exposure associated with the statistically-significant covariates identified with the popPK model (body weight, gender, ATA, albumin, and tumor burden) would be expected to be clinically meaningful or require dose adjustment.
- The fold-reduction in atezolizumab exposure when evaluated at extreme values (i.e., 90th percentile) of weight compared to the typical patient following administration of the atezolizumab 1200 mg q3w flat dose would not be expected to be clinically meaningful or require dose adjustment by body size.

Urothelial Carcinoma Exposure-Safety Relationship

- No statistically significant ER relationships were identified with AEG35 or AESIs following atezolizumab 15 mg/kg and 1200 mg q3w in patients with UC in the Phase Ia Study PCD4989g and in the Phase II Study IMvigor 210 (Cohort 1 and Cohort 2).
- These results suggest no improved safety would be expected with atezolizumab doses lower than 1200 mg q3w.
- None of the fold-changes in atezolizumab exposure associated with the statistically significant covariates identified with the popPK model (body weight, gender, ATA, albumin, and tumour burden) would be expected to be clinically meaningful or require dose adjustment.
- The fold-elevation in atezolizumab exposure when evaluated at extreme values (i.e., 10th percentile) of weight compared to the typical patient following administration of the atezolizumab 1200 mg q3w flat dose would not be expected to be clinically meaningful or require dose adjustment by body size.

2.6.2. Main studies

- IMvigor 210 (GO29293) which is the pivotal study is a single-arm open-label Phase II study in patients with locally advanced or metastatic urothelial (bladder) cancer (UC) for the metastatic urothelial carcinoma indication.
- IMvigor 211 (Study GO29294) is a Phase III Study (a randomized study that compares atezolizumab monotherapy versus chemotherapy [investigator's choice of one of vinflunine or a taxane such as paclitaxel or docetaxel] in second-/third-line patients with UC).

IMvigor 210 (GO29293)

Methods

Study participants

Main Inclusion Criteria

- Patients with histologically or cytologically documented locally advanced inoperable (T4b, any N; or any T, N 2−3) or metastatic (M1, Stage IV) transitional cell carcinoma of the urothelium (including renal pelvis, ureters, urinary bladder, urethra)
- Representative tumour specimen evaluable for PD-L1 expression by IHC (PD-L1 unselected)
- Adequate haematologic and end-organ function, calculated creatinine clearance ≥ 30 mL/min
- Measurable disease at baseline by RECIST v1.1
- Life expectancy ≥ 12 weeks

Specific for Cohort 1 [1L cis-ineligible UC]:

- No prior chemotherapy for inoperable locally advanced or metastatic or recurrent urothelial carcinoma:

    - For patients who received prior adjuvant/neoadjuvant chemotherapy or chemoradiation for urothelial carcinoma, a treatment-free interval >12 months between the last treatment administration and the date of recurrence was required in order to be considered treatment-naive in the metastatic setting.
    - Prior local intravesical chemotherapy or immunotherapy was allowed if completed at least 4 weeks prior to the initiation of study treatment.
- Ineligible ("unfit") for cisplatin-based chemotherapy as defined by any one of the following criteria:
    - Impaired renal function (GFR > 30 but < 60 mL/min);
    - A hearing loss of 25 dB at two contiguous frequencies;
    - Grade ≥ 2 peripheral neuropathy;
    - ECOG of 2
- Performance status ECOG PS of 0, 1 or 2

Specific for Cohort 2 [2L+ UC]:

- Disease progression during or following treatment with at least one platinum-containing regimen (containing either cisplatin or carboplatin e.g., GC, MVAC, CarboGem) for inoperable locally advanced or metastatic urothelial carcinoma or disease recurrence
    - A regimen was defined as patients receiving at least two cycles of a platinum-containing regimen. Patients who had received one cycle of platinum-containing regimen but discontinued due to Grade 4 hematologic toxicity or Grade 3 or 4 non-hematologic toxicity (defined as intolerant to platinum-containing regimen) could also be eligible.
    - Patients who received prior adjuvant/neoadjuvant chemotherapy and progressed within 12 months of treatment with a platinum-containing adjuvant/neoadjuvant regimen were considered as second-line patients.
- Performance status ECOG PS of 0 or 1

Key Exclusion Criteria

- Active or untreated CNS metastases
- History of autoimmune disease;
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications
- History of idiopathic pulmonary fibrosis, organising pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies or treatment with systemic corticosteroids or other systemic immunosuppressive medications
- Uncontrolled tumour-related pain
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
- Uncontrolled hypercalcemia
- Serum albumin < 2.5 g/dL

- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within the previous 3 months, unstable arrhythmias, or unstable angina

PD-L1 Expression, Scoring, and Selection Criteria in Urothelial Carcinoma

In Study IMvigor 210 an investigational use only (IUO)-labeled assay was used to prospectively assess PD-L1 expression status in patients at baseline. The PD-L1 IHC assay and scoring system was developed to measure PD-L1-specific signals on both TCs and ICs using the VENTANA PD-L1 [SP142] IHC assay. The diagnostic assignment for ICs is shown in the Table below. Of note, although the IHC assay is optimized to measure PD-L1 expression on both TCs and ICs, the prevalence of PD-L1 expression on TCs in UC is low. Therefore the VENTANA PD-L1 (SP142) IHC assay was not validated for intended use to measure PD-L1 expression on TCs in UC. PD-L1 expression on ICs was reported as the percentage of ICs with PD-L1 staining. Briefly, the scores of IC0, IC1, and IC2/3 were assigned to tumor samples with PD-L1 staining in < 1%, ≥ 1% to < 5%, and ≥ 5%, respectively of the ICs.

Table 58: IHC Scoring Algorithm Used in Study IMvigor 210

Description of IHC Scoring Algorithm	PD-L1 Expression Level
Absence of any discernible PD-L1 staining OR Presence of discernible PD-L1 staining of any intensity in ICs covering < 1% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC0
Presence of discernible PD-L1 staining of any intensity in ICs covering between ≥ 1% and < 5% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC1
Presence of discernible PD-L1 staining of any intensity in ICs covering ≥ 5% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC2/3

PD-L1 Prevalence and Overlap of TC and IC in UC

PD-L1 Prevalence	IMvigor210 Screened * (n > 658)
IC2/3	≈ 32%
IC1/2/3	≈ 67%
IC0	≈ 33%

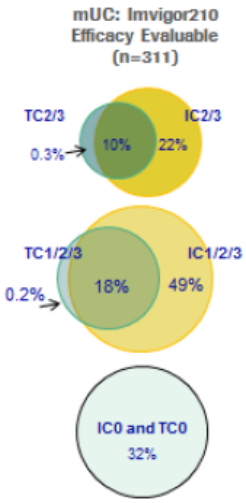


Figure 28: PD-L1 Prevalence and Overlap of TC and IC in UC

Treatments

Patients were administered 1200 mg atezolizumab by IV infusion every 3 weeks (q3w). The initial dose of atezolizumab was delivered over 60 (± 15) minutes. If the first infusion was tolerated without infusion-associated AEs, the second infusion could be delivered over 30 (± 10) minutes. If the 30-minute infusion was well tolerated, all subsequent infusions could be delivered over 30 (± 10) minutes.

No premedication was allowed for the first dose of atezolizumab. Premedication could be administered for Cycles ≥ 2 at the discretion of the treating physician after consultation with the Medical Monitor. The management of infusion-related reactions was performed according to severity.

Patients enrolled in Cohort 1 had to discontinue treatment at the first occurrence of unequivocal radiographic progression per RECIST v1.1.

In Cohort 2, patients were permitted to continue study treatment beyond PD (per RECIST v1.1) if they met all of the following criteria:

- Evidence of clinical benefit (defined as the stabilization or improvement of disease-related symptoms) as assessed by the investigator
- Absence of symptoms and signs indicating unequivocal progression of disease (including worsening of laboratory values; [e.g., new or worsening hypercalcemia])
- No decline in ECOG PS from baseline that could be attributed to disease progression
- Absence of tumour growth at critical anatomical sites (e.g., leptomeningeal disease) that could not be managed by protocol-allowed medical interventions

At the discretion of the investigator, Cohort 2 patients for whom radiographic disease progression was confirmed at a subsequent tumour assessment could be considered for continued study treatment if they continued to meet the criteria above.

Objectives

Primary objective:

- Independent review facility (IRF)-assessed **ORR** according to the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1;
- Investigator-assessed ORR according to modified RECIST (applicable only to Cohort 2).

Secondary objectives:

- To evaluate PFS and duration of response (DOR) according to RECIST v1.1 as assessed by an IRF and according to modified RECIST as assessed by the investigator (applicable only to Cohort 2);
- To evaluate ORR, DOR, and PFS according to RECIST v1.1 as assessed by the investigator;
- To evaluate OS and 1-year OS, safety and tolerability, pharmacokinetics (PK) and the incidence and titers of anti-tumour antibodies (ATAs) against atezolizumab;

Outcomes/endpoints

Primary:

- ORR by IRF-assessment per RECIST v1.1
- ORR by investigator assessment per modified RECIST (different criteria for definition of initial PD as most important difference compared to RECIST v 1.1) (Cohort 2 only)

Secondary:

- ORR by investigator assessment per RECIST v1.1
- DOR and PFS by IRF assessment and by investigator-assessment per RECIST v1.1
- DOR and PFS by investigator assessment per modified RECIST (Cohort 2 only)
- OS and 1-year OS

Sample size

Enrollment of approximately 100 patients (minimum of 30 patients with IC2/3) was planned for Cohort 1 of this study. With 30 IC2/3 patients dosed in Cohort 1, the 95% CI using the Clopper-Pearson method for an observed ORR of 40% would be 22.7%, 59.4%, and the study would have 98% power to detect a 30% increase in ORR from 10% to 40%.

Enrollment of approximately 300 patients was planned for Cohort 2 of this study. The prevalence of IC2/3 was assumed to be approximately 30% in the overall locally advanced or metastatic urothelial carcinoma population. With 100 IC2/3 patients dosed in Cohort 2, the 95% CI using the Clopper-Pearson method for an observed ORR of 40% would be 30.3%, 50.3%, and the study would have 100% power to detect a 30% increase in ORR from 10% to 40%. Number planned: 400 patients (Cohort 1: approximately 100 patients; Cohort 2: approximately 300 patients). Number enrolled: 438 patients (Cohort 1: 123 patients; Cohort 2: 315 patients). Number treated: 429 patients (Cohort 1: 119 patients; Cohort 2: 310 patients).

Randomisation

No randomisation as this is a single-arm study.

Blinding (masking)

No blinding as this is a single-arm study.

Statistical methods

A hierarchical fixed-sequence testing procedure was used to compare the ORR in the three populations i.e., objective response-evaluable patients with an IHC score of IC2/3, objective response-evaluable patients with an IHC score of IC1/2/3, and all objective response-evaluable patients) separately in Cohorts 1 and 2, between the treatment arm with a historical control of 10%, while controlling the overall Type I error rate of 0.05. Estimates of ORR and 95% confidence intervals (CIs) were calculated using the Clopper-Pearson method. The exact binomial test was used to evaluate whether atezolizumab treatment resulted in a statistically significant difference in ORR between the observed ORR and the historical control ORR of 10%.

Median OS, PFS, and DORs were estimated using the Kaplan-Meier method; the 95% CIs for the median durations were computed using the Brookmeyer and Crowley method. Kaplan-Meier methods were used to estimate the OS rate at various timepoints (e.g., 1 year after enrollment); along with the corresponding 95% Cis constructed using Greenwood's formula for the standard error.

An interim efficacy analysis of Cohort 1 patients was planned to be performed at the final analysis of Cohort 2 when the last patient enrolled into Cohort 2 had at least 24 weeks of follow-up. For the Cohort 1 interim analyses, the efficacy analyses were performed on patients with at least 24 weeks of follow-up. The safety analyses were performed on patients treated as of the clinical cutoff date. The Cohort 1 final analysis will be performed when the last patient enrolled into Cohort 1 had at least 24 weeks of follow-up. The alfa for the interim and final analyses for Cohort 1 was set as 0.001 and 0.049, respectively.

Results

Participant flow

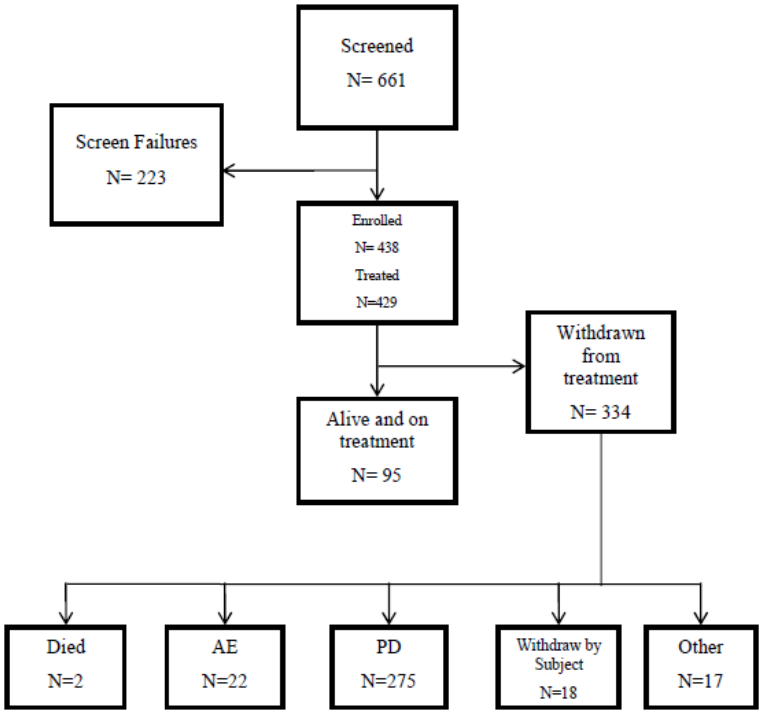


Figure 29 Schematic Representation of Patient Disposition

Recruitment

USA (43 centres), Canada (7 centres), Spain (7 centres), France (3 centres), Great Britain (3 centres), Germany (3 centres), Italy (2 centres), and The Netherlands (1 centre).

First Patient/Subject Entered: 13-May-2014. Last Patient/Subject Entered: 30-Mar-2015

Data cut-off / LPLV: 14-Sep-2015.

Conduct of the study

IMvigor 210 (GO29293) was an open label study and as such any change in study design during study conduct is considered critical. In this context, the major methodological changes introduced with amendment 6 (dated: 06.02.2015) are: Initially ORR was to be analysed in cohort 2 patients with IHC 2/3, all treated patients with IHC 2/3 and all treated patients, however, with amendment 6 a statistical testing approach was introduced separately for cohort 1 and cohort 2 respectively with separate alpha spending for each cohort. Furthermore, in cohort 1, ORR according RECIST v1.1 should be analysed as primary endpoint while ORR according to modified RECIST v1.1 was no longer a primary endpoint in this cohort. These changes impact the value of p-values and the coverage of 95%-CI's provided.

Baseline data

1L Cisplatin-ineligible UC

Table 59 Pivotal Study IMvigor 2010 Cohort 1: Demographic and Baseline Characteristics (ITT Population) (Primary Analysis: Data Cut-off of 14 September 2015)

	Pre-Defined Populations			Exploratory IC subgroups	
	IC2/3 n=32	IC1/2/3 n=80	All Comers n=119	IC0 n=39	IC1 n=48
Age, years					
Mean (SD)	70.3 (9.2)	71.8 (8.4)	71.8 (8.9)	71.7 (9.9)	72.8 (7.8)
Median (range)	67 (51–86)	73 (51–89)	73 (51–92)	72 (54–92)	75 (51–89)
Age group, n (%)					
<65 years	6 (18.8)	11 (13.8)	20 (16.8)	9 (23.1)	5 (10.4)
≥65 to 80 years	19 (59.4)	55 (68.8)	74 (62.2)	19 (48.7)	36 (75.0)
≥80 years	7 (21.9)	14 (17.5)	25 (21.0)	11 (28.2)	7 (14.6)
Male, n (%)	26 (81.3)	66 (82.5)	96 (80.7)	30 (76.9)	40 (83.3)
Race, n (%)					
White	28 (87.5)	75 (93.8)	108 (90.8)	33 (84.6)	47 (97.9)
Asian	0	0	2 (1.7)	2 (5.1)	0
Black or African American	2 (6.3)	3 (3.8)	3 (2.5)	0	1 (2.1)
Other	2 (6.3)	2 (2.5)	5 (4.2)	3 (7.7)	0
Unknown	0	0	1 (0.8)	1 (2.6)	0
Baseline ECOG PS, n (%)					
0	14 (43.8)	29 (36.3)	45 (37.8)	16 (41.0)	15 (31.3)
1	9 (28.1)	33 (41.3)	50 (42.0)	17 (43.6)	24 (50.0)
2	9 (28.1)	18 (22.5)	24 (20.2)	6 (15.4)	9 (18.8)

Site of primary bladder tumor, n (%)					
Bladder	23 (71.9)	51 (63.8)	77 (64.7)	26 (66.7)	28 (58.3)
Renal pelvis	3 (9.4)	14 (17.5)	20 (16.8)	6 (15.4)	11 (22.9)
Ureter	4 (12.5)	10 (12.5)	12 (10.1)	2 (5.1)	6 (12.5)
Urethra	2 (6.3)	4 (5.0)	8 (6.7)	4 (10.3)	2 (4.2)
Other	0	1 (1.3)	2 (1.7)	1 (2.6)	1 (2.1)
Visceral metastasis, n (%)	18 (56.3)	50 (62.5)	78 (65.5)	28 (71.8)	32 (66.7)
Liver metastasis, n (%)	8 (25.0)	18 (22.5)	25 (21.0)	7 (17.9)	10 (20.8)
Prior cystectomy, n (%)	13 (40.6)	28 (35.0)	41 (34.5)	13 (33.3)	15 (31.3)
Hemoglobin <10 g/dL, n (%)	4 (12.5)	15 (18.8)	19 (16.0)	4 (10.3)	11 (22.9)
Baseline creatinine clearance, n (%)					
< 60 mL/min	21 (65.6)	59 (73.8)	84 (70.6)	25 (64.1)	38 (79.2)
≥ 60 mL/min	11 (34.4)	21 (26.3)	35 (29.4)	14 (35.9)	10 (20.8)
Number of Bajorin risk factors [a], n (%)					
0	10 (31.3)	25 (31.3)	35 (29.4)	10 (25.6)	15 (31.3)
1	17 (53.1)	42 (52.5)	66 (55.5)	24 (61.5)	25 (52.1)
2	5 (15.6)	13 (16.3)	18 (15.1)	5 (12.8)	8 (16.7)
Prior comorbidities, n (%)	29 (90.6)	73 (91.3)	104 (87.4)	31 (79.5)	44 (91.7)
Prior urinary diversion, n (%)	14 (43.8)	34 (42.5)	49 (41.2)	15 (38.5)	20 (41.7)
Prior nephroureterectomy, n (%)	12 (37.5)	31 (38.8)	48 (40.3)	17 (43.6)	19 (39.6)
Prior chemotherapy, n (%)	8 (25.0)	14 (17.5)	20 (16.8)	6 (15.4)	6 (12.5)
Ineligibility for cisplatin-based chemotherapy, n (%)					
Baseline impaired renal function	21 (65.6)	58 (72.5)	83 (69.7)	25 (64.1)	37 (77.1)
Prior hearing loss of 25 dB	5 (15.6)	10 (12.5)	15 (12.6)	5 (12.8)	5 (10.4)
Prior peripheral neuropathy Grade ≥ 2	3 (9.4)	5 (6.3)	7 (5.9)	2 (5.1)	2 (4.2)
Baseline ECOG PS of 2	9 (28.1)	18 (22.5)	24 (20.2)	6 (15.4)	9 (18.8)
Baseline ECOG PS of 2 and impaired renal function	4 (12.5)	7 (8.8)	8 (6.7)	1 (2.6)	3 (6.3)

ECOG = Eastern Cooperative Oncology Group; IC = tumor–infiltrating immune cell; ITT = intent-to-treat; PS = performance status; SD = standard deviation.

[a] Bajorin risk score (0/1/2): Risk factors are baseline ECOG PS > 1 and baseline visceral metastasis. Count # of positive as the Bajorin risk score.

Source: Study IMvigor 210 Update CSR Table 6, Study IMvigor 210 Update CSR/t_demog1_ICPOOLED2_C1_IT, Study IMvigor 210 Update CSR/t_priorhx_ICPOOLED2_C1_IT, Study IMvigor 210 Update CSR/t_demog_abase_ICPOOLED2_C1_IT.

2L+ UC

Table 60 Demographic and Baseline Characteristics across Studies

	IMvigor 210 Cohort 2	PCD4989g Urothelial Carcinoma Cohort	Pooled Efficacy Population [b]		
	n=311 [a]	n=92 [a]	IC0 n=121	IC1 n=138	IC2/3 n=119
Median age, years (range)	66 (32–91)	66 (36–89)	65 (36–88)	67 (32–91)	66 (41–89)
Age group, n (%)					
<65 years	126 (40.5)	38 (41.3)	54 (44.6)	53 (38.4)	49 (41.2)
≥65 years	185 (59.5)	54 (58.7)	67 (55.4)	85 (61.6)	70 (58.8)
Male, n (%)	242 (77.8)	69 (75.0)	95 (78.5)	102 (73.9)	94 (79.0)
Race, n (%)					
White	283 (91.0)	73 (79.3)	110 (90.9)	120 (87.0)	105 (88.2)
Asian	7 (2.3)	2 (2.2)	3 (2.5)	0	5 (4.2)
Black or African American	6 (1.9)	1 (1.1)	0	5 (3.6)	2 (1.7)
American Indian or Alaska Native	1 (0.3)	0	0	0	1 (0.8)
Native Hawaiian or other Pacific Islander	1 (0.3)	0	0	0	1 (0.8)
Other	7 (2.3)	16 (17.4)	8 (6.6)	8 (5.8)	4 (3.4)
Unknown	6 (1.9)	0	0	5 (3.6)	1 (0.8)
Baseline ECOG PS, n (%)					
0	117 (37.6)	37 (40.2)	41 (33.9)	53 (38.4)	49 (41.2)
1	193 (62.1)	55 (59.8)	80 (66.1)	84 (60.9)	70 (58.8)
2	1 (0.3)	0	0	1 (0.7)	0
Site of primary bladder tumor, n (%)					
Bladder	231 (74.3)	73 (79.3)	86 (71.1)	104 (75.4)	97 (81.5)
Renal Pelvis	41 (13.2)	5 (5.4)	15 (12.4)	19 (13.8)	12 (10.1)
Ureter	23 (7.4)	9 (9.8)	13 (10.7)	10 (7.2)	5 (4.2)
Urethra	6 (1.9)	5 (5.4)	1 (0.8)	3 (2.2)	3 (2.5)
Other	10 (3.2)	0	6 (5.0)	2 (1.4)	2 (1.7)
Visceral metastasis, n (%)	243 (78.1)	75 (81.5)	107 (88.4)	111 (80.4)	79 (66.4)
Liver metastasis, n (%)	96 (30.9)	34 (37.0)	43 (35.5)	45 (32.6)	33 (27.7)
Prior cystectomy, n (%)	117 (37.6)	42 (45.7)	39 (32.2)	52 (37.7)	56 (47.1)
Hemoglobin <10 g/dL, n (%)	69 (22.2)	16 (17.4)	22 (18.2)	28 (20.3)	28 (23.5)
Number of Bellmunt risk factors [c], n (%)					
0	83 (26.7)	26 (28.3)	26 (21.5)	39 (28.3)	37 (31.1)
1	118 (37.9)	32 (34.8)	52 (43.0)	49 (35.5)	42 (35.3)
2	89 (28.6)	29 (31.5)	36 (29.8)	41 (29.7)	31 (26.1)
3	21 (6.8)	5 (5.4)	7 (5.8)	9 (6.5)	9 (7.6)
Time from prior chemotherapy (<=3 months), n (%)					
Yes	121 (38.9)	37 (41.6)	43 (35.5)	55 (40.1)	49 (41.5)
No	190 (61.1)	52 (58.4)	78 (64.5)	82 (59.9)	69 (58.5)
Prior systemic therapy [d], n (%)					
Yes	310 (99.7)	90 (97.8)	120 (99.2)	137 (99.3)	119 (100.0)
No	1 (0.3)	2 (2.2)	1 (0.8)	1 (0.7)	0
No. of prior systemic regimens in the metastatic setting, n (%)					
0	68 (21.9)	22 (23.9)	25 (20.7)	26 (18.8)	30 (25.2)
1	120 (38.6)	4 (4.3)	44 (36.4)	55 (39.9)	41 (34.5)
>=2	123 (39.5)	66 (71.7)	52 (43.0)	57 (41.3)	48 (40.3)

ECOG=Eastern Cooperative Oncology Group; IC=tumor–infiltrating immune cell; PS=performance status.

[a] Safety-evaluable population.

[b] 25 patients with unknown IC scores at baseline were excluded from the pooled efficacy analysis.

[c] Bellmunt risk score (0/1/2/3): Risk factors are baseline ECOG PS≥1, having liver metastasis (Y) and hemoglobin < 10g/dL. Count # of positive as the Bellmunt risk scores.

[d] Prior systemic therapy is defined slightly differently for Studies IMvigor 210 and PCD4989g.

Source: Study IMvigor 210 Primary CSR Table 10 and t_priorhx_ICPOOLED2_C2_IT, Study PCD4989g CSR Table 20 and t_dm_BTCC_SE, pooled/t_dm_ICPOOLED4_SE and t_cm_ICPOOLED4_SE.

Numbers analysed

Table 61 Analysis Populations (All Patients)

Patient Population	Cohort1 (N=123)	Cohort2 (N=315)
Intent-to-treat	119 (96.7%)	310 (98.4%)
Intent-to-treat with 24 week follow-up	119 (96.7%)	310 (98.4%)
Objective Response Evaluable	119 (96.7%)	310 (98.4%)
Objective Response Evaluable with 24 week follow-up	119 (96.7%)	310 (98.4%)
Safety Evaluable	119 (96.7%)	310 (98.4%)
All Enrolled	123 (100.0%)	315 (100.0%)

Datacut date: 14Sep2015.

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Page 1 of 1
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Outcomes and estimation

Primary and secondary endpoints – Cohort 1

Table 62: Pivotal Study IMvigor 210 Cohort 1: Overview of Efficacy Results by IC Subgroup and All Comers (Primary Analysis; Data Cut-off 14 September 2015)

	Pre-Defined Populations			Exploratory IC subgroups	
Efficacy Endpoint	IC2/3	IC1/2/3	All Comers	IC0	IC1
Primary Efficacy Endpoint					
ORR (IRF-assessed; RECIST v1.1)	n=32	n=80	n=119	n=39	n=48
Responders (%)	7 (21.9)	15 (18.8)	23 (19.3)	8 (20.5)	8 (16.7)
95% CI	(9.28, 39.97)	(10.89, 29.03)	(12.66, 27.58)	(9.30, 36.46)	(7.48, 30.22)
Secondary Efficacy Endpoints					
ORR (investigator-assessed; RECIST v1.1)	n=32	n=80	n=119	n=39	n=48
Responders (%)	10 (31.3)	19 (23.8)	27 (22.7)	8 (20.5)	9 (18.8)
95% CI	(16.12, 50.01)	(14.95, 34.58)	(15.52, 31.27)	(9.30, 36.46)	(8.95, 32.63)
DOR (IRF-assessed; RECIST v1.1)	n=7	n=15	n=23	n=8	n=8
Patients with event (%)	0	0	1 (4.3)	1 (12.5)	0
Median (months)	NE	NE	NE	NE	NE
Range	(2.0*–10.6*)	(2.0*–10.6*)	(2.0*–11.1*)	(2.1*–11.1*)	(2.1*–8.2*)
DOR (investigator-assessed; RECIST v1.1)	n=10	n=19	n=27	n=8	n=9
Patients with event (%)	0	0	1 (3.7)	1 (12.5)	0
Median (months)	NE	NE	NE	NE	NE
Range	(2.0*–10.6*)	(2.0*–10.6*)	(2.0*–11.1*)	(4.2*–11.1*)	(2.1*–8.3*)
PFS (IRF-assessed; RECIST v1.1)	n=32	n=80	n=119	n=39	n=48
Patients with event (%)	20 (62.5)	55 (68.8)	81 (68.1)	26 (66.7)	35 (72.9)
Median (months)	2.92	2.30	2.40	2.56	2.10
95% CI	(2.10, 4.17)	(2.10, 4.17)	(2.10, 4.14)	(2.07, 5.68)	(2.07, 4.80)
PFS (investigator-assessed; RECIST v1.1)	n=32	n=80	n=119	n=39	n=48
Patients with event (%)	18 (56.3)	48 (60.0)	75 (63.0)	27 (69.2)	30 (62.5)
Median (months)	4.17	4.17	4.17	4.14	4.12
95% CI	(2.07, NE)	(2.10, 6.08)	(2.30, 5.75)	(2.04, 6.11)	(2.10, 8.67)
OS	n=32	n=80	n=119	n=39	n=48
Patients with event (%)	14 (43.8)	32 (40.0)	46 (38.7)	14 (35.9)	18 (37.5)
Median (months)	10.58	10.58	10.58	NE	10.41
95% CI	(6.01, NE)	(8.08, NE)	(8.08, NE)	(6.74, NE)	(7.72, NE)
1-year OS	n=32	n=80	n=119	n=39	n=48
Patients at risk	1	4	7	3	3
OS rate	35.81%	46.48%	49.29%	57.09%	49.75%
95% CI	(4.02, 67.59)	(30.36, 62.60)	(36.29, 62.30)	(39.13, 75.05)	(30.08, 69.42)

*=censored value; CI=confidence interval; DOR=duration of objective response; IC= tumor–infiltrating immune cell; IRF=Independent Review Facility; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors.

Source: Study IMvigor 210 Update CSR Table 12 and Table 13.

Table 63: ORR (IRF-Assessed) per RECIST v1.1 (Cohort 1 Objective Response Evaluable Population) – IMvigor 210

	IC0 (N=39)	IC1 (N=48)	IC0/1 (N=87)	IC2/3 (N=32)	IC1/2/3 (N=80)	All (N=119)
Responders	8 (20.5%)	8 (16.7%)	16 (18.4%)	7 (21.9%)	15 (18.8%)	23 (19.3%)
Non-Responders	31 (79.5%)	40 (83.3%)	71 (81.6%)	25 (78.1%)	65 (81.3%)	96 (80.7%)
95% CI for Response Rates	(9.30, 36.46)	(7.48, 30.22)	(10.89, 28.14)	(9.28, 39.97)	(10.89, 29.03)	(12.66, 27.58)
Complete Response (CR)	3 (7.7%)	2 (4.2%)	5 (5.7%)	1 (3.1%)	3 (3.8%)	6 (5.0%)
95% CI	(1.62, 20.87)	(0.51, 14.25)	(1.89, 12.90)	(0.08, 16.22)	(0.78, 10.57)	(1.87, 10.65)
Partial Response (PR)	5 (12.8%)	6 (12.5%)	11 (12.6%)	6 (18.8%)	12 (15.0%)	17 (14.3%)
95% CI	(4.30, 27.43)	(4.73, 25.25)	(6.48, 21.50)	(7.21, 36.44)	(8.00, 24.74)	(8.55, 21.88)
Stable Disease (SD)	10 (25.6%)	10 (20.8%)	20 (23.0%)	9 (28.1%)	19 (23.8%)	29 (24.4%)
95% CI	(13.04, 42.13)	(10.47, 34.99)	(14.64, 33.25)	(13.75, 46.75)	(14.95, 34.58)	(16.97, 33.09)
Progressive Disease (PD)	14 (35.9%)	23 (47.9%)	37 (42.5%)	10 (31.3%)	33 (41.3%)	47 (39.5%)
95% CI	(21.20, 52.82)	(33.29, 62.81)	(31.99, 53.59)	(16.12, 50.01)	(30.35, 52.82)	(30.66, 48.87)
Unevaluable	2 (5.1%)	1 (2.1%)	3 (3.4%)	1 (3.1%)	2 (2.5%)	4 (3.4%)
Missing	5 (12.8%)	6 (12.5%)	11 (12.6%)	5 (15.6%)	11 (13.8%)	16 (13.4%)

95% CIs for response rates are computed using the Clopper-Pearson method.
Missing refers to no post-baseline tumor scans.
Datacut date: 14Sep2015.

The result of the primary endpoint of IRF-assessed ORR per RECIST v1.1 did not meet statistical significance (p = 0.0717) compared to the historical control ORR of 10% in the IC2/3 subgroup, which was tested first in the hierarchical fixed-sequence procedure. The p-values for the IC1/2/3 subgroup and for all comers were 0.0247 and 0.0031, respectively. The p-values are provided for descriptive purposes only since the analyses in these populations were not to be formally conducted according to the pre-specified hierarchical fixed-sequence procedure.

Updated data for Cohort 1 were provided with a clinical cut-off date (CCOD) of 4 July 2016 and a median survival follow-up of 17.2 months in the all comers population (representing approximately 10 additional months of follow-up from the time of the primary analysis, 14 September 2015).

Table 64: Top-line Efficacy Results for IMvigor 210, Cohort 1 (CCOD 4 July 2016)

Efficacy Endpoint	IC2/3	IC1/2/3	All Comers	IC0	IC1
IRF-assessed ORR	n = 32	n = 80	n = 119	n = 39	n = 48
Responders (%) (95% CI)	9 (28.1) (13.8, 46.8)[a]	19 (23.8) (15.0, 34.6)[a]	27 (22.7) (15.5, 31.3)[a]	8 (20.5) (9.3, 36.5)	10 (20.8) (10.5, 35.0)
Complete response(%) (95% CI)	4 (12.5) (3.5, 29.0)	8 (10.0) (4.4, 18.8)	11 (9.2) (4.7, 15.9)	3 (7.7) (1.6, 20.9)	4 (8.3) (2.3, 20.0)
IRF-assessed DOR	n = 9	n = 19	n = 27	n = 8	n = 10
Median DOR (months) (95% CI)	NE (11.1, NE)	NE (NE)	NE (14.1, NE)	NE (12.8, NE)	NE (NE)
Patients with event (%)	3 (33.3)	5 (26.3)	8 (29.6)	3 (37.5)	2 (20.0)
Patients with ongoing response (%)	6 (66.7)	14 (73.7)	19 (70.4)	5 (62.5)	8 (80.0)
12-month DOR (%) (95% CI)	59.3 (23.0, 95.5)	72.2 (51.3, 93.1)	76.7 (60.2, 93.1)	87.5 (64.6, 100.0)	80.0 (55.2, 100.0)
OS	n = 32	n = 80	n = 119	n = 39	n = 48
Median (months) (95% CI)	12.3 (6.0, NE)	14.1 (9.1, NE)	15.9 (10.4, NE)	NE (6.7, NE)	16.3 (7.7, NE)
Patients with event (%)	18 (56.3)	42 (52.5)	59 (49.6)	17 (43.6)	24 (50.0)
12-month rate (%) (95% CI)	52.4 (34.9, 69.9)	54.8 (43.7, 65.9)	57.2 (48.2, 66.3)	62.2 (46.6, 77.8)	56.3 (42.0, 70.7)

CCOD = clinical cutoff date; DOR = duration of response; IC = tumor-infiltrating immune cell; INV = investigator; IRF = Independent Review Facility; NE = not estimable; ORR = objective response rate; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors,

Version 1.1.
Notes: All responses are confirmed responses.
ORR and DOR were assessed per RECIST v1.1.
[a] The lower bound of the 95% confidence interval excludes the 10% historical control in all of the pre-specified subgroups.

Primary and secondary endpoints – Cohort 2

Primary analysis

Table 65: Pivotal Study IMvigor 2010 Cohort 2: Overview of Efficacy results by IC Subgroups and All Comers (Primary Analysis: Data Cut-off of 5 May 2015)

	Pre-Defined Populations			Exploratory IC subgroups	
Efficacy Endpoint	IC2/3	IC1/2/3	All Comers	IC0	IC1 [a]
Co-Primary Efficacy Endpoints					
ORR (IRF-assessed; RECIST v1.1)	n=100	n=208	n=311	n=103	n=108
Responders (%)	27 (27.0)	38 (18.3)	47 (15.1)	9 (8.7)	11 (10.2)
95% CI	(18.61, 36.80)	(13.26, 24.20)	(11.32, 19.58)	(4.07, 15.94)	(5.20, 17.49)
ORR (investigator-assessed; modified RECIST)	n=100	n=208	n=311	n=103	n=108
Responders (%)	26 (26.0)	44 (21.2)	57 (18.3)	13 (12.6)	18 (16.7)
95% CI	(17.74, 35.73)	(15.81, 27.34)	(14.19, 23.08)	(6.89, 20.62)	(10.19, 25.06)
Secondary Efficacy Endpoints					
ORR (investigator-assessed; RECIST v1.1)	n=100	n=208	n=311	n=103	n=108
Responders (%)	23 (23.0)	37 (17.8)	50 (16.1)	13 (12.6)	14 (13.0)
95% CI	(15.17, 32.49)	(12.84, 23.68)	(12.17, 20.64)	(6.89, 20.62)	(7.27, 20.79)
DOR (IRF-assessed; RECIST v1.1)	n=27	n=38	n=47	n=9	n=11
Patients with event (%)	4 (14.8)	4 (10.5)	4 (8.5)	0	0
Median (months)	NE	NE	NE	NE	NE
Range	(2.1*–8.3*)	(2.1*–8.3*)	(2.1*–8.3*)	2.1*–6.4*	2.1*–6.6*
DOR (investigator-assessed; modified RECIST)	n=26	n=44	n=57	n=13	n=18
Patients with event (%)	1 (3.8)	3 (6.8)	4 (7.0)	1 (7.7)	2 (11.1)
Median (months)	NE	NE	NE	NE	NE
Range	(2.1*–8.3*)	(2.1*–8.3*)	(1.6*–8.3*)	1.6*–6.4*	2.1*–6.6*
DOR (investigator-assessed; RECIST v1.1)	n=23	n=37	n=50	n=13	n=14
Patients with event (%)	1 (4.3)	2 (5.4)	3 (6.0)	1 (7.7)	1 (7.1)
Median (months)	NE	NE	NE	NE	NE
Range	(2.1*–8.3*)	(2.1*–8.3*)	(1.6*–8.3*)	1.6*–6.4*	2.1*–6.6*
PFS (IRF-assessed; RECIST v1.1)	n=100	n=208	n=311	n=103	n=108
Patients with event (%)	74 (74.0)	163 (78.4)	241 (77.5)	78 (75.7)	89 (82.4)
Median (months)	2.14	2.10	2.10	2.07	2.07
95% CI	(2.10, 4.14)	(2.07, 2.14)	(2.07, 2.14)	(2.00, 2.27)	(2.04, 2.10)
PFS (investigator-assessed; modified RECIST)	n=100	n=208	n=311	n=103	n=108
Patients with event (%)	67 (67.0)	151 (72.6)	228 (73.3)	77 (74.8)	84 (77.8)
Median (months)	4.17	2.92	2.73	2.56	2.12
95% CI	(2.69, 6.21)	(2.14, 4.17)	(2.14, 3.94)	(2.07, 3.94)	(2.04, 3.84)
PFS (investigator-assessed; RECIST v1.1)	n=100	n=208	n=311	n=103	n=108
Patients with event (%)	73 (73.0)	163 (78.4)	243 (78.1)	80 (77.7)	90 (83.3)
Median (months)	2.48	2.12	2.10	2.07	2.07
95% CI	(2.10, 4.17)	(2.10, 2.27)	(2.07, 2.23)	(2.00, 2.63)	(2.00, 2.14)
OS	n=100	n=208	n=311	n=103	n=108
Patients with event (%)	35 (35.0)	93 (44.7)	141 (45.3)	48 (46.6)	58 (53.7)
Median (months)	NE	7.95	7.89	7.46	6.41
95% CI	(7.62, NE)	(6.70, NE)	(6.70, NE)	(4.50, NE)	(5.39, 8.02)
1-year OS [b]	n=100	n=208	n=311	n=103	n=108
Patients at risk	NE	NE	NE	NE	NE
OS rate	NE	NE	NE	NE	NE
95% CI	NE	NE	NE	NE	NE

*=censored value; CI=confidence interval; DOR=duration of objective response; IC=tumor-infiltrating immune cell; IRF=Independent Review Facility; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors.
[a] Patients who were negative for IC2/3 but positive on IC1/2/3 were deemed IC1.
[b] 1-year OS was not estimable because it was not yet reached. Patients had not yet been on the study for a year as of the data cutoff.
Source: Study IMvigor 210 Primary CSR Table 16 and Table 17.

Table 66 ORR (IRF-Assessed) per RECIST v1.1 (Cohort 2 Objective Response Evaluable Population) – Imvigor210

	IC0 (N=103)	IC1 (N=107)	IC0/1 (N=210)	IC2/3 (N=100)	IC1/2/3 (N=207)	All (N=310)
Responders	8 (7.8%)	11 (10.3%)	19 (9.0%)	26 (26.0%)	37 (17.9%)	45 (14.5%)
Non-Responders	95 (92.2%)	96 (89.7%)	191 (91.0%)	74 (74.0%)	170 (82.1%)	265 (85.5%)
95% CI for Response Rates	(3.41, 14.73)	(5.24, 17.65)	(5.54, 13.77)	(17.74, 35.73)	(12.91, 23.79)	(10.79, 18.94)
Complete Response (CR)	2 (1.9%)	2 (1.9%)	4 (1.9%)	11 (11.0%)	13 (6.3%)	15 (4.8%)
95% CI	(0.24, 6.84)	(0.23, 6.59)	(0.52, 4.80)	(5.62, 18.83)	(3.39, 10.50)	(2.73, 7.86)
Partial Response (PR)	6 (5.8%)	9 (8.4%)	15 (7.1%)	15 (15.0%)	24 (11.6%)	30 (9.7%)
95% CI	(2.17, 12.25)	(3.92, 15.37)	(4.05, 11.51)	(8.65, 23.53)	(7.57, 16.76)	(6.62, 13.53)
Stable Disease (SD)	25 (24.3%)	18 (16.8%)	43 (20.5%)	16 (16.0%)	34 (16.4%)	59 (19.0%)
95% CI	(16.36, 33.71)	(10.29, 25.28)	(15.23, 26.57)	(9.43, 24.68)	(11.65, 22.19)	(14.82, 23.85)
Progressive Disease (PD)	52 (50.5%)	63 (58.9%)	115 (54.8%)	44 (44.0%)	107 (51.7%)	159 (51.3%)
95% CI	(40.46, 60.49)	(48.95, 68.30)	(47.77, 61.62)	(34.08, 54.28)	(44.66, 58.67)	(45.58, 56.98)
Unevaluable	5 (4.9%)		5 (2.4%)	2 (2.0%)	2 (1.0%)	7 (2.3%)
Missing	13 (12.6%)	15 (14.0%)	28 (13.3%)	12 (12.0%)	27 (13.0%)	40 (12.9%)

95% CIs for response rates are computed using the Clopper-Pearson method.
Missing refers to no post-baseline tumor scans.
Datacut date: 14Sep2015.

Updated analyses – Cohort 2 (4 July 2016)

Table 67: Pivotal Study IMvigor 210 Cohort 2: Efficacy Results by IC Subgroups and All Comers (updated Analysis: Data Cut-off of 4 July 2016)

	Primary Analysis (CCOD 5 May 2015) mF/U = 7.1 months N=311			20-Month F/U Analysis (CCOD 4 Jul 2016) mF/U = 21.1 months N=310 [a]		
		PD-L1 Diagnostic Status [b]			PD-L1 Diagnostic Status [a]	
Efficacy Endpoint	All Comers	IC2/3	IC1/2/3	All Comers	IC2/3	IC1/2/3
ORR (IRF-Assessed; RECIST v1.1)	*n = 311*	*n = 100*	*n = 208*	*n = 310*	*n = 100*	*n = 207*
No. of Responders (%)	47 (15.1)	27 (27.0)	38 (18.3)	49 (15.8)	28 (28.0)	40 (19.3)
95% CI	11.3, 19.6	18.6, 36.8	13.3, 24.2	11.9, 20.4	19.5, 37.9	14.2, 25.4
CR (%)	12 (3.9)	8 (8.0)	11 (5.3)	19 (6.1)	14 (14.0)	17 (8.2)
95% CI	2.0, 6.6	3.5, 15.2	2.7, 9.3	3.7, 9.4	7.9, 22.4	4.9, 12.8
PR (%)	35 (11.3)	19 (19.0)	27 (13.0)	30 (9.7)	14 (14.0)	23 (11.1)
95% CI	8.0, 15.3	11.8, 28.1	8.7, 18.3	6.6, 13.5	7.9, 22.4	7.2, 16.2
ORR (INV-Assessed; mRECIST)	*n = 311*	*n = 100*	*n = 208*	*n = 310*	*n = 100*	*n = 207*
No. of Responders (%)	57 (18.3)	26 (26.0)	44 (21.2)	61 (19.7)	29 (29.0)	49 (23.7)
95% CI	14.2, 23.1	17.7, 35.7	15.8, 27.3	15.4, 24.6	20.4, 38.9	18.1, 30.1
CR (%)	10 (3.2)	5 (5.0)	9 (4.3)	21 (6.8)	11 (11.0)	19 (9.2)
95% CI	1.6, 5.8	1.6, 11.3	2.0, 8.1	4.2, 10.2	5.6, 18.8	5.6, 14.0
PR (%)	47 (15.1)	21 (21.0)	35 (16.8)	40 (12.9)	18 (18.0)	30 (14.5)
95% CI	11.3, 19.6	13.5, 30.3	12.0, 22.6	9.4, 17.2	11.0, 27.0	10.0, 20.0
ORR (INV-Assessed; RECIST v1.1)	*n = 311*	*n = 100*	*n = 208*	*n = 310*	*n = 100*	*n = 207*
No. of Responders (%)	50 (16.1)	23 (23.0)	37 (17.8)	51 (16.5)	25 (25.0)	39 (18.8)
95% CI	12.2, 20.6	15.2, 32.5	12.8, 23.7	12.5, 21.1	16.9, 34.7	13.8, 24.8
CR (%)	10 (3.2)	5 (5.0)	9 (4.3)	20 (6.5)	11 (11.0)	18 (8.7)
95% CI	1.6, 5.8	1.6, 11.3	2.0, 8.1	4.0, 9.8	5.6, 18.8	5.2, 13.4
PR (%)	40 (12.9)	18 (18.0)	28 (13.5)	31 (10.0)	14 (14.0)	21 (10.1)
95% CI	9.4, 17.1	11.0, 27.0	9.1, 18.9	6.9, 13.9	7.9, 22.4	6.4, 15.1
DOR (IRF-Assessed; RECIST v1.1)	*n = 47*	*n = 27*	*n = 38*	*n = 49*	*n = 28*	*n = 40*
No. of Patients with Event (%) [c]	4 (8.5)	4 (14.8)	4 (10.5)	17 (34.7)	9 (32.1)	12 (30.0)
Median Time to Event (months)	NE	NE	NE	NE	NE	NE
Range	2.1*–8.3*	2.1*–8.3*	2.1*–8.3*	2.1*–22.6*	4.2–22.6*	2.1*–22.6*
No. of Ongoing Responders (%)	43 (91.5)	23 (85.2)	34 (89.5)	32 (65.3)	19 (67.9)	28 (70.0)
DOR Landmark Analysis at 12 months						
No. of Patients at Risk	NE	NE	NE	29	19	25
Event-Free Rate (%)	NE	NE	NE	65.3	67.9	68.4
95% CI	NE	NE	NE	51.5, 79.0	50.6, 85.2	53.6, 83.2
PFS (IRF-Assessed; RECIST v1.1)	*n = 311*	*n = 100*	*n = 208*	*n = 310*	*n = 100*	*n = 207*
No. of Patients with Event (%)	241 (77.5)	74 (74.0)	163 (78.4)	274 (88.4)	80 (80.0)	177 (85.5)
Median Time to Event (months)	2.1	2.1	2.1	2.1	2.1	2.1
95% CI	2.1, 2.1	2.1, 4.1	2.1, 2.1	2.1, 2.1	2.1, 4.2	2.1, 2.1
OS	*n = 311*	*n = 100*	*n = 208*	*n = 310*	*n = 100*	*n = 207*
No. of Patients with Event (%)	141 (45.3)	35 (35.0)	93 (44.7)	226 (72.9)	58 (58.0)	142 (68.6)
Median Time to Event (months)	7.9	NE	8.0	7.9	11.9	9.0
95% CI	6.7, NE	7.6, NE	6.7, NE	6.7, 9.3	9.0, NE	7.1, 10.9
12-month OS Rate	NE	NE	NE	36.9	49.9	40.2
95% CI	NE	NE	NE	31.4, 42.3	40.0, 59.9	33.4, 46.9

CCOD = clinical (data) cutoff (date); CR = complete response; DOR = duration of response; F/U = follow-up; IC = tumor-infiltrating immune cells; INV = investigator; IRF = independent review facility; mF/U = median follow-up; NE = not estimable; ORR = objective response rate; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; mRECIST = modified Response Evaluation Criteria in Solid Tumors.

* denotes a censored value.

[a] As a result of ongoing data cleaning of cohort eligibility, two patients (one within the IC0 and one within the IC1 subgroups) assigned to Cohort 2 and one patient (within the IC0 subgroup) assigned to Cohort 1 as of the primary analysis (5 May 2015) were re-assigned to the alternate cohort as of 14 September 2015. As a result, there are 310 patients in the all-comer group of Cohort 2. No additional patients switched cohorts as of 14 March 2016.

[b] IC subgroups are diagnostic subgroups supported by the Premarket Approval (PMA).

[c] Event refers to either disease progression or death.

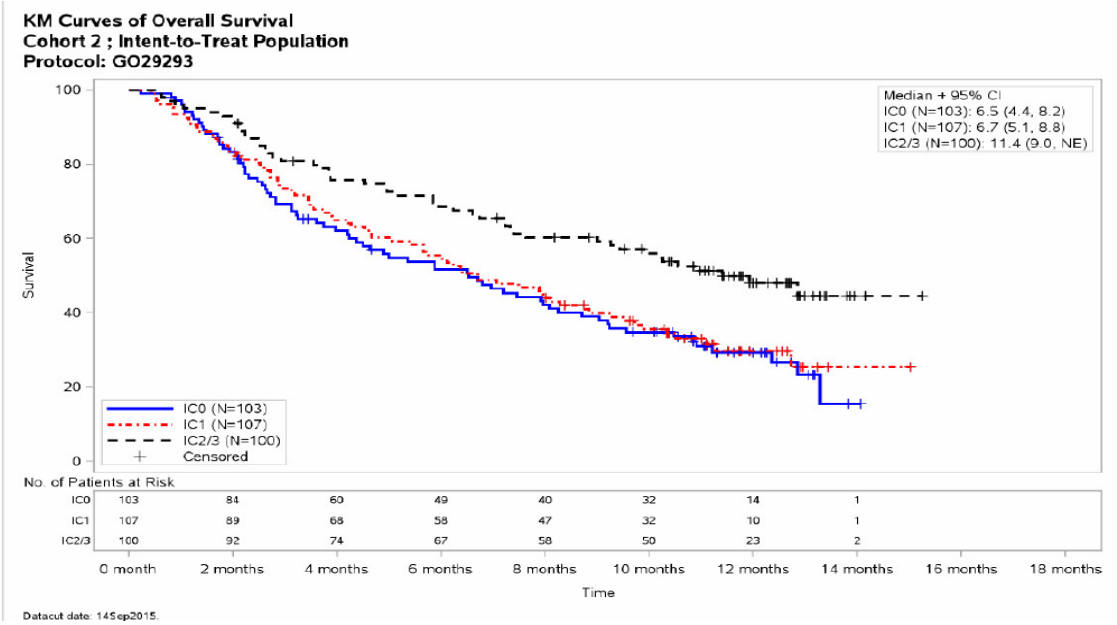


Figure 30: Kaplan-Meier Curves for OS with IC0 vs IC1 vs IC2/3 in Cohort 2 (ITT Population) – Imvigor 210

- **Summary of main efficacy results**

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 68: Summary of efficacy for study IMvigor 210

Title: A phase II, multicenter, single-arm study of MPDL3280A in patients with locally advanced or metastatic urothelial bladder cancer			
Study identifier	IMvigor 210 (GO29293)		
Design	Phase II, multicenter, single-arm two-cohort study in patients with locally advanced or metastatic urothelial bladder cancer Cohort 1: treatment-naïve patients considered ineligible to receive cisplatin therapy [1L cis-ineligible UC] Cohort 2: previously treated patients [2L+ UC])		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		13-May-2014 (First patient entered) 30-Mar-2015 (Last patient entered) N/A N/A
Hypothesis	Superiority compared with a historical control of 10%, separate analyses for Cohort 1 and 2		
Treatments groups	Cohort 1		Atezolizumab 1200 mg IV q3w until progression per RECIST 1.1, n=119
	Cohort 2		Atezolizumab 1200 mg IV q3w as long as clinical benefit, n=310
Endpoints and definitions	Primary endpoint Cohort 1	ORR (response rate)	Independent review facility (IRF)-assessed ORR according to the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1
	Co-primary Endpoint Cohort 2	ORR	- IRF-assessed ORR per RECIST v1.1 - Investigator-assessed ORR according to modified RECIST

	Secondary	DOR (Response duration)	The time from the first occurrence of a documented PR or CR (whichever occurred first) to the time of first radiographic progression or death, whichever occurred first
	Secondary endpoint	PFS	The time from the first dose of the study drug to the time of first radiographic progression or death, whichever occurred first
	Secondary endpoint	OS	The time from the first dose of the study drug to the time of death from any cause on study
Database lock	Primary CSR: 05 May 2015 (=primary analysis of Cohort 2, IA Cohort 1) Update CSR: 14 Sept. 2015 (primary analysis Cohort 1, update Cohort 2) Supplemental Results Report: 27 November 2015 (update key data Cohort 2)		

Results and Analysis

Analysis description	**Cohort 1: Updated Analysis** (data cutoff 4 July 2016) **Cohort 2: Updated Analysis** (data cutoff 4 July 2016)		
Analysis population and time point description	A hierarchical fixed-sequence testing procedure was used to compare the ORR in the three populations (i.e., objective response-evaluable patients with an IHC score of IC2/3, objective response-evaluable patients with an IHC score of IC1/2/3, and all objective response-evaluable patients) separately in Cohorts 1 and 2. Cohort 1: Median follow up 17.2 months (minimum 15 months after LPI) Cohort 2: Median follow up 21.1 months (minimum 20 months after LPI)		
Descriptive statistics and estimate variability	Treatment group	**Cohort 1** **(All comers)**	**Cohort 2** (All comers)
	Number of subject	n=119	n=310
	ORR IRF, RECIST 1.1	22.7%	15.8%
	95% CI	15.5, 31.3	11.9, 20.4
	DOR, Per IRF, RECIST 1.1	NE (3.7, 21.0), Ongoing response in 19/27 patients	NE (2.1, 22.6), Ongoing response in 32/49 patients
	PFS (months) median, Per IRF, RECIST (95% CI)	2.7 (2.1, 4.2)	2.1* (2.1, 2.1*)
	OS (months) median (95% CI)	15.9 (10.4, NE)	7.9 (6.7, 9.3)
		(IC 2/3)	
	Number of subject	32	
	ORR IRF, RECIST 1.1	28.1%	
	95% CI	13.8, 46.8	
	DOR, Per IRF, RECIST 1.1	NE (9.1, 19.3), Ongoing response in 6/9 patients	
	PFS (months) median, Per IRF, RECIST (95% CI)	4.1 (2.3, 11.8)	

	OS (months) median (95% CI)	12.3 (6.0, NE)	
Notes	Cohort 1: Primary endpoint (ORR per IRF, RECIST 1.1) in primary analysis (data cut-off 14 Sept. 2015) not statistical significant (ORR 21.9% for IC2/3; p = 0.0717 compared to historical control of 10%, pre-specified level of α = 0.049). Cohort 2: ORR results of the co-primary endpoints were statistical significant in the primary analysis (May 2015 data cut-off) for IC2/3, IC1/2/3 subgroups and all comers (compared to historical control of 10%). Statistical testing was not formally conducted for the updated analyses.		

NE: Not evaluable, LPI: Last patient enrolled, N/A: not applicable

Clinical studies in special populations

Atezolizumab has not been investigated in a paediatric patient population, this is reflected in section 4.2.of the SmPC.

No dose adjustment is required in patients with mild or moderate renal impairment and for patients with mild hepatic impairment; this is also reflected in section 4.2 of the SmPC.

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

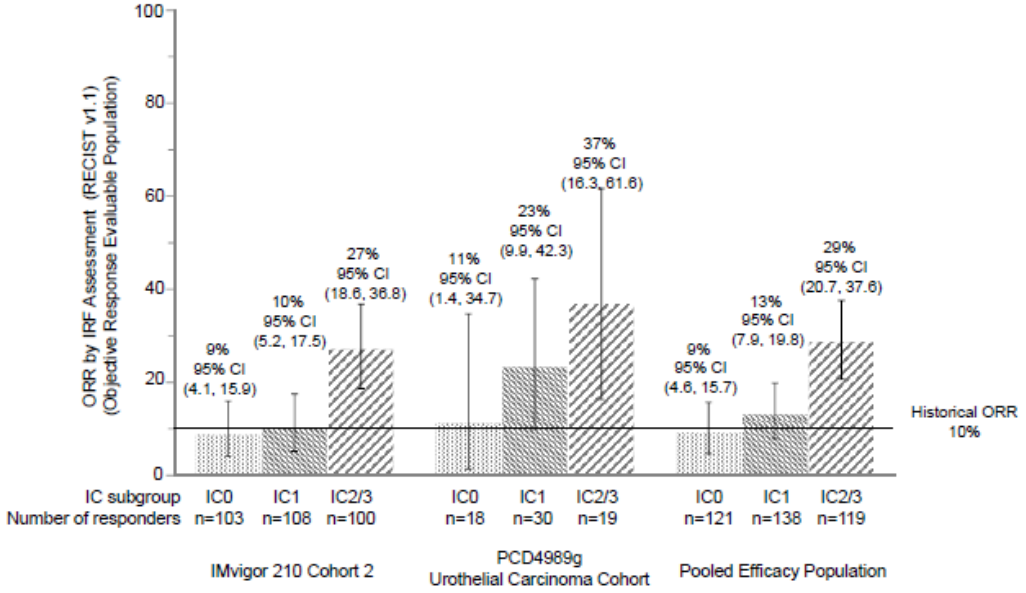
- Efficacy data from the primary analysis of Study IMvigor 210 Cohort 1 (data cutoff of 14 September 2015) on 1L cisplatin-ineligible UC patients who received treatment with atezolizumab (1L cis-ineligible). Study IMvigor 210 is the first study in which atezolizumab is tested in this treatment-naive and cisplatin-ineligible UC population, and there are therefore no other studies on this population to be used for comparison in the following sections.
- Efficacy data from the primary analysis of Study IMvigor 210 Cohort 2 (data cutoff of 5 May 2015) and the analysis of Study PCD4989g UC Cohort as of 2 December 2014 on 2L+ UC patients who received treatment with atezolizumab (2L+ UC). Data from selected efficacy endpoints from these individual studies are presented either side-by-side or in exploratory pooled analyses.

Data are discussed for the pre-defined IC subgroups IC2/3 and IC1/2/3, all comers, as well as for the IC0 and IC1 subgroups for Study IMvigor 210 Cohort 1 and Cohort 2. Data are discussed by the IC subgroups IC0, IC1, IC2/3 for Study PCD4989g UC Cohort, the side-by-side presentations of Study IMvigor 210 Cohort 2 and Study PCD4989g UC Cohort, and the pooled efficacy population.

Table 69: Pooled Efficacy Population: Number of Patients by Study

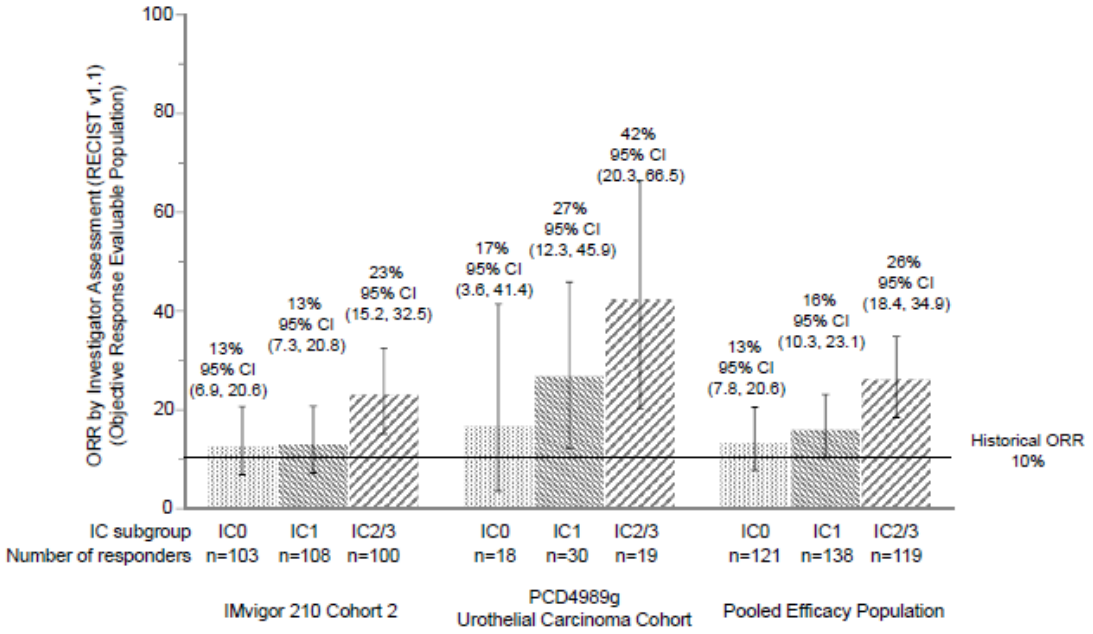
	IC0 n=121 (%)	IC1 n=138 (%)	IC2/3 n=119 (%)
Safety-evaluable, n (%)			
PCD4989g urothelial carcinoma Cohort	18 (14.9)	30 (21.7)	19 (16.0)
IMvigor 210 Cohort 2	103 (85.1)	108 (78.3)	100 (84.0)
Objective response-evaluable, n (%)			
PCD4989g urothelial carcinoma Cohort	18 (14.9)	30 (21.7)	19 (16.0)
IMvigor 210 Cohort 2	103 (85.1)	108 (78.3)	100 (84.0)
All enrolled, n (%)			
PCD4989g urothelial carcinoma Cohort	18 (14.9)	30 (21.7)	19 (16.0)
IMvigor 210 Cohort 2	103 (85.1)	108 (78.3)	100 (84.0)

IC=tumor–infiltrating immune cell.
Note: 25 patients with unknown IC scores at baseline were excluded from the analysis.
Source: pooled/t_pop.



CI=confidence interval; IC=tumor–infiltrating immune cell; IRF=Independent Review Facility; OR=objective response; ORR=objective response rate; RECIST=Response Evaluation Criteria in Solid Tumors.
Source: Study IMvigor 210 Primary CSR/t_rsp_sub2_ORRIRF_ORE_C2, Study PCD4989g/t_ef_bor_icg4_BTCC_BESRSPR1_OR12, pooled/t_ef_bor_ORRIRF_ICPOOLED3_ORE.

Figure 31 Objective Response Rate by IRF-Assessment per RECIST v1.1 (OR-Evaluable Population)



CI = confidence interval; IC = tumor–infiltrating immune cell; IRF = Independent Review Facility; OR = objective response; ORR = objective response rate; RECIST = Response Evaluation Criteria in Solid Tumors.
Source: Study IMvigor 210 Primary CSR/t_rsp_sub2_ORRINV_ORE_C2, Study PCD4989g/t_ef_bor_icg4_BTCC_BESRSPI_OR12, pooled/t_ef_bor_ORRINV_ICPOOLED3_ORE.

Figure 32 Objective Response Rate by Investigator-Assessment per RECIST v1.1 (OR-Evaluable Population)

Table 70: Pooled Efficacy Population: Duration of Response (OR-Evaluable Population, for Responder)

	IC0	IC1	IC2/3
DOR per IRF-RECIST v1.1			
Number of responders	11	18	34
Patients with event (%)	0	3 (16.7%)	5 (14.7%)
Time to event (months)			
Median	NE	NE	NE
95% CI	NE	(9.63, NE)	(9.20, NE)
Range	2.1*–15.2*	2.1*–15.9*	2.1*–14.7*
DOR per INV-RECIST v1.1			
Number of responders	16	22	31
Patients with event (%)	3 (18.8%)	3 (13.6%)	3 (9.7%)
Time to event (months)			
Median	15.21	NE	NE
95% CI	(6.21, 15.21)	(11.33, NE)	(9.20, NE)
Range	1.6*–15.2	2.1*–15.9*	2.1*–14.7*

*= censored value; CI = confidence interval; DOR = duration of response; IC = tumor–infiltrating immune cell; INV = investigator; IRF = Independent Review Facility; NE = not estimable; OR = objective response; RECIST = Response Evaluation Criteria in Solid Tumors.

Table 71: Pivotal Study IMvigor 2010 Cohort 2 vs Supportive Study PDC4989g Urothelial Carcinoma Cohort: Progression Free Survival Assessed by Investigator-Assessment per RECIST v1.1

	IMvigor 210 Cohort 2 (ITT Population)			PCD4989g Urothelial Carcinoma Cohort (Efficacy-Evaluable Population)		
	IC0 n=103	IC1 n=108	IC2/3 n=100	IC0 n=18	IC1 n=30	IC2/3 n=19
Patient with event, n (%)	80 (77.7)	90 (83.3)	73 (73.0)	17 (94.4)	22 (73.3)	12 (63.2%)
Time to event (months)						
Median	2.07	2.07	2.48	1.82	4.17	5.52
95% CI	(2.00, 2.63)	(2.00, 2.14)	(2.10, 4.17)	(1.41, 2.66)	(1.41, 8.61)	(1.38, NE)
Range	0.0*–9.0*	0.0*–10.5*	0.6–9.9*	1.2–16.5	0.6–17.2*	0.3–17.2*
Landmark analysis						
1 year						
Patients at risk, n	NE	NE	NE	1	5	4
PFS rate (95% CI)	NE (NE)	NE (NE)	NE (NE)	8.33 (0.0, 22.74)	29.63 (13.15, 46.11)	32.75 (10.57, 54.93)
6 months						
Patients at risk, n	19	24	31	3	11	8
PFS rate (95% CI)	22.25 (13.81, 30.70)	24.29 (16.08, 32.50)	32.76 (23.52, 42.00)	16.67 (0.00, 33.88)	36.67 (19.42, 53.91)	44.91 (21.92, 67.90)

*=censored value; CI=confidence interval; IC=tumor–infiltrating immune cell; ITT=intent-to-treat; NE=not estimable; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors.

Table 72 Pivotal Study IMvigor 210 Cohort vs Supportive Study PDC4989g Urothelial Carcinoma Cohort: Overvall Survival

	IMvigor 210 Cohort 2 (ITT Population)			PCD4989g Urothelial Carcinoma Cohort (Efficacy-Evaluable Patients)		
	IC0 n=103	IC1 n=108	IC2/3 n=100	IC0 n=18	IC1 n=30	IC2/3 n=19
Patient with event, n (%)	48 (46.6)	58 (53.7)	35 (35.0)	8 (44.4)	15 (50.0)	8 (42.1)
Time to event (months)						
Median	7.46	6.41	NE	6.93	13.08	NE
95% CI	4.50, NE	5.39, 8.02	7.62, NE	3.98, NE	6.90, NE	6.34, NE
Range	0.2–10.4*	0.4*–10.6*	0.6–10.4*	1.5–16.6*	0.7–17.5*	0.7–17.5*
Landmark analysis						
1 year						
Patients at risk, n	NE	NE	NE	1	10	6
Survival rate (95% CI)	NE (NE)	NE (NE)	NE (NE)	35.56 (5.43, 65.68)	50.61 (31.06, 70.16)	53.68 (30.01, 77.36)

*=censored value; CI=confidence interval; IC=tumor–infiltrating immune cell; ITT=intent-to-treat; NE=not estimable.

IMvigor 211 – Study GO29294

During the procedure the Applicant provided top-line results of the ongoing Study IMvigor211, a Phase III, global, multicenter, open-label, two-arm, randomized, controlled study designed to evaluate the efficacy and safety of atezolizumab compared with chemotherapy in patients with locally advanced or metastatic urothelial carcinoma (UC).

Methods

Study participants

Main Inclusion Criteria:

- Ability to comply with protocol
- Age ≥ 18 years
- Histologically or cytologically documented locally advanced (T4b, any N; or any T, N 2−3) or metastatic (M1, Stage IV) UBC (also termed transitional cell carcinoma [TCC] or urothelial cell carcinoma [UCC] of the urinary tract; including renal pelvis, ureters, urinary bladder, and urethra)
    - Patients with mixed histologies are required to have a dominant transitional cell pattern.
    - Locally advanced bladder cancer must be inoperable on the basis of involvement of pelvic sidewall or adjacent viscera (clinical stage T4b) or bulky nodal metastasis (N2−N3).
- Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:

    Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)

    No ongoing requirement for corticosteroids as therapy for CNS disease

    No stereotactic radiation within 7 days

    No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

    Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to enrollment [or randomization], if all other criteria are met.
- Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (blocks preferred) or at least 15 unstained slides, with an associated pathology report, for central testing and determined to be evaluable for tumor PD-L1 expression prior to study enrollment;
- Disease progression during or following treatment with at least one platinum-containing regimen (e.g., GC, MVAC, CarboGem, etc.) for inoperable, locally advanced or metastatic UBC or disease recurrence

    A regimen is defined as patients receiving at least two cycles of a platinum-containing regimen.

    Patients who received prior adjuvant/neoadjuvant chemotherapy and progressed within 12 months of treatment with a platinum-containing adjuvant/neoadjuvant regimen will be considered as second-line patients.

Patients may have received no more than two prior regimens of treatment (including the required platinum-based regimen) for their advanced UBC. Patients must have demonstrated disease progression during or following all prior regimen(s).

Patients who have received one cycle of a platinum-containing regimen but discontinued because of a Grade 4 hematologic toxicity or a Grade ¾ non-hematologic toxicity may also be eligible.

• Patients with disease progression following chemoradiotherapy must demonstrate progression outside the prior radiotherapy port.

• ECOG performance status of 0 or 1

• Life expectancy ≥ 12 weeks

• Measurable disease, as defined by RECIST v1.1

Previously irradiated lesions should not be counted as target lesions.

• Adequate hematologic and end-organ function

Exclusion Criteria:

Cancer-Specific Exclusions

• Any approved anti-cancer therapy, including chemotherapy or hormonal therapy, within 3 weeks prior to initiation of study treatment; the following exceptions are allowed:

- Palliative radiotherapy for bone metastases or soft tissue lesions should be completed > 7 days prior to baseline imaging
- Hormone-replacement therapy or oral contraceptives

• Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days prior to enrolment

• Active or untreated CNS metastases as determined by computed tomography (CT) or magnetic resonance imaging (MRI) evaluation during screening and prior radiographic assessments

• Leptomeningeal disease

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

• Patients with indwelling catheters (e.g., PleurX) are allowed.

• Uncontrolled tumor-related pain

• Uncontrolled hypercalcemia (defined as any one or more of the following criteria:

• Malignancies other than UBC within 5 years prior to Cycle 1, Day 1

General Medical Exclusions

• Pregnant and lactating

• Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)

• Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina

• Patients with a known left ventricular ejection fraction (LVEF) < 40% will be excluded.

• Severe infections within 4 weeks prior to randomization including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia

• Received therapeutic oral or intravenous (IV) antibiotics within 2 weeks prior to randomization

• Major surgical procedure within 4 weeks prior to randomization or anticipation of need for a major surgical procedure during the course of the study other than for diagnosis

• Inability to understand the local language(s) for which the EORTC QLQ-C30 and EQ-5D (3L) questionnaires are available

Exclusion Criteria Related to Paclitaxel

• Prior treatment with paclitaxel for assignment of paclitaxel in the chemotherapy control arm prior to randomization

• History of severe hypersensitivity to paclitaxel or to other drugs formulated with polyoxyethylated castor oil

Exclusion Criteria Related to Docetaxel

• Prior treatment with docetaxel for assignment of docetaxel in the chemotherapy control arm prior to randomization

• History of severe hypersensitivity to docetaxel or to other drugs formulated with polysorbate 80

• Grade ≥ 2 peripheral neuropathy as defined by NCI CTCAE v4.0 criteria

• Inability to discontinue use of strong cytochrome P450 (CYP)3A4 inhibitors including but not limited to ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, or voriconazole

Exclusion Criteria Related to Vinflunine

• Prior treatment with vinflunine for assignment of vinflunine in the chemotherapy control arm prior to randomization

• History of severe hypersensitivity to vinflunine or other vinca alkaloids

Exclusion Criteria Related to Atezolizumab

• 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 including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's

granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

• Patients with prior allogeneic stem cell or solid organ transplantation

• History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan

• Serum albumin < 2.5 g/dL

• Positive test for HIV

• Patients with active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C.

• Active tuberculosis (TB)

• Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study

• Prior treatment with CD137 agonists, anti−programmed death−1 (PD-1), or anti−PD-L1 therapeutic antibody or pathway-targeting agents

• Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin [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 (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumor necrosis factor [TNF] agents) within 2 weeks prior to randomization or anticipated requirement for systemic immunosuppressive medications during the trial

Treatments

Eligible patients were randomized 1:1 to treatment with either chemotherapy (vinflunine 320 mg/m2 intravenous [IV] q3w, paclitaxel 175 mg/m2 IV q3w, or docetaxel 75 mg/m2 IV q3w) or atezolizumab (1200 mg IV q3w). Within the chemotherapy arm, the percentage of patients treated with a taxane was intended to be capped at approximately 40%; until that cap was reached, the selection of the specific chemotherapy (vinflunine or taxane) was per investigator's choice. Patients in the chemotherapy arm received treatment until disease progression. Patients randomized to the atezolizumab arm received atezolizumab as long as they continued to experience clinical benefit in the opinion of the investigator or until unacceptable toxicity or symptomatic deterioration attributed to disease progression (i.e., pain secondary to disease or unmanageable ascites, etc.), as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status.

Objectives

Primary objective:

- OS, defined as the time between the date of randomization and death due to any cause. Patients who were not reported as having died by the date of data cutoff for primary analysis were censored at the date when they were last known to be alive. Patients who do not have post-baseline information were censored at the date of randomization plus one day.

Secondary objectives:

- ORR, defined as the proportion of patients with an objective response (either a complete response [CR] or partial response [PR]) as determined by the investigator with use of Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)
- PFS, defined as the time between the date of randomization and the date of first documented disease progression as determined by the investigator with use of RECIST v1.1 or death due to any cause, whichever occurs first
- DOR, defined as the time between the date of first documented response and the date of first documented disease progression as determined by the investigator with use of RECIST v1.1 or death due to any cause, whichever occurs first.
- Patient Reported Outcomes: UBC cancer symptoms, patient functioning, and health-related quality of life, (HRQoL) as measured by the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30).

Outcomes/endpoints

Primary:

- OS

Secondary:

- ORR, PFS and DOR by investigator assessment per RECIST v1.1

Sample size

A total of 1360 patients were screened; of these, 931 patients were randomized: 464 patients to the chemotherapy arm (250 to vinflunine and 214 to taxanes) and 467 patients to the atezolizumab arm. A 40% cap on randomization to the taxanes within the chemotherapy arm was implemented as a protocol amendment after enrolment had begun. The number of events required to demonstrate efficacy of the atezolizumab treatment arm over the chemotherapy arm (i.e., vinflunine, paclitaxel, or docetaxel) with regard to OS were estimated on the basis of the following assumptions:

• Two-sided significance level of 5%

• 94% power for the primary analysis of OS in the IC2/3 population with an HR of 0.57, corresponding to an improvement in median OS from 7.5 months to 13.2 months

• 98% power for the primary analysis of OS in the IC1/2/3 population with an HR of 0.68, corresponding to an improvement in median OS from 7.5 months to 11 months

• 97% power for the primary analysis of OS in the ITT population with an HR of 0.74, corresponding to an improvement in median OS from 7.5 months to 10.1 months

• 1:1 randomization ratio

• Dropout rate of 5% per year over 24 months

Randomisation

Eligible patients were randomized 1:1 to treatment with either chemotherapy (vinflunine 320 mg/m2 intravenous [IV] q3w, paclitaxel 175 mg/m2 IV q3w, or docetaxel 75 mg/m2 IV q3w) or atezolizumab (1200 mg IV q3w). Patients will receive atezolizumab as long as they continue to experience clinical benefit in the opinion of the investigator until unacceptable toxicity or symptomatic deterioration attributed to disease progression (i.e., pain secondary to disease or unmanageable ascites, etc.) as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status. Within the chemotherapy arm, the percentage of patients treated with a taxane was intended to be capped at approximately 40%; until that cap was reached, the selection of the specific chemotherapy (vinflunine or taxane) was per investigator's choice.

Randomization was stratified by chemotherapy (vinflunine vs. taxane), PD-L1 IHC status (IC0/1 vs. IC2/3), liver metastasis (yes vs. no) and number of baseline prognostic risk factors (0 vs. 1/2/3). Prognostic risk factors included time from prior chemotherapy of <3 months, Eastern Cooperative Oncology Group (ECOG) performance status >0 and hemoglobin <10 g/dL. The choice of chemotherapy (vinflunine vs. taxane) was pre-specified by the investigator prior to randomization.

Blinding (masking)

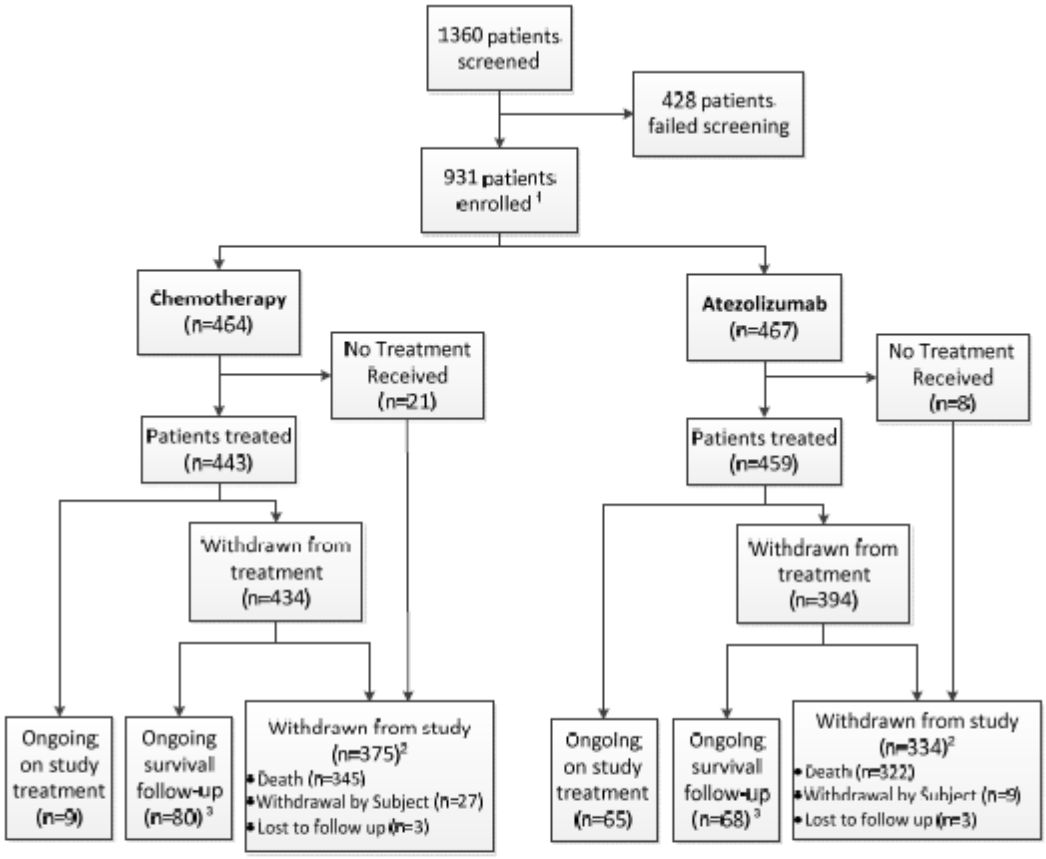
IMvigor 211 was an open label study.

Statistical methods

Comparisons with respect to OS between the treatment arm and control arm within the IC2/3, IC1/2/3, and intent-to-treat (ITT, i.e. all-comers) populations were tested using a hierarchical fixed-sequence procedure based on a stratified log-rank test at two-sided level of 5% as follows: step 1) IC2/3 population; step 2) IC1/2/3 population; step 3) all-comers population. Each of steps 2 and 3 were to be tested only if the null hypothesis of its preceding step is rejected i.e. the IC1/2/3 population could be tested for statistical significance only if the primary endpoint was statistically significant in the IC2/3 population, and similarly the all-comers population could be tested for statistical significance only if the primary endpoint was statistically significant in the IC1/2/3 population. The analysis hierarchy also specified that the secondary endpoints of ORR and PFS were each to be tested in a similarly hierarchical fashion following the analysis of OS. The primary analysis was planned when approximately 152, 403, and 652 deaths had been observed in the IC2/3, IC1/2/3, and all-comers populations, respectively, whichever occurred later.

Results

Participant flow



[1] Due to a randomization error (choice of chemotherapy), a patient was randomized twice to the chemotherapy arm; the patient was first randomized to docetaxel, and was then re-randomized to vinflunine prior to receiving any dose of docetaxel. This patient was counted once in all the tables and plots included in this report.

[2] An additional 5 deaths (4 chemotherapy, 1 atezolizumab) were collected from public records. These 5 patients are captured in the study discontinuation eCRF as "withdrawal by patient", but were included as deaths (i.e., not censored) in the efficacy analyses.

[3] An additional 2 deaths (1 chemotherapy, 1 atezolizumab) were reported during survival follow-up, but were not captured in the study discontinuation eCRF at the time of the clinical cutoff date. These 2 patients are included as deaths (i.e., not censored) in the efficacy analyses.

Source: Summary tables for treatment discontinuation and study discontinuation.

Figure 33 Patient Disposition (ITT Population) – IMvigor211

Recruitment

Australia, Belgium, Bosnia and Herzegovina, Brazil, Canada, Chile, China, Czech Republic, Estonia, Finland, Georgia, Greece, Hong King, Israel, Italy, Korea, Malaysia, Mexico, The Netherlands, Poland, Portugal, Romania, Russia, Serbia, Singapore, South Africa, Spain, Taiwan, Thailand, Turkey, Ukraine, UK, USA.

Baseline data

Table 73: Demographic and Baseline Characteristics, (ITT) – IMvigor 211

	Chemotherapy (N=464)	Atezolizumab (N=467)	All Patients (N=931)
Age (Years)			
n	464	467	931
Mean (SD)	66.1 (9.3)	65.9 (9.6)	66.0 (9.4)
Median	67.0	67.0	67.0
Min - Max	31 - 84	33 - 88	31 - 88
Age Group (Years)			
n	464	467	931
< 65	185 (39.9%)	186 (39.8%)	371 (39.8%)
65 - < 75	193 (41.6%)	188 (40.3%)	381 (40.9%)
75 - < 85	86 (18.5%)	91 (19.5%)	177 (19.0%)
>= 85	0	2 (0.4%)	2 (0.2%)
Age Group < 65 or >= 65 (Years)			
n	464	467	931
< 65	185 (39.9%)	186 (39.8%)	371 (39.8%)
>= 65	279 (60.1%)	281 (60.2%)	560 (60.2%)
Gender			
n	464	467	931
Male	361 (77.8%)	357 (76.4%)	718 (77.1%)
Female	103 (22.2%)	110 (23.6%)	213 (22.9%)

	Chemotherapy (N=464)	Atezolizumab (N=467)	All Patients (N=931)
Race			
n	464	467	931
Asian	55 (11.9%)	63 (13.5%)	118 (12.7%)
Black or African American	2 (0.4%)	1 (0.2%)	3 (0.3%)
White	336 (72.4%)	335 (71.7%)	671 (72.1%)
Multiple	1 (0.2%)	0	1 (0.1%)
Unknown	70 (15.1%)	68 (14.6%)	138 (14.8%)
Smoking History			
n	462	466	928
Current	60 (13.0%)	60 (12.9%)	120 (12.9%)
Previous	280 (60.6%)	266 (57.1%)	546 (58.8%)
Never	122 (26.4%)	140 (30.0%)	262 (28.2%)
Baseline Creatinine Clearance Category			
n	464	467	931
< 60 ml/min	180 (38.8%)	179 (38.3%)	359 (38.6%)
>= 60 ml/min	226 (48.7%)	227 (48.6%)	453 (48.7%)
Unknown	58 (12.5%)	61 (13.1%)	119 (12.8%)
Hemoglobin <10 g/dL			
n	464	467	931
Yes	73 (15.7%)	65 (13.9%)	138 (14.8%)
No	391 (84.3%)	402 (86.1%)	793 (85.2%)
Chemotherapy Stratification			
n	464	467	931
Vinflunine	250 (53.9%)	252 (54.0%)	502 (53.9%)
Taxane	214 (46.1%)	215 (46.0%)	429 (46.1%)
Baseline ECOG Score			
n	464	467	931
0	207 (44.6%)	218 (46.7%)	425 (45.6%)
1	257 (55.4%)	249 (53.3%)	506 (54.4%)
Time from Prior Chemotherapy (< 3 Months)			
n	464	467	931
Yes	160 (34.5%)	160 (34.3%)	320 (34.4%)
No	304 (65.5%)	307 (65.7%)	611 (65.6%)
Liver Metastases			
n	464	467	931
Yes	130 (28.0%)	138 (29.6%)	268 (28.8%)
No	334 (72.0%)	329 (70.4%)	663 (71.2%)
Number of Prognostic Risk Factors			
n	464	467	931
0	130 (28.0%)	136 (29.1%)	266 (28.6%)
1/2/3	334 (72.0%)	331 (70.9%)	665 (71.4%)
Number of Bellmunt Risk Factors			
n	464	467	931
0	140 (30.2%)	145 (31.0%)	285 (30.6%)
1	208 (44.8%)	214 (45.8%)	422 (45.3%)
2	96 (20.7%)	86 (18.4%)	182 (19.5%)
3	20 (4.3%)	22 (4.7%)	42 (4.5%)
PD-L1 IC score			
n	464	467	931
IC2/3	118 (25.4%)	116 (24.8%)	234 (25.1%)
IC1	191 (41.2%)	200 (42.8%)	391 (42.0%)
IC0	155 (33.4%)	151 (32.3%)	306 (32.9%)
n	464	467	931
IC2/3	118 (25.4%)	116 (24.8%)	234 (25.1%)
IC0/1	346 (74.6%)	351 (75.2%)	697 (74.9%)
n	464	467	931
IC1/2/3	309 (66.6%)	316 (67.7%)	625 (67.1%)
IC0	155 (33.4%)	151 (32.3%)	306 (32.9%)

Number of Prognostic Risk Factors was based on baseline ECOG score >=1, prior chemo <3 month, hemoglobin <10 g/dL. Number of Bellmunt Risk Factors was based on baseline ECOG score >=1, liver metastases, hemoglobin <10 g/dL. ULN = Upper Limit of Normal; LLN = Lower Limit of Normal
Data Cut-off: 13 Mar 2017; RAVE Data Extracted: 28 Apr 2017

Table 74: Baseline Disease Characteristics (ITT Population) – IMvigor211

	Chemotherapy (N=464)	Atezolizumab (N=467)	All Patients (N=931)
Urothelial Bladder Cancer Site			
n	464	467	931
Bladder	338 (72.8%)	324 (69.4%)	662 (71.1%)
Renal Pelvis	52 (11.2%)	66 (14.1%)	118 (12.7%)
Ureter	58 (12.5%)	60 (12.8%)	118 (12.7%)
Urethra	9 (1.9%)	9 (1.9%)	18 (1.9%)
Other	7 (1.5%)	8 (1.7%)	15 (1.6%)
Histology at Initial Diagnosis			
n	463	467	930
TCC	427 (92.2%)	425 (91.0%)	852 (91.6%)
Mixed histology	36 (7.8%)	42 (9.0%)	78 (8.4%)
Lymph Node Only Disease			
n	464	467	931
Yes	66 (14.2%)	54 (11.6%)	120 (12.9%)
No	398 (85.8%)	413 (88.4%)	811 (87.1%)
Visceral Metastases			
n	464	467	931
Yes	355 (76.5%)	361 (77.3%)	716 (76.9%)
No	109 (23.5%)	106 (22.7%)	215 (23.1%)
Prior Cystectomy			
n	464	467	931
Yes	200 (43.1%)	199 (42.6%)	399 (42.9%)
No	264 (56.9%)	268 (57.4%)	532 (57.1%)
No. of Prior Metastatic Systemic Regimens			
n	464	467	931
0	120 (25.9%)	131 (28.1%)	251 (27.0%)
1	261 (56.3%)	249 (53.3%)	510 (54.8%)
2	74 (15.9%)	79 (16.9%)	153 (16.4%)
>=3	9 (1.9%)	8 (1.7%)	17 (1.8%)
Prior Systemic Regimen Settings			
n	464	467	931
Adjuvant or Neo-Adjuvant having first PD			
- beyond 12 months	4 (0.9%)	4 (0.9%)	8 (0.9%)
- within 12 months	108 (23.3%)	117 (25.1%)	225 (24.2%)
- unknown	0	2 (0.4%)	2 (0.2%)
Metastatic	344 (74.1%)	336 (71.9%)	680 (73.0%)
Others	8 (1.7%)	8 (1.7%)	16 (1.7%)

Investigator text for medical history conditions was coded using MedDRA version 19.1.
BCG = Bacillus Calmette-Guerin
Data Cut-off: 13 Mar 2017; RAVE Data Extracted: 28 Apr 2017

Numbers analysed

Table 75: Patients Disposition from Study, Intent-to-Treat Patients

	Chemotherapy (N=464)	Atezolizumab (N=467)	All Patients (N=931)
Received Treatment	443 (95.5%)	459 (98.3%)	902 (96.9%)
Discontinued Study	375 (80.8%)	334 (71.5%)	709 (76.2%)
Death	345 (74.4%)	322 (69.0%)	667 (71.6%)
Lost To Follow-Up	3 (0.6%)	3 (0.6%)	6 (0.6%)
Withdrawal By Subject	27 (5.8%)	9 (1.9%)	36 (3.9%)

Data Cut-off: 13 Mar 2017; RAVE Data Extracted: 28 Apr 2017

Outcomes and estimation

Table 76: Key Efficacy Analyses – IC2/3, IC1/2/3, and All Comers

Efficacy Endpoint	IC2/3		IC1/2/3		All Comers	
	Chemotherapy	Atezolizumab	Chemotherapy	Atezolizumab	Chemotherapy	Atezolizumab
Primary Efficacy Endpoint: Overall Survival	n=118	n=116	n=309	n=316	n=464	n=467
No. of Patients with Event (%) [a]	88 (74.6%)	72 (62.1%)	232 (75.1%)	220 (69.6%)	350 (75.4%)	324 (69.4%)
Median Duration of Survival (months)	10.6	11.1	8.2	8.9	8.0	8.6
95% CI	8.4, 12.2	8.6, 15.5	7.4, 9.5	8.2, 10.9	7.2, 8.6	7.8, 9.6
Stratified Analysis						
Hazard Ratio	0.87		0.87		0.85	
95% CI	0.63, 1.21		0.71, 1.05		0.73, 0.99	
p-value (log-rank)	0.4134		0.1392		0.0378 [d]	
12-month OS rate (KM estimate) (95% CI)	41.2% (32.2, 50.3)	46.4% (37.3, 55.6)	33.2% (27.7, 38.6)	40.0% (34.6, 45.5)	32.4% (28.0, 36.8)	39.2% (34.8, 43.7)
Exploratory Endpoints [b]						
Confirmed ORR (INV-Assessed; RECIST v1.1)	n=116	n=113	n=306	n=312	n=461	n=462
No. of Responders (%)	25 (21.6%)	26 (23.0%)	45 (14.7%)	44 (14.1%)	62 (13.4%)	62 (13.4%)
95% CI	14.46, 30.15	15.61, 31.87	10.93, 19.18	10.44, 18.47	10.47, 16.91	10.45, 16.87
Difference in Response Rates	1.46		−0.60		−0.03	
95% CI	−9.32, 12.24		−6.14, 4.93		−4.43, 4.37	
DOR (Confirmed responders) (INV-Assessed; RECIST v1.1)	n=25	n=26	n=45	n=44	n=62	n=62
No. of Patients with Event (%) [c]	20 (80.0%)	10 (38.5%)	35 (77.8%)	18 (40.9%)	49 (79.0%)	23 (37.1%)
No. of Ongoing Responders (%)	5 (20.0%)	16 (61.5%)	10 (22.2%)	26 (59.1%)	13 (21.0%)	39 (62.9%)
Median Time to Event (months) 95%CI	8.3 (5.6, 13.2)	15.9 (10.4, NE)	8.3 (6.3, 13.2)	15.9 (9.9, NE)	7.4 (6.1, 10.3)	21.7 (13.0, 21.7)

CR = complete response; DOR = duration of response; IC = tumor-infiltrating immune cells; INV = investigator-assessed; NE = not estimable; ORR = objective response rate; OS = overall survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Event refers to death.

[b] ORR and DOR for confirmed responders are presented in this table. Unconfirmed ORR and DOR results are provided in Sections 6.3.2 and 6.4.2, respectively.

[c] Event refers to either disease progression or death.

[d] Due to the results of the hierarchical testing procedure, the OS comparison for the ITT population cannot be considered statistically significant

Source: OS (All comers, IC2/3, IC1/2/3), Confirmed ORR (All comers, IC2/3 , IC1/2/3), Confirmed DOR (All comers, IC2/3 , IC1/2/3)

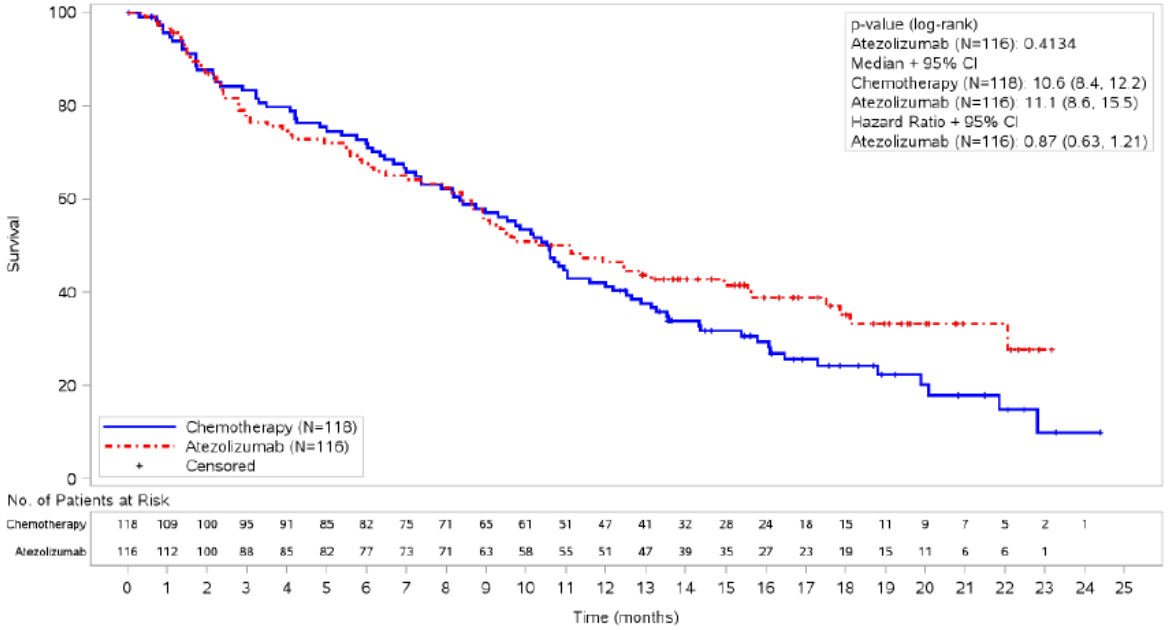
Table 77: Duration of OS – All comers and PD-L1 subgroups

	IC2/3		IC1/2/3		All Comers	
	Chemotherapy	Atezolizumab	Chemotherapy	Atezolizumab	Chemotherapy	Atezolizumab
	n=118	n=116	n=309	n=316	n=464	n=467
No. of Patients with Event (%)	88 (74.6%)	72 (62.1%)	232 (75.1%)	220 (69.6%)	350 (75.4%)	324 (69.4%)
Median Duration of Survival (months)[a]	10.6	11.1	8.2	8.9	8.0	8.6
95% CI	8.4, 12.2	8.6, 15.5	7.4, 9.5	8.2, 10.9	7.2, 8.6	7.8, 9.6
Stratified Analysis						
Hazard Ratio	0.87		0.87		0.85	
95% CI	0.63, 1.21		0.71, 1.05		0.73, 0.99	
p-value (log-rank)	0.4134		0.1392		0.0378	
12-month OS rate (KM estimate) (95% CI)	41.2% (32.2, 50.3)	46.4% (37.3, 55.6)	33.2% (27.7, 38.6)	40.0% (34.6, 45.5)	32.4% (28.0, 36.8)	39.2% (34.8, 43.7)

	IC0		IC1	
	Chemotherapy	Atezolizumab	Chemotherapy	Atezolizumab
	n=155	n=151	n=191	n=200
No. of Patients with Event (%)	118 (76.1%)	104 (68.9%)	144 (75.4%)	148 (74.0%)
Median Duration of Survival (months)[a]	6.7	7.2	7.5	8.4
95% CI	5.6, 8.6	5.4, 9.8	6.3, 8.5	6.8, 9.8
Unstratified Analysis				
Hazard Ratio	0.82		0.85	
95% CI	0.63, 1.07		0.68, 1.08	
12-month OS rate (KM estimate) (95% CI)	30.9% (23.4, 38.4)	37.6% (29.8, 45.4)	28.0% (21.4, 34.6)	36.3% (29.6, 43.1)

A. IC2/3

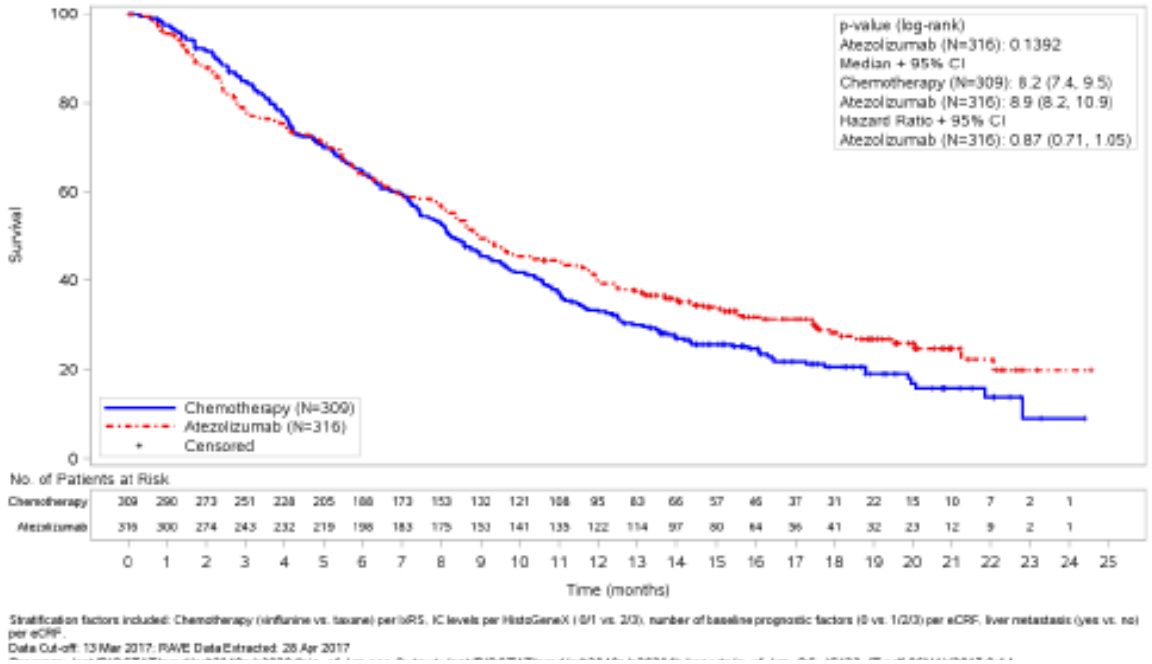
Kaplan-Meier Curves of Overall Survival by Treatment Arm, Stratified Analysis, IC2/3, Intent-to-Treat Patients
Protocol: GO29294 (Datacut date: 13Mar2017)



Stratification factors included: Chemotherapy (vinflunine vs. taxane) per IxRS, number of baseline prognostic factors (0 vs. 1/2/3) per eCRF, liver metastasis (yes vs. no) per eCRF.
Data Cut-off: 13 Mar 2017; RAVE Data Extracted: 28 Apr 2017
Program: /opt/BIOSTAT/prod/cdt3840p/s29294h/g_ef_km.sas Output: /opt/BIOSTAT/prod/cdt3840p/s29294h/reports/g_ef_km_OS_IC23_IT.pdf 06MAY2017 9:13

B. IC1/2/3

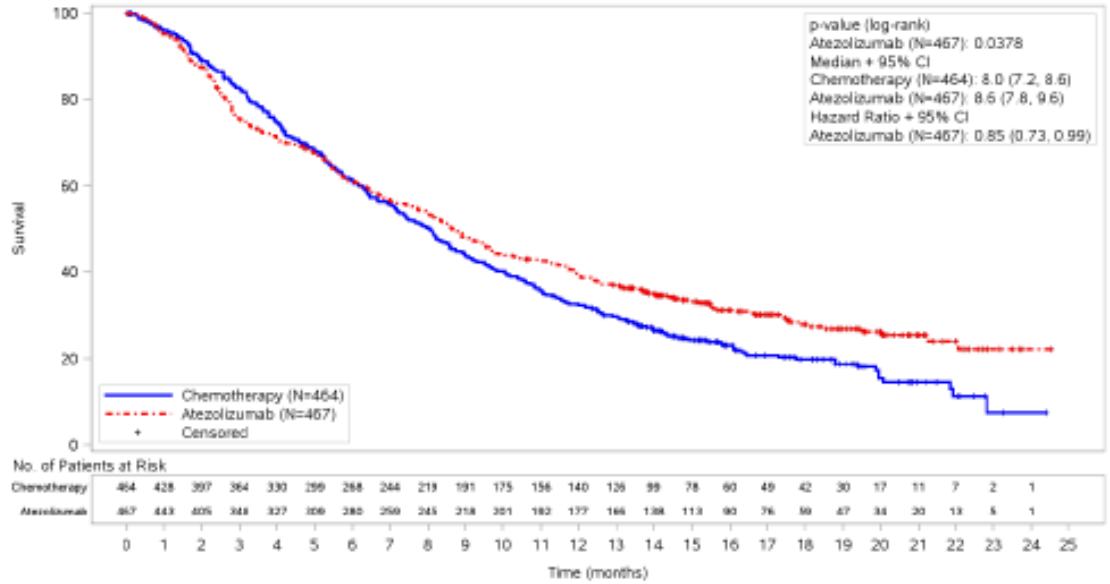
Kaplan-Meier Curves of Overall Survival by Treatment Arm, Stratified Analysis, IC1/2/3, Intent-to-Treat Patients
Protocol: GO29294 (Datacut date: 13Mar2017)



Stratification factors included: Chemotherapy (vinflunine vs. taxane) per IxRS, IC levels per HistoGeneX (0/1 vs. 2/3), number of baseline prognostic factors (0 vs. 1/2/3) per eCRF, liver metastasis (yes vs. no) per eCRF.
Data Cut-off: 13 Mar 2017; RAVE Data Extracted: 28 Apr 2017

C. All comers

Kaplan-Meier Curves of Overall Survival by Treatment Arm, Stratified Analysis, Intent-to-Treat Patients
Protocol: GO29294 (Datacut date: 13Mar2017)



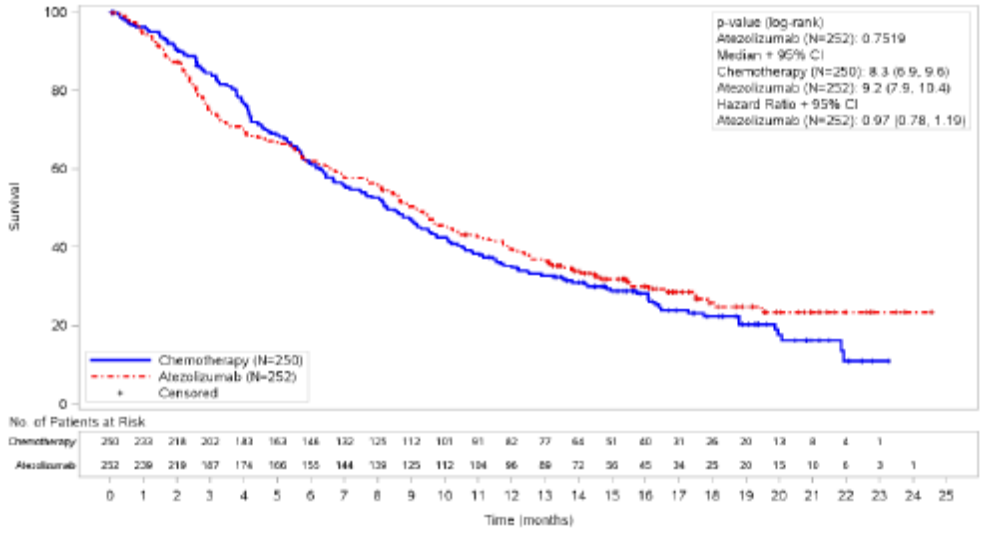
Stratification factors included: Chemotherapy (vinflunine vs. taxane) per IxRS, IC levels per HistoGeneX (0/1 vs. 2/3), number of baseline prognostic factors (0 vs. 1/2/3) per eCRF, liver metastasis (yes vs. no) per eCRF.
Data Cut-off: 13 Mar 2017; RAVE Data Extracted: 28 Apr 2017

Figure 34: Kaplan-Meier Curves of OS by Treatment Arm

OS results were different according to the chemotherapy subgroup (taxane vs. vinflunine as specified by the investigator at the time of randomization). For patients who were intended to treat with taxane, a numerical OS improvement was observed in the atezolizumab arm (n=215) compared with taxanes (n=214); the HR was 0.75 (95%CI: 0.60, 0.94). In the vinflunine subgroup, no OS improvement was observed when comparing atezolizumab (n=252) with vinflunine (n=250) (HR=0.92 [0.75, 1.13]). KM curves are provided in Figure 35

A. Patients intended to be treated with vinflunine (all-comers)

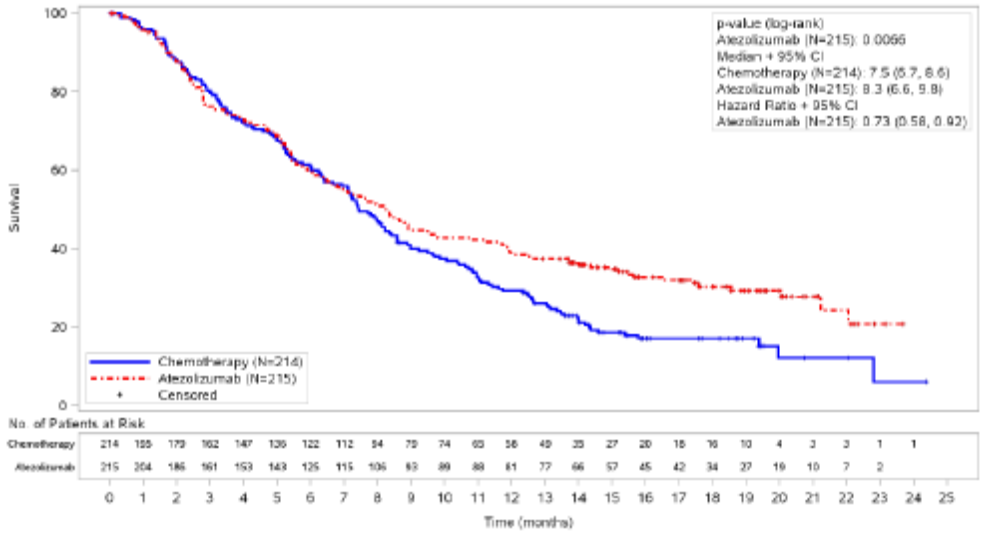
Kaplan-Meier Curves of Overall Survival by Treatment Arm, Stratified Analysis, Vinflunine, Intent-to-Treat Patients
Protocol: GO29294 (Datacut date: 13Mar2017)



Stratification factors included: IC levels per HistoGeneX (0/1 vs. 2/3), number of baseline prognostic factors (0 vs. 1/2/3) per eCRF, liver metastasis (yes vs. no) per eCRF.
Data Cut-off: 13 Mar 2017; RWE Data Extracted: 28 Apr 2017
Program: /opt/BIOSTAT/prod/cdt3840p/s29294h/ig_ef_km.sas Output: /opt/BIOSTAT/prod/cdt3840p/s29294h/reports/ig_ef_km_OS_VIN_IT.pdf 12MAY2017 3:56

B. Patients intended to be treated with taxane (all-comers)

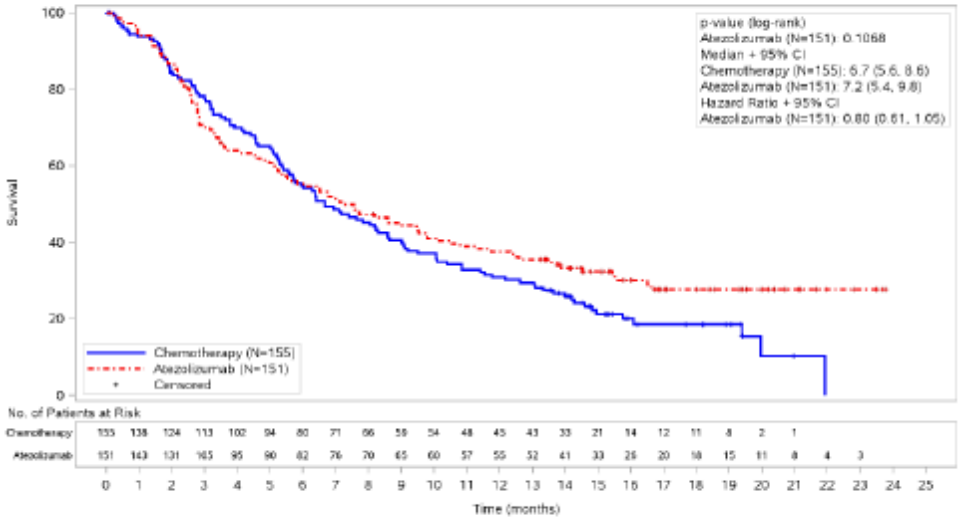
Kaplan-Meier Curves of Overall Survival by Treatment Arm, Stratified Analysis, Taxane, Intent-to-Treat Patients
Protocol: GO29294 (Datacut date: 13Mar2017)



Stratification factors included: IC levels per HistoGeneX (0/1 vs. 2/3), number of baseline prognostic factors (0 vs. 1/2/3) per eCRF, liver metastasis (yes vs. no) per eCRF.
Data Cut-off: 13 Mar 2017; RWE Data Extracted: 28 Apr 2017
Program: /opt/BIOSTAT/prod/cdt3840p/s29294h/ig_ef_km.sas Output: /opt/BIOSTAT/prod/cdt3840p/s29294h/reports/ig_ef_km_OS_TAX_IT.pdf 12MAY2017 3:56

D. IC0

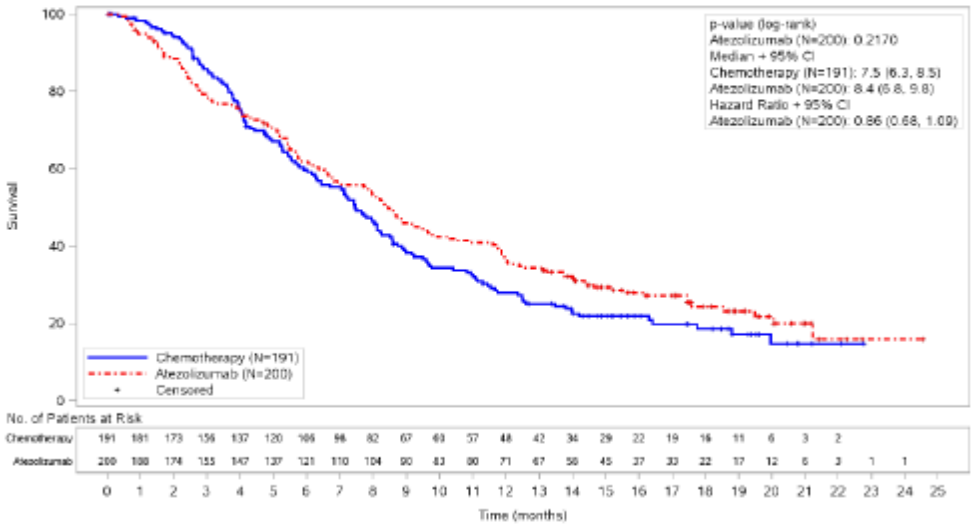
Kaplan-Meier Curves of Overall Survival by Treatment Arm, Stratified Analysis, IC0, Intent-to-Treat Patients
Protocol: GO29294 (Datacut date: 13Mar2017)



Stratification factors included: Chemotherapy (vinflunine vs. taxane) per IxRS, number of baseline prognostic factors (0 vs. 1/2/3) per eCRF, liver metastasis (yes vs. no) per eCRF.
Data Cut-off: 13 Mar 2017; RAVE Data Extracted: 28 Apr 2017
Program: /opt/BIOSTAT/prod/cdt3840p/s29294/sj_ef_km.sas Output: /opt/BIOSTAT/prod/cdt3840p/s29294/reports/g_ef_km_OS_IC0_IT.pdf 08MAY2017 17:48

E. IC1

Kaplan-Meier Curves of Overall Survival by Treatment Arm, Stratified Analysis, IC1, Intent-to-Treat Patients
Protocol: GO29294 (Datacut date: 13Mar2017)



Stratification factors included: Chemotherapy (vinflunine vs. taxane) per IxRS, number of baseline prognostic factors (0 vs. 1/2/3) per eCRF, liver metastasis (yes vs. no) per eCRF.
Data Cut-off: 13 Mar 2017; RAVE Data Extracted: 28 Apr 2017
Program: /opt/BIOSTAT/prod/cdt3840p/s29294/sj_ef_km.sas Output: /opt/BIOSTAT/prod/cdt3840p/s29294/reports/g_ef_km_OS_IC1_IT.pdf 08MAY2017 17:49

Figure 35 Kaplan-Meier Curves of OS by Chemotherapy Regimen (Vinflunine vs. Taxanes)

Table 78: Overall survival data in 2L UC across IMvigor 210 and IMvigor 211

Median OS (months) (12 months OS %)	IMvigor 210 Cohort 2 (n=310)	IMvigor 211 Atezolizumab (n=467)	Imvigor 211 Chemo (n=464)	Imvigor 211 HR OS (95% CI)
All comers	7.9 (36.9%)	8.6 (39.2%)	8.0 (32.4%)	0.85 (0.73, 0.99)
IC1/2/3	9.0 (40.2%)	8.9 (40%)	8.2 (33.2%)	0.87 (0.71, 1.05)
IC2/3	11.9 (49.9%)	11.1 (46.4%)	10.6 (41.2%)	0.87 (0.63, 1.21)
IC1	6.7 (31.2%)	8.4 (36.3%)	7.5 (28%)	0.85 (0.68, 1.08)
ICO	6.5 (30%)	7.2 (37.6%)	6.7 (30.9%)	0.82 (0.63, 1.07)

Supportive study – Study PCD4989g (GO27831)

Study PCD4989g is an ongoing Phase Ia, multicentre, first-in-human, open-label, dose-escalation trial designed to evaluate the safety, tolerability, and pharmacokinetics of atezolizumab in patients with locally advanced or metastatic solid malignancies or hematologic malignancies, including a cohort of patients with UC (2L+ UC).

Study participants:

Study PCD4989g UC Cohort enrolled patients with locally advanced and metastatic or recurrent UC, with measurable disease at baseline assessed per RECIST v1.1 and ECOG PS of 0 or 1. Disease was progressing since the last antitumor therapy.

Treatment:

Atezolizumab IV infusion q3w at 15 mg/kg or 1200 mg. Overall, 86 patients received a weight-based dosing of 15 mg/kg and 6 patients were dosed with a fixed flat dose of 1200 mg of atezolizumab.

Patients remained on study treatment as long as they continued to experience clinical benefit (or occurrence of unacceptable toxicity or symptomatic deterioration attributed to radiographic PD).

Analysis populations:

The primary analysis population identified for the UC indication was the safety-evaluable population, which comprised all enrolled patients who received any amount of atezolizumab (n = 92) as of 2 December 2014.

Efficacy Endpoints

Primary:

- Confirmed ORR per investigator RECIST v1.1 and by IRF RECIST v1.1 assessments

Secondary:

- BOR (best overall response) (unconfirmed), DOR, 6-month PFS, 1-year PFS per RECIST v1.1; and 1-year OS IRF per RECIST v1.1

In the updated analysis of the PCD4989g UC Cohort, there were 93 patients who were OR-evaluable with at least a 24-week follow-up. The median duration of follow-up in this updated analysis was 20.0

months (range: 0.7 to 27.6 months; 0.7 is a censored value) compared with 10.9 months (range: 0.7 to 19.7 months; 0.7 is a censored value) as of 2 December 2014. The updated efficacy analyses for the ORR, BOR, and DOR by IRF-assessment per RECIST v1.1 are summarised in Table 79.

Table 79: Supportive Study PDC4989g: Updated Efficacy Data in Urothelial Carcinoma (OR-Evaluable Population) (Data Cut-off of 7 August 2015)

Efficacy Endpoint	PD-L1 Diagnostic Status				
	IC2/3	IC0/1	IC1	IC0	All patients
ORR (IRF-Assessed; RECIST v1.1)	n = 21	n = 48	n = 30	n = 18	n = 93
No. of responders (%)	7 (33.3)	10 (20.8)	8 (26.7)	2 (11.1)	24 (25.8)
95% CI	(14.59, 56.97)	(10.47, 34.99)	(12.28, 45.89)	(1.38, 34.71)	(17.29, 35.92)
BOR (IRF-Assessed; RECIST v1.1)	n = 21	–	n = 30	n = 18	n = 93
No. of responders (%)	8 (38.1)	–	9 (30.0)	3 (16.7)	27 (29.0)
95% CI	(18.11, 61.56)	–	(14.73, 49.40)	(3.58, 41.42)	(20.08, 39.36)
DOR (IRF-Assessed; RECIST v1.1) [a]	n = 7	–	n = 8	n = 2	n = 24
No. of patients with event (%)	2 (28.6)	–	4 (50.0)	0	8 (33.3)
Median (months)	NE	–	9.63	NE	NE
Range	(9.2–24.0*)	–	(2.9–21.4*)	(16.1*–18.1*)	(2.9–26.3*)

BOR = best overall response; CI = confidence interval; DOR = duration of response; IC = tumor–infiltrating immune cell; IRF = Independent Review Facility; NE = not estimable; OR = objective response; ORR = objective response rate; PD-L1 = programmed death–ligand 1; RECIST = Response Evaluation Criteria in Solid Tumors.
Note: * denotes a censored value. - denotes that the analyses were not performed.
[a] DOR is evaluated in patients with a confirmed OR.
Source: Supplemental Results Report for Study PCD4989g (data cutoff of 7 August 2015) Table 2 and t_ef_bor_icg1_BTCC_BESRSPR1_OR24.

2.6.3. Discussion on clinical efficacy

- **Design and conduct of clinical studies**

The pivotal study is a single-arm study. The inclusion and exclusion criteria are uncontroversial and clearly define the target population as treatment-naïve cisplatin-ineligible patients or as patients that have progressed during or following a platinum-containing regimen.

A single-arm trial design can be appropriate for a setting where there is no approved or acceptable therapeutic option. In the 1L cisplatin ineligible patients, there is no established standard of care, and having in mind the poor prognosis in these patient, it may be justified not randomizing patients to "physicians best choice". With regard to 2L patients, vinflunine is currently the only approved option for patients that have progressed after or on first-line treatment with platinum-containing chemotherapy regimen.

The 10% historical control rate was based on the SEER-medicare data, where the Applicant has calculated a weighted average where approximately 75% of the patients enrolled in Cohort 1 would not receive therapy (the expected ORR would be 0%), and 25% of the patients would receive carboplatinum-based therapy (the expected ORR would be 36%). The Applicant acknowledges that the patients enrolled in Cohort 1 did not match the expected population, and that statistical significance could not be demonstrated.

During the procedure the Applicant provided top-line results from study IMvigor 211, a randomised phase 3 study in the second line setting comparing atezolizumab to chemotherapy (vinflunine or taxanes (docetaxel or paclitaxel)).

- **Efficacy data and additional analyses**

IMvigor 210 - Cohort 1 – 1L cisplatin-ineligible

The Applicant adjusted for multiplicity by using a hierarchical testing procedure, since the result in the IC2/3 subgroup was statistically non-significant (p=0.0717), statistical testing in the IC1/2/3 and the all comers group cannot formally be conducted. The p-value in these subgroups are significant (IC1/2/3 subgroup (p = 0.02469) and all comers (p = 0.0031)), but are as a consequence only for descriptive purposes alone. It is also important to mention that the number of patients in the IC2/3 subgroup is very small (n=32). The ORR by INV is 31.3%, but only three more patients have been deemed to have a response.

The effect of atezolizumab seems to be independent of PD-L1 expression level in 1L cisplatin-ineligible. In the primary analyses, patients with IC0 and IC1 obtain response rates of 20.5% and 16.7% respectively. The median duration of response (DOR) was not reached in any IC subgroup or all comers. Responses appear to be durable, with 22 of 23 responders having an ongoing response by the clinical cut-off date. However in the primary analysis this was based on a median duration of follow-up of 8.5 months (in the all comer population) and only 14 of 23 responders have a duration of follow-up of ≥ 6 months, 4 responders ≥ 9 months and none ≥ 12 months.

The patient population enrolled into Cohort 1 did not match the expectations to include both chemotherapy eligible and ineligible patient populations. The 10% historical control response rate that was assumed at the time of the study design is therefore not appropriate as historical comparator. The patient population ultimately enrolled in Cohort 1 may be best compared to the population enrolled in the EORTC 30986 trial (with CarboGem representing the most appropriate historical comparator). The Applicant presented the baseline characteristics of the EORTC 30986 trial compared with IMvigor 210 in order to justify that the two populations may be considered comparable. However some clinically relevant prognostic criteria appear more favourable for Cohort 1, such as the lower proportion of patients with ECOG PS 2, lower proportion of subjects with both impaired renal function and PS2, lower proportion of Bajorin risk group 2 and the inclusion of subjects with only prior chemotherapy in the neoadjuvant/adjuvant setting. Nonetheless it is acknowledged that overall subjects included in Cohort 1 can be considered representative of a patient population that would be considered eligible for a carboplatin containing combination chemotherapy.

Medians of IRF-assessed PFS per RECIST v1.1 were similar across the pre-defined IC subgroups and all comers (2.92, 2.30, and 2.40 months in the IC2/3 subgroup, the IC1/2/3 subgroup, and all comers, respectively).

Median OS was 10.6 months in each of the IC2/3, IC1/2/3 subgroups, and in all comers. However, OS data were immature based on a median duration of follow-up of only 8.5 months.

Updated data for Cohort 1 were provided with a clinical cut-off date (CCOD) of 4 July 2016 and a median survival follow-up of 17.2 months in the all comer population (representing approximately 10 additional months of follow-up from the time of the primary analysis, 14 September 2015). With longer follow-up the number of responses increased from 23 to 27 leading to an ORR of 22.7% in the all comer population. With five additional complete responses updated CR rate was 9.2%. Responses remain ongoing for the majority of patients (70.4%), the median duration of response was not reached (range for all comers: 3.7 to 21.0 months). Median OS was 15.9 months (95% CI: 10.4, NE) in the all-comers population, with a 12 months OS rate of 57.2%.

Table 80 Main results of Cohort 1 in comparison with historical control for Carbo/Gem:

	IMvigor 210- **Cohort 1** (n=119) IRF-assessed; RECIST v.1.1 Data cutoff 4 July 2016 All comer population	**De Santis**, 2012 (n=119) * Carbo/Gem
ORR CR	22.7% 9.2%	36.1% (confirmed) 2.5%
DOR	NE (median survival follow-up of 17.2 months) Ongoing response: 19/27 (70%)	5.3 months
PFS (median, months)	2.7	5.8
OS (median, months)	15.9 (95% CI: 10.4, NE)	9.3
1-year OS (%)	57.2 (95% CI: 48.2, 66.3)	37

* De Santis et. al, JCO, Jan. 2012; Randomized Phase II/III Trial Assessing Gemcitabine/Carboplatin and Methotrexate/Carboplatin/ Vinblastine in Patients With Advanced Urothelial Cancer Who Are Unfit for Cisplatin-Based Chemotherapy: EORTC Study 30986

Although overall response rates of atezolizumab compare less favourably to the best historical comparator of CarboGem (22.7% vs. 36.1%), responses were ongoing in 70% of patients with a median follow-up of 17.2 months (median DOR not reached compared to 5.3 months for Carbo/Gem).

In order to further support the efficacy of atezolizumab treatment in 1L UC patients, the applicant should submit the results of the ongoing post authorisation efficacy study (PAES) IMvigor 130, a Phase III randomized study evaluating the safety and efficacy of Atezolizumab monotherapy vs. Atezolizumab and carboplatin/gemcitabine vs cisplatin/gemcitabine in cisplatin-ineligible and –eligible patients which are expected to be available by 31 July 2021 (see Annex II). This data will provide further confirmation of the efficacy assumptions as determined from this application in a randomised controlled trial providing direct comparative efficacy results including PFS and OS.

IMvigor 210 Cohort 2 – 2L+

Efficacy results of the non-randomized Study Imvigor 210 (Cohort 2) demonstrated an ORR of 15.8% and a median OS of 7.9 months in the overall study population (n=310). These data are in the range of historical chemotherapy controls.

IMvigor 211

Overall, IMvigor 211 confirmed the efficacy results of IMvigor 210. Although ORR results are numerically slightly lower in IMvigor 211 compared to IMvigor 210 (about 5%), OS data are comparable. Median PFS of atezolizumab was 2.1 months both in IMvigor 211 and in IMvigor 210.

With the applied hierarchical testing (based on the assumption of a predictive value of PD-L1 expression) the study failed to demonstrate a statistically significant OS benefit.

With a median duration of follow up of 17.3 months, response in the all-comers population was ongoing in a majority of responders in the atezolizumab arm (62.9%) compared to 21% in chemotherapy arm. The Kaplan-Meier estimate of median DOR in the atezolizumab arm was 21.7 months compared to 7.4 months in the chemotherapy arm.

A retrospective review of OS events in the period from randomization until the time of the crossing of the Kaplan Meier OS curves was performed. However, no specific characteristics could be identified to select a patient population likely not deriving benefit from atezolizumab.

Study IMvigor 211 resolved the concerns of a lower treatment effect of atezolizumab in subjects with lower PD-L1 expression subgroups (IC0/IC1), but failed to demonstrate significance in the primary OS analysis (which is partly attributed to the fact that PD-L1 expression proved to be rather of prognostic than of predictive value in this data set).

OS data for atezolizumab were numerically superior to SOC for the overall study population and across all IC subgroups. Although this OS advantage appeared to be driven by the comparison to taxanes (HR 0.75), OS for atezolizumab was similar based on visual exploration compared to vinflunine (the only approved drug in this disease setting) (HR 0.92).

Hence, in order to further support the efficacy of atezolizumab treatment in 1L and 2L+ UC the applicant should submit the final results of the PAES IMvigor 210 which are expected to be available by 30 June 2019 (see Annex II). In addition, the applicant should submit the final results of PAES IMvigor 211 (see Annex II) by 31 May 2019.

These data from studies IMvigor 210 and IMvigor 211 will provide further confirmation of the efficacy assumptions as determined from this application in terms of more mature efficacy outcomes and detailed results from study IMvigor 211 as only top-line results were available during the procedure.

Finally, the applicant is recommended to provide a "biomarker analysis plan" with timelines and should submit the results of all ongoing and planned biomarker analyses post-approval.

2.6.4. Conclusions on the clinical efficacy

Overall, study IMvigor 211 resolved the concerns of a lower treatment effect of atezolizumab in subjects with lower PD-L1 expression subgroups (IC0/IC1), but failed to demonstrate significance in the primary OS analysis.

Response rates in the same range as for chemotherapy have been demonstrated consistently in 767 2L UC patients across IMvigor 210 and IMvigor 211. Duration of responses was substantially longer for treatment with atezolizumab (median DOR 21.7 vs. 7.4 months in the atezolizumab vs. control arm). OS data for atezolizumab were numerically superior to SOC for the overall study population and across all IC subgroups. It is recognised that response rates (and the proportion of patients that clearly benefit from atezolizumab) are small in 2L UC (and in this setting there is ultimately a need for combination therapies). But given the sustained responses, the overall numerically favourable OS results, efficacy can be considered established.

With regard to 1L cisplatin ineligible UC there is a high unmet medical need and durable responses have been demonstrated in Cohort 1 of IMvigor 210 that seem to be translated in a survival benefit.

Results from the on-going randomized Study IMvigor 130, study IMvigor 210 and Study IMvigor 211 are requested as PAES. Finally, the applicant is recommended to provide a "biomarker analysis plan" with timelines and should submit the results of all ongoing and planned biomarker analyses post-approval.

2.7. Clinical safety

The overall safety database includes a total of 2160 patients (All Patients Population), including 1636 (75.7%) patients with NSCLC and 524 (24.3%) patients with UC, as per the below table.

Study No.	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	Data Cut-off Date
Pivotal studies					
IMvigor 210 (GO29293)	Phase II, global, multicenter, two-cohort, single-arm trial	Patients with locally advanced or 1L metastatic (no prior chemotherapy in the metastatic setting and ineligible for cisplatin-based chemotherapy) and 2L+ UC patients (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 in each cohort was planned to be PD-L1 – selected (IC2/3).	All patients = 429 Cohort 1 (1L cis-ineligible) = 119 Cohort 2 (2L +) = 310	Atezolizumab 1200 mg IV q3w	4 July 2016
OAK (GO28915)	Phase III, 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 versus 2), histology (non-squamous versus squamous).	609 patients treated with atezolizumab[a]	Atezolizumab 1200 mg IV q3w vs. Docetaxel 75 mg/m^2 q3w	7 July 2016
Supportive studies					
BIRCH (GO28754)	Phase II, global, multicenter, three cohort, single-arm trial	Patients with locally advanced or metastatic NSCLC who were treatment-naive 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).	All patients = 659 Cohort 1 (1L) = 139 Cohort 2 (2L) = 268 Cohort 3 (3L +) = 252	Atezolizumab 1200 mg IV q3w	1 December 2015

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 versus 2), and histology (non-squamous versus squamous).	142 patients treated with atezolizumab[b]	Atezolizumab 1200 mg IV q3w vs. Docetaxel 75 mg/m^2 q3w	1 December 2015
FIR (GO28625)	Phase II, global, multicenter, single-arm trial	Patients with locally advanced or metastatic NSCLC who were treatment-naïve (in metastatic setting; 1L) or progressed during or after one (2L) prior platinum-containing regimen. Patients were PD-L1 – selected (TC2/3 or IC2/3).	All patients=137 Cohort 1 (1L) = 31 Cohort 2 (2L+) = 93 Cohort 3 (2L+)[c] = 13	Atezolizumab 1200 mg IV q3w	7 January 2015
PCD4989g (GO27831)	Phase I, open-label, dose-escalation and dose-expansion stages	Patients with locally advanced or metastatic solid tumors (including UC and NSCLC) and hematologic malignancies.	UC = 95 NSCLC = 89	UC Cohort: 15 mg/kg and fixed 1200 mg[d] NSCLC Cohort: 1, 10, 15, 20 mg/kg	31 March 2016

1L = first-line; 2L+ = second-line and beyond; IC = tumor-infiltrating immune cells; IV = intravenous; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; TC = tumor cell; mUC = metastatic urothelial carcinoma; UC = urothelial carcinoma; q3w = every 3 weeks.

[a] 578 patients were treated with docetaxel 75 mg/m2 q3w in Study OAK

[b] 135 patients were treated with docetaxel 75 mg/m2 q3w in Study POPLAR

[c] 2L + patients with previously treated brain metastases (Study FIR)

[d] Equivalent to an average body weight-based dose of 15 mg/kg.

From these studies, 3 main pooled safety populations were defined:

- Pooled All Patients (N=2160): all safety evaluable patients enrolled in Studies, OAK (atezolizumab treated patients only), BIRCH, POPLAR (atezolizumab treated patients only), FIR, the UC and NSCLC Cohorts of Study PCD4989g and the Cohorts 1 and 2 of study IMvigor 210.
- Pooled All NSCLC population (N=1636): all NSCLC safety evaluable patients from Studies OAK (atezolizumab treated patients only), BIRCH, POPLAR (atezolizumab treated patients only), FIR, and the NSCLC Cohort of Study PCD4989g.
    - A subpopulation analysis was performed based on all treated 2L+NSCLC patients (atezolizumab arm of OAK study, Cohorts 2 and 3 of BIRCH study, atezoluzumab arm of POPLAR, Cohorts 2 and 3 of FIR and NSCLC cohort (2L+) of study PCD4989g).
- Pooled All UC population (N=524): all safety evaluable patients with UC and comprises patients enrolled in Study IMvigor 210 (both Cohorts 1 and 2), and the UC Cohort of Study PCD4989g.

In all atezolizumab clinical studies, patients were categorized based on PD-L1 expression in tumour cells (TC) (NCSLC setting only) and immune-cell (IC) (UC and NCSLC settings). Safety was also evaluated in the TC/IC subpopulations as described in the below table.

Table 81 Safety Analysis Populations

Population	Patients Included	Number of Patients
1. All Patients	All safety evaluable patients enrolled in Studies IMvigor 210 (both Cohorts 1 and 2), OAK[b], BIRCH, POPLAR[b], FIR, and the UC and NSCLC Cohorts of Study PCD4989g	2160
2. All UC	All safety-evaluable patients with UC from Studies IMvigor 210 and PCD4989g	524
1L cis-in UC all comers	All safety-evaluable patients from Cohort 1 of Study IMvigor 210	119
1L cis-in UC IC0	All safety-evaluable patients from Cohort 1 of Study IMvigor 210 with IC score of 0	39
1L cis-in UC IC1	All safety-evaluable patients from Cohort 1 of Study IMvigor 210 with IC score of 1	48
1L cis-in UC IC1/2/3	All safety-evaluable patients from Cohort 1 of Study IMvigor 210 with IC score of 1, or 2/3	80
1L cis-in UC IC2/3	All safety-evaluable patients from Cohort 1 of Study IMvigor 210 with IC score of 2/3	32
2L+UC all comers	All safety-evaluable patients with UC from Studies IMvigor 210[a] (Cohort 2 only) and PCD4989g[e]	405
2L+UC IC0	All safety-evaluable patients with UC with IC score of 0 from Studies IMvigor 210[a] (Cohort 2 only) and PCD4989g	121
2L+UC IC1	All safety-evaluable patients with UC with IC score of 1 from Studies IMvigor 210[a] (Cohort 2 only) and PCD4989g	137
2L+UC IC1/2/3	All safety-evaluable patients with UC with IC score of 1, 2 or 3 from Studies IMvigor 210[a] (Cohort 2 only) and PCD4989g	259
2L+UC IC2/3	All safety-evaluable patients with UC with IC scores of 2 or 3 from Studies IMvigor 210[a] (Cohort 2 only) and PCD4989g	122
3. All NSCLC	All safety-evaluable patients with NSCLC from Studies OAK[b], BIRCH, POPLAR[b], FIR and PCD4989g	1636
2L+NSCLC all patients	All safety-evaluable patients with 2L+ NSCLC from Studies OAK[b], BIRCH[c], POPLAR[b], FIR[c] and PCD4989g	1452
2L+NSCLC TC1/2/3 or IC1/2/3	All safety-evaluable patients with 2L+ NSCLC with TC or IC score of 1, 2 or 3 from Studies OAK[b], POPLAR[b] and PCD4989g	488[d]
2L+NSCLC TC2/3 or IC2/3	All safety-evaluable patients with 2L+ NSCLC with TC or IC scores of 2 or 3 from Studies OAK[b], BIRCH[c], POPLAR[b], FIR[c] and PCD4989g	882
2L+NSCLC TC3 or IC3	All safety-evaluable patients with 2L+ NSCLC with TC or IC scores of 3 from Studies OAK[b], BIRCH[c], POPLAR[b], FIR[c] and PCD4989g	416
2L+NSCLC TC0 and IC0	All safety-evaluable patients with TC and IC scores of 0 from Studies OAK, and POPLAR (atezolizumab and docetaxel treated patients)	292 (docetaxel) 309 (atezolizumab)

1L cis-in: first line cisplatin ineligible; 2L: second line; UC: urothelial carcinoma; NSCLC: non-small cell lung cancer; IC = tumor-infiltrating immune cell; TC = tumor cell.

In addition, supportive safety data were provided from Study IMvigor 211. In this study, patients with locally advanced or metastatic urothelial carcinoma (UC) who have progressed during or following a platinum-containing regimen were randomized to treatment with either chemotherapy (vinflunine 320 mg/m2 intravenous [IV] q3w, paclitaxel 175 mg/m2 IV q3w, or docetaxel 75 mg/m2 IV q3w) or atezolizumab (1200 mg IV q3w).

Atezolizumab-treated patients from this study were not included in the pooled analysis.

Patient exposure

All patients in the IMvigor 210, OAK, BIRCH, POPLAR and FIR studies were exposed to atezolizumab 1200 mg given q3w. In the supportive study PCD4989g, 86 patients from the UC Cohort and 26 patients from the NSCLC Cohort of PCD4989g received atezolizumab at a dose of 15 mg/kg q3w (equivalent to 1200 mg for an 80 kg adult patient), and 50 patients, 11 patients, and 1 patient in the NSCLC Cohort of PCD4989g received 20 mg/kg q3w, 10 mg/kg q3w, and 1 mg/kg q3w, respectively.

At the fixed dose of 1200 mg, the median duration of exposure to atezolizumab was 3.5 months in the All Patients population (range 0.0-26.3 months): 2.9 months in the All UC population and 3.6 months in the All NSCLC population. Overall, 54.7% of patients had received more than 3 months of atezolizumab treatment, 37.0% had received more than 6 months of treatment, and 21.4% had received more than 12 months of treatment. The median number of treatment cycles received was 6 (range: 1 - 38).

Table 82 Exposure to atezolizumab at a dose of 1200mg every three weeks (safety –evaluable patients who received 1200mg of atezolizumab)

UC and NSCLC Safety Evaluable Patients
Protocols: GO27831 (UC and NSCLC Cohort), GO28625, GO28753, GO28754, GO29293, GO28915

	All Patients (N=2160)	All UC (N=524)	All NSCLC (N=1636)
Treatment duration (M)			
n	1986	438	1548
Mean (SD)	6.33 (6.51)	6.37 (7.29)	6.32 (6.28)
Median	3.48	2.89	3.55
Min - Max	0.0 - 26.3	0.0 - 24.0	0.0 - 26.3
Treatment duration (M)			
n	1986	438	1548
<=3	900 (45.3%)	222 (50.7%)	678 (43.8%)
>3-6	352 (17.7%)	70 (16.0%)	282 (18.2%)
>6-12	309 (15.6%)	58 (13.2%)	251 (16.2%)
>12-18	257 (12.9%)	25 (5.7%)	232 (15.0%)
>18-24	152 (7.7%)	63 (14.4%)	89 (5.7%)
>24	16 (0.8%)	0	16 (1.0%)
Dose intensity (%)			
n	1986	438	1548
Mean (SD)	97.3 (6.5)	98.6 (5.8)	96.9 (6.6)
Median	100.0	100.0	99.5
Min - Max	33 - 147	50 - 100	33 - 147
Number of cycles			
n	1986	438	1548
Mean (SD)	9.74 (9.11)	9.79 (10.22)	9.73 (8.77)
Median	6.00	5.00	6.00
Min - Max	1.0 - 38.0	1.0 - 35.0	1.0 - 38.0

M=Months. Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Dose intensity is the number of doses actually received divided by the expected number of doses.
GO27831=PCD4989g; GO28625=FIR; GO28753=POPLAR; GO28754=BIRCH; GO29293=IMvigor 210; GO28915=OAK.
Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO29293:04JUL2016, GO28915:07JUL2016.

The median duration of safety follow-up was 4.5 months (range: 0.5 -53.0 months); 3.9 months in the All UC population and 4.5 months in the All NSCLC population.

At the time of data cut-off for each study, 63.6% of study participants in the All Patients had withdrawn from the study. The majority, representing 69.1%, discontinued due to progressive disease.

Table 83 Overview of frequency and reasons for study treatment discontinuation (safety –evaluable patients)

	All Patients (N=2160)	All UC (N=524)	All NSCLC (N=1636)
Discontinued treatment	1797 (83.2%)	447 (85.3%)	1350 (82.5%)
Adverse Event	148 (6.9%)	30 (5.7%)	118 (7.2%)
Completed	21 (1.0%)	6 (1.1%)	15 (0.9%)
Death	14 (0.6%)	0	14 (0.9%)
Lost To Follow-Up	2 (<0.1%)	1 (0.2%)	1 (<0.1%)
Non-Compliance	7 (0.3%)	3 (0.6%)	4 (0.2%)
Other	9 (0.4%)	4 (0.8%)	5 (0.3%)
Physician Decision	21 (1.0%)	6 (1.1%)	15 (0.9%)
Progressive Disease	1493 (69.1%)	371 (70.8%)	1122 (68.6%)
Protocol Violation	13 (0.6%)	0	13 (0.8%)
Withdrawal By Subject	69 (3.2%)	26 (5.0%)	43 (2.6%)

Adverse events

Per the study protocols for Study IMvigor 210, OAK, POPLAR, BIRCH, FIR and PCD4989g, adverse events were collected from the day of administration of the first dose of study treatment until 30 days (IMvigor210, OAK and BIRCH) or 90 days (POPLAR, FIR and PCD4989g) after the last does of study drug or until initiation of another non-protocol anti-cancer therapy, whichever occurred first. For AESIs and treatment-related SAEs, no 30-day or 90-day window was applied.

A categorical overview of the AE safety profile for the different populations is presented in the table below.

Table 84 Overview of Safety (Safety-Evaluable Patients)

	All Patients N = 2160	All UC N = 524	All NSCLC N = 1636	IMvigor 210 Cohort 1 N = 119	IMvigor 210 Cohort 2 N = 310	OAK N = 609	BIRCH N = 659	POPLAR N = 142	FIR N = 137	PCD4989g UC Cohort N = 95	PCD4989g NSCLC Cohort N = 89
Total number of patients with at least one AE	2061 (95.4%)	510 (97.3%)	1551 (94.8%)	114 (95.8%)	303 (97.7%)	573 (94.1%)	618 (93.8%)	136 (95.8%)	136 (99.3%)	93 (97.9%)	88 (98.9%)
Total number of patients with at least one treatment-related AE	1437 (66.5%)	362 (69.1%)	1075 (65.7%)	79 (66.4%)	220 (71.0%)	390 (64.0%)	429 (65.1%)	95 (66.9%)	93 (67.9%)	63 (66.3%)	68 (76.4%)
Total number of patients with:											
Grade 3-4 AE	948 (43.9%)	288 (55.0%)	660 (40.3%)	54 (45.4%)	186 (60.0%)	227 (37.3%)	275 (41.7%)	58 (40.8%)	66 (48.2%)	48 (50.5%)	34 (38.2%)
Treatment-related Grade 3-4 AE	302 (14.0%)	84 (16.0%)	218 (13.3%)	19 (16.0%)	56 (18.1%)	90 (14.8%)	81 (12.3%)	17 (12.0%)	20 (14.6%)	9 (9.5%)	10 (11.2%)
Grade 5 AE	52 (2.4%)	8 (1.5%)	44 (2.7%)	4 (3.4%)	3 (1.0%)	10 (1.6%)	21 (3.2%)	7 (4.9%)	5 (3.6%)	1 (1.1%) [a]	1 (1.1%) [a]
Treatment-related Grade 5 AE	4 (0.2%)	1 (0.2%)	3 (0.2%)	1 (0.8%)	0	0	1 (0.2%)	1 (0.7%)	1 (0.7%)	0	0
SAE	832 (38.5%)	234 (44.7%)	598 (36.6%)	45 (37.8%)	144 (46.5%)	194 (31.9%)	252 (38.2%)	51 (35.9%)	65 (47.4%)	45 (47.4%)	36 (40.4%)
Treatment-related SAE	221 (10.2%)	55 (10.5%)	166 (10.1%)	12 (10.1%)	38 (12.3%)	63 (10.3%)	68 (10.3%)	12 (8.5%)	14 (10.2%)	5 (5.3%)	9 (10.1%)
AE leading to treatment withdrawal	143 (6.6%)	25 (4.8%)	118 (7.2%)	9 (7.6%)	12. (3.9%)	46 (7.6%)	43 (6.5%)	12 (8.5%)	13 (9.5%)	4 (4.2%)	4 (4.5%)
AE leading to dose modification/interruption	597 (27.6%)	164 (31.3%)	433 (26.5%)	41 (34.5%)	100 (32.3%)	152 (25.0%) [b]	187 (28.4%)	36 (25.4%)	32 (23.4%)	23 (24.2%)	27 (30.3%)
AESI of Any Grade	648 (30.0%)	165 (31.5%)	483 (29.5%)	37 (31.1%)	93 (30.0%)	184 (30.2%)	196 (29.7%)	44 (31.0%)	31 (22.6%)	35 (36.8%)	28 (31.5%)
AESI of Grade 3-4	122 (5.6%)	37 (7.1%)	85 (5.2%)	9 (7.6%)	20 (6.5%)	31 (5.1%)	37 (5.6%)	9 (6.3%)	6 (4.4%)	8 (8.4%)	2 (2.2%)
AESI of Grade 5	1 (<0.1%)	0	1 (<0.1%)	0	0	0	1 (0.2%)	0	0	0	0

Note: All AEs collected after first treatment dose and within 30 days from last treatment dose, start of a non-protocol cancer therapy, or discontinuation from study are included, except for AESIs and treatment-related SAEs where no 30 day-time window was applied.
Atezolizumab treated patients only.
Clinical cutoff dates: IMvigor 210 (4 July 2016); OAK (7 July 2016); BIRCH (1 December 2015); POPLAR (1 December 2015); FIR (7 January 2015); PCD4989g (31 March 2016).

In the All Patients population, most patients experienced at least one AE of any grade (95.4%). Overall, AEs of Grade 1 or 2 maximum intensity were experienced by 49.1% of patients, and Grade 3 or Grade 4 AEs (maximum intensity) by 43.9% of patients. Grade 5 AEs occurring within 30 days after last dose of study treatment or prior to initiation of non-protocol anti-cancer therapy were reported in 2.4% (52/2160) of All Patients.

The most common AEs per SOC (> 20% of patients) and PT (> 10% of patients) reported were:

- General disorders and administration site conditions (67.6%), most commonly fatigue, pyrexia, asthenia, peripheral oedema
- Gastrointestinal disorders (57.1%), most commonly nausea, diarrhoea, constipation, vomiting
- Respiratory, thoracic and mediastinal disorders (51.9%), most commonly dyspnoea, cough,
- Musculoskeletal and connective tissue disorders (47.5%), most commonly back pain, arthralgia,
- Metabolism and nutrition disorders (41.3%), most commonly decreased appetite,
- Infections and infestations (41.6%),
- Skin and subcutaneous tissue disorders (33.5%), most commonly pruritus, rash
- Nervous system disorders (31.2%), most commonly headache
- Investigations (26.3%)

Table 85 Common Adverse Events Reported in ≥ 10% of Patients (All Patients Population)

MedDRA Preferred Term	All Patients (N=2160)	All UC (N=524)	All NSCLC (N=1636)
Total number of patients with at least one adverse event	1855 (85.9%)	472 (90.1%)	1383 (84.5%)
Total number of events	9049	2670	6379
FATIGUE	762 (35.3%)	249 (47.5%)	513 (31.4%)
DECREASED APPETITE	547 (25.3%)	143 (27.3%)	404 (24.7%)
COUGH	492 (22.8%)	87 (16.6%)	405 (24.8%)
NAUSEA	486 (22.5%)	134 (25.6%)	352 (21.5%)
DYSPNOEA	461 (21.3%)	80 (15.3%)	381 (23.3%)
CONSTIPATION	408 (18.9%)	122 (23.3%)	286 (17.5%)
DIARRHOEA	399 (18.5%)	112 (21.4%)	287 (17.5%)
PYREXIA	391 (18.1%)	106 (20.2%)	285 (17.4%)
VOMITING	320 (14.8%)	93 (17.7%)	227 (13.9%)
ARTHRALGIA	306 (14.2%)	86 (16.4%)	220 (13.4%)
BACK PAIN	302 (14.0%)	93 (17.7%)	209 (12.8%)
ASTHENIA	296 (13.7%)	58 (11.1%)	238 (14.5%)
ANAEMIA	289 (13.4%)	99 (18.9%)	190 (11.6%)
PRURITUS	244 (11.3%)	81 (15.5%)	163 (10.0%)
RASH	227 (10.5%)	60 (11.5%)	167 (10.2%)
HEADACHE	216 (10.0%)	46 (8.8%)	170 (10.4%)
OEDEMA PERIPHERAL	216 (10.0%)	82 (15.6%)	134 (8.2%)
URINARY TRACT INFECTION	194 (9.0%)	117 (22.3%)	77 (4.7%)
ABDOMINAL PAIN	154 (7.1%)	68 (13.0%)	86 (5.3%)
BLOOD CREATININE INCREASED	107 (5.0%)	59 (11.3%)	48 (2.9%)
HAEMATURIA	93 (4.3%)	72 (13.7%)	21 (1.3%)

Grade 5 AEs due to PD are excluded for studies GO27831 and GO28625.

The incidence of fatigue, urinary tract infection (UTI), oedema peripheral, abdominal pain, and haematuria was higher in the All UC population, whereas dyspnoea and cough were more frequent in the All NSCLC population.

The most common Grade 3 or 4 AEs (> 2% of patients) by preferred term were dyspnoea, anaemia, fatigue, hyponatraemia and pneumonia.

Table 86 Grade 3 or 4 AEs by Preferred Term occurring in >2% of patients in the All Patients Population (safety-evaluable patients)

AE (Preferred Term)	All Patients N = 2160	All UC N = 524	All NSCLC N = 1636
Dyspnoea	78 (3.6%)	13 (2.5%)	65 (4.0%)
Anaemia	82 (3.8%)	42 (8.0%)	40 (2.4%)
Fatigue	71 (3.3%)	27 (5.2%)	44 (2.7%)
Hyponatraemia	61 (2.8%)	19 (3.6%)	42 (2.6%)
Pneumonia	65 (3.0%)	6 (1.1%)	59 (3.6%)

Adverse events of special interest (AESI)

Overall, 30.0% of the All Patients Population reported at least one AESI. The most common AESIs (> 2% of patients) were reported in the following SOCs (with the most common AE PTs, reported in at least 2% of patients): *skin and subcutaneous tissue disorders* (16.0%), most commonly rash (10.6%) and maculo-papular rash (2.3%); *Investigations* (7.8%), most commonly AST (5.3%) and ALT (4.9%) increased; *Endocrine disorders* (4.8%), most commonly hypothyroidism (3.9%); *Nervous system*

disorders (3.8%), most commonly neuropathy peripheral (3.2%); *Respiratory, thoracic and mediastinal disorders* (2.7%), most commonly pneumonitis (2.5%).

The majority of patients experienced AESIs of Grade 1 or Grade 2 maximum intensity (81.0%, 525/648). Overall, 79 patients (3.7%) experienced an AESI reported as serious, with the most commonly reported event of pneumonitis (1.3%, of which 24/28 were from the NSCLC population).

Serious adverse events

The proportion of patients reporting at least one SAE of any grade in the All Patients Population was 38.5%, 44.7% in the All UC and 36.6% in the All NSCLC populations. The most common SAEs were reported in the following SOCs (≥5% of patients): *Infections and infestations* (10.2%), most commonly (more than 1% of patients) pneumonia and UTI; *Respiratory, thoracic and mediastinal disorders* (9.8%), most commonly dyspnoea, pneumonitis, pulmonary embolism, and pleural effusion; *General disorders and administration site conditions* (6.1%), most commonly pyrexia; *Gastrointestinal disorders* (6.0%).

Other commonly reported SAEs by preferred term that occurred in more than 1% of patients in the 'All Patients Population' were back pain and pulmonary embolism.

Table 87 SAEs by Preferred Term Occurring in > 1% of Patients in Either the All Patients Population, All UC or All NSCLC Populations

MedDRA Preferred Term	All Patients (N=2160)	All UC (N=524)	All NSCLC (N=1636)
Total number of patients with at least one adverse event	832 (38.5%)	234 (44.7%)	598 (36.6%)
Total number of events	1372	412	960
PNEUMONIA	77 (3.6%)	8 (1.5%)	69 (4.2%)
DYSPNOEA	61 (2.8%)	13 (2.5%)	48 (2.9%)
PYREXIA	43 (2.0%)	12 (2.3%)	31 (1.9%)
URINARY TRACT INFECTION	34 (1.6%)	30 (5.7%)	4 (0.2%)
PULMONARY EMBOLISM	29 (1.3%)	11 (2.1%)	18 (1.1%)
PNEUMONITIS	27 (1.3%)	4 (0.8%)	23 (1.4%)
PLEURAL EFFUSION	26 (1.2%)	1 (0.2%)	25 (1.5%)
SEPSIS	22 (1.0%)	14 (2.7%)	8 (0.5%)
BACK PAIN	21 (1.0%)	8 (1.5%)	13 (0.8%)
HAEMOPTYSIS	19 (0.9%)	1 (0.2%)	18 (1.1%)
ACUTE KIDNEY INJURY	18 (0.8%)	13 (2.5%)	5 (0.3%)
DEHYDRATION	17 (0.8%)	11 (2.1%)	6 (0.4%)
ANAEMIA	15 (0.7%)	5 (1.0%)	10 (0.6%)
HAEMATURIA	15 (0.7%)	14 (2.7%)	1 (<0.1%)
HYPERCALCAEMIA	13 (0.6%)	5 (1.0%)	8 (0.5%)
ABDOMINAL PAIN	12 (0.6%)	5 (1.0%)	7 (0.4%)
FATIGUE	12 (0.6%)	5 (1.0%)	7 (0.4%)
SMALL INTESTINAL OBSTRUCTION	12 (0.6%)	9 (1.7%)	3 (0.2%)
ASTHENIA	11 (0.5%)	5 (1.0%)	6 (0.4%)
PAIN	11 (0.5%)	5 (1.0%)	6 (0.4%)
RENAL FAILURE	10 (0.5%)	8 (1.5%)	2 (0.1%)
HYPONATRAEMIA	8 (0.4%)	5 (1.0%)	3 (0.2%)
UROSEPSIS	7 (0.3%)	6 (1.1%)	1 (<0.1%)
PYELONEPHRITIS	6 (0.3%)	5 (1.0%)	1 (<0.1%)
BLOOD CREATININE INCREASED	5 (0.2%)	5 (1.0%)	0

Grade 5 AEs due to PD are excluded for studies GO27831 and GO28625.

Treatment-related SAEs were reported in 9.4% of patients in the 'All Patients population'. Treatment-related SAEs reported in 4 or more patients (≥0.3%) were pneumonitis (1.0%), pyrexia (0.8%), diarrhoea (0.6%), colitis, nausea, AST increased (0.4% each), pneumonia, ALT increased, hypothyroidism and muscular weakness (0.3% each).

Deaths

At the time of data cut-off dates for each study, a total of 1248 patients (57.8%) had died. The majority of deaths occurred beyond 30 days after last dose (80.7% [1007/1248]). The most common reason for death was progression of the underlying disease, which accounted for 85.1% (1062/1248) of all deaths.

The causes of death are listed in the table below.

Table 88 Summary of Deaths and Primary Cause of Death (Safety Evaluable Population)

	All Patients (N=2160)	All UC (N=524)	All NSCLC (N=1636)
All deaths			
n	1248	348	900
<=30 days from last study drug administration	241 (11.2%)	66 (12.6%)	175 (10.7%)
>30 days from last study drug administration	1007 (46.6%)	282 (53.8%)	725 (44.3%)
Primary cause of death			
n	1248	348	900
ADVERSE EVENT	81 (3.8%)	10 (1.9%)	71 (4.3%)
PROGRESSIVE DISEASE	1062 (49.2%)	291 (55.5%)	771 (47.1%)
OTHER	105 (4.9%)	47 (9.0%)	58 (3.5%)
n	105	47	58
Dead	1 (<0.1%)	0	1 (<0.1%)
Death Due to Cardiac Arrest	1 (<0.1%)	1 (0.2%)	0
Death Due to Cerebral Infarction	1 (<0.1%)	0	1 (<0.1%)
Death Due to Death During Follow Up	1 (<0.1%)	0	1 (<0.1%)
Death Due to Death in Follow Up	1 (<0.1%)	0	1 (<0.1%)
Death Due to Death Occurred During Follow Up and Reason Unknown	1 (<0.1%)	1 (0.2%)	0
Death Due to Death Occurred During Follow-up and No Further Details Were Provided in Source	1 (<0.1%)	1 (0.2%)	0
Death Due to Fungal Pneumonia During Follow Follow up Period	1 (<0.1%)	0	1 (<0.1%)
Death Due to Ileus (Patient Refused Treatment)	1 (<0.1%)	1 (0.2%)	0
Death Due to Not Followed, Patient Went Back to Pakistan. Reason of Death Unknown	1 (<0.1%)	1 (0.2%)	0
Death Due to Not Known	3 (0.1%)	3 (0.6%)	0
Death Due to Renal Failure	1 (<0.1%)	1 (0.2%)	0
Death Due to Euthanasia	1 (<0.1%)	0	1 (<0.1%)
Death Due To Intracranial Bleed	1 (<0.1%)	1 (0.2%)	0
Death Due To Unknown	4 (0.2%)	3 (0.6%)	1 (<0.1%)
Death Due To Unknown Cause Of Death - Suspected Thrombotic Thrombocytopenic Purpura (TTP) And Disseminated Intravascular Coagulation (DIC)Multiple Factors And Cannot Determine Cause Of Death	1 (<0.1%)	1 (0.2%)	0
Death During Follow-Up	83 (3.8%)	33 (6.3%)	50 (3.1%)
Death Recorded As Per Public Records	1 (<0.1%)	0	1 (<0.1%)

GO27831=PCD4989g; GO28625=FIR; GO28753=POPLAR; GO28754=BIRCH; GO29293=IMvigor 210; GO28915=OAK.
Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO29293:04JUL2016, GO28915:07JUL2016.

Overall, 80 deaths[1] were attributed to AEs. Grade 5 AEs occurring within 30 days after last dose of study treatment or prior to initiation of non-protocol anti-cancer therapy were reported in 2.4% (52/2160) of All Patients, including 8 patients (1.5%) from the ALL UC population and 44 patients (2.7%) from the All NSCLC population. Grade 5 AEs were reported in a variety of system organ classes (SOCs) and the following AE preferred terms were reported for more than one patient: pneumonia (6), death (4), cardiac arrest (3), sepsis (3), sudden death (3), septic shock (2), respiratory failure (2), lung infection (2), and cardiac failure (2).

Four Grade 5 AEs occurring within 30 days after the last dose of study treatment or prior to initiation of non-protocol therapy were considered by the investigator as treatment related. No patient experienced a fatal AE within 30 days after the last dose of study treatment or prior to initiation of non-protocol therapy that was considered by the investigator to be related to atezolizumab treatment in Studies OAK and PCD4989g.

[1] One patient death in Study BIRCH included in Table 88 was reported as a death due to AE at the time of data cut-off but was actually a death due to progressive disease.

Table 89 Grade 5 Adverse Events Occurring within 30 Days of Last Dose or Prior to Initiation of Non-protocol Anti-cancer Therapy (Safety Evaluable Population)

MedDRA System Organ Class MedDRA Preferred Term	All Patients (N=2160)	All UC (N=524)	All NSCLC (N=1636)
- Any adverse events -	52 (2.4%)	8 (1.5%)	44 (2.7%)
INFECTIONS AND INFESTATIONS			
- Overall -	14 (0.6%)	2 (0.4%)	12 (0.7%)
PNEUMONIA	6 (0.3%)	0	6 (0.4%)
SEPSIS	3 (0.1%)	1 (0.2%)	2 (0.1%)
LUNG INFECTION	2 (<0.1%)	0	2 (0.1%)
SEPTIC SHOCK	2 (<0.1%)	0	2 (0.1%)
PULMONARY SEPSIS	1 (<0.1%)	1 (0.2%)	0
CARDIAC DISORDERS			
- Overall -	10 (0.5%)	2 (0.4%)	8 (0.5%)
CARDIAC ARREST	3 (0.1%)	1 (0.2%)	2 (0.1%)
CARDIAC FAILURE	2 (<0.1%)	0	2 (0.1%)
ACUTE CORONARY SYNDROME	1 (<0.1%)	0	1 (<0.1%)
CARDIAC TAMPONADE	1 (<0.1%)	0	1 (<0.1%)
MYOCARDIAL INFARCTION	1 (<0.1%)	1 (0.2%)	0
MYOCARDIAL ISCHAEMIA	1 (<0.1%)	0	1 (<0.1%)
PERICARDITIS CONSTRICTIVE	1 (<0.1%)	0	1 (<0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
- Overall -	10 (0.5%)	1 (0.2%)	9 (0.6%)
RESPIRATORY FAILURE	2 (<0.1%)	1 (0.2%)	1 (<0.1%)
DYSPNOEA	1 (<0.1%)	0	1 (<0.1%)
PNEUMONIA ASPIRATION	1 (<0.1%)	0	1 (<0.1%)
PNEUMONITIS	1 (<0.1%)	0	1 (<0.1%)
PNEUMOTHORAX	1 (<0.1%)	0	1 (<0.1%)
PULMONARY EMBOLISM	1 (<0.1%)	0	1 (<0.1%)
PULMONARY HAEMORRHAGE	1 (<0.1%)	0	1 (<0.1%)
RESPIRATORY DISORDER	1 (<0.1%)	0	1 (<0.1%)
RESPIRATORY DISTRESS	1 (<0.1%)	0	1 (<0.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
- Overall -	8 (0.4%)	0	8 (0.5%)
DEATH	4 (0.2%)	0	4 (0.2%)
SUDDEN DEATH	3 (0.1%)	0	3 (0.2%)
ULCER HAEMORRHAGE	1 (<0.1%)	0	1 (<0.1%)
NERVOUS SYSTEM DISORDERS			
- Overall -	3 (0.1%)	1 (0.2%)	2 (0.1%)
CEREBRAL HAEMORRHAGE	1 (<0.1%)	1 (0.2%)	0
CEREBRAL INFARCTION	1 (<0.1%)	0	1 (<0.1%)
CEREBROVASCULAR ACCIDENT	1 (<0.1%)	0	1 (<0.1%)
VASCULAR DISORDERS			
- Overall -	2 (<0.1%)	0	2 (0.1%)
EMBOLISM	1 (<0.1%)	0	1 (<0.1%)
INTERNAL HAEMORRHAGE	1 (<0.1%)	0	1 (<0.1%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
- Overall -	1 (<0.1%)	0	1 (<0.1%)
DISSEMINATED INTRAVASCULAR COAGULATION	1 (<0.1%)	0	1 (<0.1%)
GASTROINTESTINAL DISORDERS			
- Overall -	1 (<0.1%)	1 (0.2%)	0
SUBILEUS	1 (<0.1%)	1 (0.2%)	0
HEPATOBILIARY DISORDERS			
- Overall -	1 (<0.1%)	0	1 (<0.1%)
HEPATIC FAILURE	1 (<0.1%)	0	1 (<0.1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
- Overall -	1 (<0.1%)	1 (0.2%)	0
OVERDOSE	1 (<0.1%)	1 (0.2%)	0
RENAL AND URINARY DISORDERS			
- Overall -	1 (<0.1%)	0	1 (<0.1%)
RENAL FAILURE	1 (<0.1%)	0	1 (<0.1%)

Grade 5 AEs due to PD are excluded for studies GO27831 and GO28625.

An additional 28 patients had a Grade 5 AE occurring beyond 30 days after the last dose of study treatment or after initiation of non-protocol anti-cancer therapy. The causes of death were death (5), pneumonia (4), disease progression (3), and sepsis (3). The one respiratory failure event was the only event considered related to atezolizumab (onset of AE occurred 52 days after last study drug administration).

Adverse Drug Reactions for Atezolizumab

Overall, 84.4% of the patients in the All Patients population treated with atezolizumab had at least one ADR.

The most common adverse reactions (any grade) were fatigue (35.4%), decreased appetite (25.5%), nausea (22.9%), dyspnoea (21.8%), diarrhoea (18.6%), rash (18.6%), pyrexia (18.3%), vomiting (15.0%), arthralgia (14.2%), asthenia (13.8%) and pruritus (11.3%). The majority of adverse drug reactions were mild to moderate (Grades 1 or 2).

Table 90: Summary of adverse reactions occurring in patients treated with Tecentriq in clinical trials

Blood and lymphatic system disorders	
Common	Thrombocytopenia (2.4%)
Immune system disorders	
Common	Hypersensitivity (1.1%)
Endocrine disorders	
Common	hypothyroidism[a] (4.7%), hyperthyroidism[b] (1.7%)
Uncommon	diabetes mellitus[c] (0.3%), adrenal insufficiency[d] (0.3%)
Rare	Hypophysitis (<0.1%)
Metabolism and nutrition disorders	
Very common	decreased appetite (25.5%)
Common	Hypokalaemia (4.8%), hyponatremia (5.1%)
Nervous system disorders	
Uncommon	Guillain-Barré syndrome[e] (0.2%), noninfective meningitis[f] (0.1%)
Rare	noninfective encephalitis[g] (<0.1%), myasthenic syndrome[h] (<0.1%)
Vascular disorders	
Common	Hypotension (3.6%)
Respiratory, thoracic, and mediastinal disorders	
Very Common	Dyspnoea (21.8%)
Common	pneumonitis[i] (3.1%), hypoxia (2.5%), nasal congestion (2.9%),
Gastrointestinal disorders	
Very common	Nausea (22.9%), vomiting (15.0%), diarrhoea (18.6%)
Common	abdominal pain (7.1%), colitis[j] (1.1%), dysphagia (2.6%),
Uncommon	pancreatitis[k] (0.2%), lipase increased (0.2%),
Rare	amylase increase (<0.1%)
Hepatobiliary disorders	
Common	AST increased (5.3%), ALT increased (4.9%)
Uncommon	hepatitis[l] (0.3%)

Skin and subcutaneous tissue disorders	
Very Common	rash[m] (18.6%), pruritus (11.3%)
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia (14.2%)
Common	musculoskeletal pain (8.8%)
General disorders and administration site conditions	
Very Common	Pyrexia (18.3%), fatigue (35.4%), asthenia (13.8%)
Common	infusion related reaction (1.2%), influenza like illness (5.6%), chills (5.8%)

[a] Includes reports of hypothyroidism, blood thyroid stimulating hormone increased, thyroiditis, blood thyroid stimulating hormone decreased, myxoedema, thyroid function test abnormal, thyroiditis acute, thyroxine decreased.
[b] Includes reports of hyperthyroidism, blood thyroid stimulating hormone increased, thyroiditis, blood thyroid stimulating hormone decreased, endocrine ophthalmopathy, exophthalmus, thyroid function test abnormal, thyroiditis acute, thyroxine decreased.
[c] Includes reports of diabetes mellitus and type 1 diabetes mellitus.
[d] Includes reports of adrenal insufficiency, primary adrenal insufficiency, and Addison's disease.
[e] Includes reports of Guillain-Barré syndrome and demyelinating polyneuropathy.
[f] Includes reports of meningitis.
[g] Includes reports of encephalitis.
[h] Reported in studies other than those in metastatic UC and NSCLC patients. The frequency is based on the exposure in 6,000 patients across all atezolizumab clinical trials.
[i] Includes reports of pneumonitis, lung infiltration, bronchiolitis, interstitial lung disease, radiation pneumonitis.
[j] Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic.
[k] Includes reports of pancreatitis and pancreatitis acute.
[l] Includes reports of autoimmune hepatitis, hepatitis, hepatitis acute.
[m] Includes reports of acne, eczema, erythema, erythema of eyelid, erythema multiforme, 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, seborrhoeic dermatitis, skin exfoliation, skin toxicity, skin ulcer, toxic skin eruption.

Within the ADRs, important immune-related events of particular clinical relevance (important ADRs) were identified and included hypothyroidism, hypophysistis, diabetes mellitus, pneumonitis, colitis, hyperthyroidism, pancreatitis, hepatitis, non-infectious meningoencephalitis, adrenal insufficiency, Guillain Barré syndrome, myasthenic syndrome, and infusion relation reactions.

Overall, 549 patients (25.4%) experienced an important ADR, the majority (83.8% [460/549]) of these being Grade 1 or 2 maximum intensity. Eighty-eight of 549 patients (16.0%) with an important ADR had a Grade 3-4 event, and one patient had a Grade 5 event (pneumonitis).

The most commonly observed immune-related events are hypothyroidism and pneumonitis. The incidence of immune-related pneumonitis is systematically higher in the All NSCLC Population, with AEs of higher Grade as compared to the All UC Population.

Systemic corticosteroid treatment was administered to 78 patients of 549 (14.2%) patients with important ADRs. Atezolizumab treatment was discontinued for 28 patients (1.3%), and 101 patients (4.7%) had a dose interruption due to an important ADR. The median time to onset and median time from onset to resolution for all important ADR groups (for all patients and patients treated with systemic corticosteroids) differ from ADR to ADR. Details are provided in the table below.

These observations were consistent between all patients' populations (UC and NSCLC).

Table 91 Summary of safety information for important adverse drug reactions for atezolizumab (All Patient population)

Important ADR group (search strategy defined in Appendix 9)	Incidence of All Grade AEs N=2160	Incidence of Grade 3-4 AEs N=2160	Incidence of Grade 5 AEs N=2160	Incidence of resolved All Grade AEs [a] N=2160	All Grade AE median time to onset in months (range)	All Grade AE median time from onset to resolution in months (range)	Patients receiving systemic corticosteroids to treat events in the important ADRs groups		
							Incidence of All Grade AEs N=2160	Median time to onset in months (range)	Median time from onset to resolution in months (range)
Any important ADR group	549 (25.4%)	88 (4.1%)	1 (<0.1%)	NR	NR	NR	78 (3.6%)	NR	NR
Infusion-related reactions**	308 (14.3%)	11 (0.5%)	0	NR	NR	NR	5 (0.2%)	NR	NR
Hypothyroidism	101 (4.7%)	4 (0.2%)	0	36 (1.7%)	5.52 0.5 – 31.3	19.12 0.0* - 22.6*	8 (0.4%)	4.19 0.5 – 13.4	6.24 0.8 - 22.6*
Diabetes mellitus **	83 (3.8%)	23 (1.1%)	0	56 (2.6%)	2.76 0.0 – 15.3	1.45 0.0* – 18.2*	2 (<0.1%)	2.43 2.1 – 2.8	0.67 0.7 – 0.7
Pneumonitis	68 (3.1%)	22 (1.0%)	1 (<0.1%)	45 (2.1%)	3.45 0.1 – 20.5	1.48 0.0 – 15.1*	34 (1.6%)	3.14 0.2 – 18.7	1.41 0.1 – 15.1*
Colitis	23 (1.1%)	10 (0.5%)	0	16 (0.7%)	3.98 0.5 – 15.2	1.41 0.1 – 17.8*	10 (0.5%)	3.29 0.7 – 19.4	0.99 0.2 - 17.8*
Hyperthyroidism	36 (1.7%)	0	0	17 (0.8%)	3.47 0.7 – 31.3	6.80 0.0* - 17.1*	6 (0.3%)	1.56 0.7 – 15.9	NE 0.9* - 12.6*
Pancreatitis	10 (0.5%)	7 (0.3%)	0	8 (0.4%)	5.54 0.3 - 16.9	0.64 0.1 – 11.2*	2 (<0.1%)	11.02 9.4 – 12.6	1.12 0.1 – 2.1
Hepatitis	7 (0.3%)	6 (0.3%)	0	6 (0.3%)	1.05 0.3 – 7.9	1.02 0.3 – 1.9*	5 (0.2%)	0.30 0.3 - 3.0	1.02 0.3 – 1.8
Noninfectious meningoencephalitis **	9 (0.4%)	4 (0.2%)	0	6 (0.3%)	0.53 0.0 - 12.5	0.95 0.4 – 14.5*	4 (0.2%)	0.49 0.5 - 0.5	2.04 0.5 – 3.4
Adrenal insufficiency	7 (0.3%) [b]	0	0	1 (<0.1%)	5.72 [b] 0.1 – 19.0	16.76 [b] 0.2* - 16.8	5 (0.2%)	5.45 0.1 – 13.4	16.76 1.0* - 16.8
Guillain Barré	5 (0.2%)	4 (0.2%)	0	3 (0.1%)	6.97 0.6 – 8.1	4.60 0.0* – 8.3*	2 (<0.1%)	0.61 0.6 – 0.7	NE 0.6 – 8.3*
Myasthenic syndrome	0	NA	NA	0	NA	NA	NA	NA	NA

Note: * Censored value, NE = Not Estimable, NA = Not Applicable, NR = Not Reported.

** Incidence reflects events included in respective SMQs and the sponsor defined AEGTs

At the clinical cut-off dates for the 6 studies, no patients had AEs in the myasthenic syndrome SMQ, however, these events were observed in other clinical studies in the atezolizumab clinical development program.

In the All Patients population, 308 patients (14.3%) treated with atezolizumab experienced infusion-related reactions (IRRs)/hypersensitivity (type I). IRR include AEs under the sponsor defined AEGT occurring within 24 hours of dosing. Signs and symptoms of IRRs included in the sponsor defined AEGT overlap with several very common atezolizumab ADRs, including chills, dyspnoea, hypotension, influenza-like illness, pyrexia, and rash. The rate of all grade IRR AEs was similar between UC (13.0%) and NSCLC (14.7%) patients. This included 10 Grade 3 events and 1 Grade 4 event. There were no Grade 5 events. Five events required systemic corticosteroid treatment. The majority of the IRRs were Grade 1 or 2 events.

Table 92 Summary of Infusion-related Reactions (Safety-Evaluable Patients)

Important Identified Adverse Drug Reaction Group MedDRA Preferred Term	Grade	All Patients (N=2160)	All UC (N=524)	All NSCLC (N=1636)
Infusion-Related Reactions				
- Overall -	- Any Grade -	308 (14.3%)	68 (13.0%)	240 (14.7%)
	1	211 (9.8%)	53 (10.1%)	158 (9.7%)
	2	86 (4.0%)	14 (2.7%)	72 (4.4%)
	3	10 (0.5%)	1 (0.2%)	9 (0.6%)
	4	1 (<0.1%)	0	1 (<0.1%)
DYSPNOEA	- Any Grade -	151 (7.0%)	23 (4.4%)	128 (7.8%)
	1	101 (4.7%)	19 (3.6%)	82 (5.0%)
	2	46 (2.1%)	4 (0.8%)	42 (2.6%)
	3	4 (0.2%)	0	4 (0.2%)
PYREXIA	- Any Grade -	51 (2.4%)	15 (2.9%)	36 (2.2%)
	1	44 (2.0%)	14 (2.7%)	30 (1.8%)
	2	7 (0.3%)	1 (0.2%)	6 (0.4%)
CHILLS	- Any Grade -	40 (1.9%)	17 (3.2%)	23 (1.4%)
	1	36 (1.7%)	16 (3.1%)	20 (1.2%)
	2	4 (0.2%)	1 (0.2%)	3 (0.2%)
HYPOTENSION	- Any Grade -	26 (1.2%)	8 (1.5%)	18 (1.1%)
	1	15 (0.7%)	5 (1.0%)	10 (0.6%)
	2	10 (0.5%)	3 (0.6%)	7 (0.4%)
	3	1 (<0.1%)	0	1 (<0.1%)
INFUSION RELATED REACTION	- Any Grade -	24 (1.1%)	6 (1.1%)	18 (1.1%)
	1	8 (0.4%)	2 (0.4%)	6 (0.4%)
	2	12 (0.6%)	4 (0.8%)	8 (0.5%)
	3	4 (0.2%)	0	4 (0.2%)
WHEEZING	- Any Grade -	21 (1.0%)	4 (0.8%)	17 (1.0%)
	1	15 (0.7%)	4 (0.8%)	11 (0.7%)
	2	6 (0.3%)	0	6 (0.4%)
HYPERSENSITIVITY	- Any Grade -	15 (0.7%)	3 (0.6%)	12 (0.7%)
	1	6 (0.3%)	1 (0.2%)	5 (0.3%)
	2	7 (0.3%)	1 (0.2%)	6 (0.4%)
	3	1 (<0.1%)	1 (0.2%)	0
	4	1 (<0.1%)	0	1 (<0.1%)
FLUSHING	- Any Grade -	13 (0.6%)	1 (0.2%)	12 (0.7%)
	1	9 (0.4%)	1 (0.2%)	8 (0.5%)
	2	3 (0.1%)	0	3 (0.2%)
	3	1 (<0.1%)	0	1 (<0.1%)
TACHYCARDIA	- Any Grade -	12 (0.6%)	3 (0.6%)	9 (0.6%)
	1	11 (0.5%)	3 (0.6%)	8 (0.5%)
	2	1 (<0.1%)	0	1 (<0.1%)
URTICARIA	- Any Grade -	9 (0.4%)	5 (1.0%)	4 (0.2%)
	1	7 (0.3%)	4 (0.8%)	3 (0.2%)
	2	2 (<0.1%)	1 (0.2%)	1 (<0.1%)
PERIORBITAL OEDEMA	- Any Grade -	4 (0.2%)	0	4 (0.2%)
	1	4 (0.2%)	0	4 (0.2%)
EYE SWELLING	- Any Grade -	2 (<0.1%)	1 (0.2%)	1 (<0.1%)
	1	2 (<0.1%)	1 (0.2%)	1 (<0.1%)
FACE OEDEMA	- Any Grade -	2 (<0.1%)	0	2 (0.1%)
	1	2 (<0.1%)	0	2 (0.1%)
BRONCHOSPASM	- Any Grade -	1 (<0.1%)	0	1 (<0.1%)
	1	1 (<0.1%)	0	1 (<0.1%)
CYTOKINE RELEASE SYNDROME	- Any Grade -	1 (<0.1%)	0	1 (<0.1%)
	1	1 (<0.1%)	0	1 (<0.1%)
DRUG HYPERSENSITIVITY	- Any Grade -	1 (<0.1%)	0	1 (<0.1%)
	2	1 (<0.1%)	0	1 (<0.1%)
EYELID OEDEMA	- Any Grade -	1 (<0.1%)	0	1 (<0.1%)
	1	1 (<0.1%)	0	1 (<0.1%)

Grade 5 AEs due to PD are excluded for studies GO27831 and GO28625.

Laboratory safety findings

Haematology

Overall, although small fluctuations were observed, medial values remained within the normal range during the entire treatment period. Of note, median values for hematocrit, hemoglobin and red blood cell counts at baseline were below or at the lower limit of the standard reference range in all studies. During treatment with atezolizumab, median values did not decrease further.

Clinically relevant hematology laboratory abnormalities that were reported as AEs (i.e., Grade 3 or 4 hematology AEs), occurred at a low incidence with the most common (≥2% of patients in any study) being anemia, and thrombocytopenia.

Serum chemistry

Abnormalities in blood chemistry parameters which were reported as Grade 3 or 4 AEs occurred at a low incidence with the most common events being hyponatraemia, hypokalaemia, ALT and AST increased. Chemistry laboratory results were consistent across the 6 studies.

Overall, 22 patients across the 6 studies fulfilled the laboratory criteria for Hy's Law: AST and/or ALT $>3\times$ULN concurrent (within 7 days) with total bilirubin (TBILI) $>2\times$ULN. In all but one patient, other confounding factors were present, so the cases do not qualify as Hy's law cases. For a patient that developed changes in liver function tests after four cycles, no alternate etiology was identified. However, based on the mechanism of action of atezolizumab, changes in liver function tests and hepatitis have been reported with atezolizumab and are considered a known risk.

No clinically meaningful changes in median values over time for any vital sign parameters were observed in any of the 6 studies.

Anti-Therapeutic Antibodies

Overall, among the safety-evaluable patients with available post-treatment ATA status 39.1% (785/2007) had ATA. Irrespective of population, the incidences of Grade 5 AEs and AEs leading to treatment discontinuation were very low and comparable. With regard to Grade 3-4 AEs, sligthly more SAEs were observed in ATA-positive patients. Some numerical differences were observed in Grade 3-4 AEs (40.7% in ATA-negative vs. 47.0% in ATA-positive patients), which was mainly driven by AEs reported in the *Metabolism and nutrition disorders* SOC (40.4% vs. 44.3%) and the decreased appetite PT (24.9% vs. 27.6%) within the *Metabolism and nutrition disorders* SOC in ATA-positive patients. The incidence of SAEs was numerically higher in ATA-positive patients (40.5%) compared with ATA-negative patients (34.0%), but this difference was not driven by any specific SOC or individual AE preferred term.

In the All Patients population, the incidence of hypersensitivity and IRRs (MedDRA PTs) (not necessarily occurring on the same day as an atezolizumab infusion) was low and consistent between ATA-positive and ATA-negative patients. Hypersensitivity events were reported in 24 patients (1.2%): 9 ATA-negative (0.7%) and 15 ATA-positive (1.9%) patients. Infusion-related reactions occurred in 25 patients (1.2%): 14 ATA-negative (1.1%) and 11 ATA-positive (1.4%) patients.

Table 93 Overview of safety by ATA status (safety-evaluable patients with available post-treatment ATA status)

	All Patients N = 2007		All UC N = 471		All NSCLC N = 1536	
	ATA-negative n=1222	ATA-positive n=785	ATA-negative n=258	ATA-positive n=213	ATA-negative n=964	ATA-positive n=572
Total number of patients with at least one AE	1171 (95.8%)	757 (96.4%)	253 (98.1%)	208 (97.7%)	918 (95.2%)	549 (96.0%)
Total number of patients with:						
Grade 3-4 AE	497 (40.7%)	369 (47.0%)	129 (50.0%)	125 (58.7%)	368 (38.2%)	244 (42.7%)
Grade 5 AE	20 (1.6%)	12 (1.5%)	2 (0.8%)	3 (1.4%)	18 (1.9%)	9 (1.6%)
SAE	416 (34.0%)	318 (40.5%)	102 (39.5%)	102 (47.9%)	314 (32.6%)	216 (37.8%)
AE leading to treatment withdrawal	73 (6.0%)	40 (5.1%)	11 (4.3%)	9 (4.2%)	62 (6.4%)	31 (5.4%)
AE leading to dose interruption	337 (27.6%)	241 (30.7%)	75 (29.1%)	78 (36.6%)	262 (27.2%)	163 (28.5%)
AESI of Any Grade	383 (31.3%)	246 (31.3%)	91 (35.3%)	65 (30.5%)	292 (30.3%)	181 (31.6%)
AESI of Grade 3-4	64 (5.3%)	46 (5.8%)	17 (6.6%)	14 (6.5%)	47 (4.9%)	32 (5.6%)
AESI of Grade 5	0	0	0	0	0	0

Note: All AEs collected after first treatment dose and within 30 days from last treatment dose, start of a non-protocol cancer therapy, or discontinuation from study are included, except for AESIs where no 30 day-time window was applied.
Clinical cutoff dates for AEs: IMvigor 210 (4 July 2016); OAK (7 July 2016); BIRCH (1 December 2015); POPLAR (1 December 2015); FIR (7 January 2015); PCD4989g (31 March 2016).
ATA status cutoff dates: IMvigor 210 (4 July 2016); OAK (7 July 2016); BIRCH (28 May 2015); POPLAR (8 May 2015); FIR (7 January 2015); PCD4989g (2 December 2014).

ECG and Vital signs

No clinically meaningful changes were observed in median values over time for any vital sign parameters (systolic and diastolic blood pressure, pulse rate or respiratory rate) in the All Patient Population.

Data available from the FIR study and extended analyses performed in the PCD4989g study showed no trend between atezolizumab concentration and QT interval in the studied dose range including the proposed dose of 1200 mg. Thus, no clinically meaningful QT changes are expected in relation to atezolizumab treatment.

Treatment group comparisons

Atezolizumab versus docetaxel in NSCLC patients

Study OAK

At the time of primary analysis, patients in the atezolizumab arm received treatment for a longer duration compared with docetaxel (median treatment duration: 2.1 months for docetaxel vs. 3.4 months for atezolizumab). The proportion of patients receiving treatment for 12 months or more was higher in the atezolizumab arm (20.5%) compared with docetaxel (2.4%).

Table 94 Study OAK: Overview of safety (cut-off date: 7 July 2016)

	Docetaxel arm N=578	Atezolizumab arm N=609
Total number of patients (%) with at least one AE	555 (96.0%)	573 (94.1%)
Total number of patients (%) with: [a]		
Grade 3 or 4 AEs	310 (53.6%)	227 (37.3%)
Related Grade 3 or 4 AEs	247 (42.7%)	90 (14.8%)
Grade 5 AEs	14 (2.4%)	10 (1.6%)
Related Grade 5 AEs	1 (0.2%)	0
SAEs	181 (31.3%)	194 (31.9%)
Related SAEs [b]	102 (17.6%)	63 (10.3%)
AE leading to withdrawal from treatment	108 (18.7%)	46 (7.6%)
AEs leading to dose modification/interruption	210 (36.3%)	152 (25.0%)
AESIs Any Grade [b]	132 (22.8%)	184 (30.2%)
AESIs of Grade 3-4 [b]	14 (2.4%)	31 (5.1%)
AESIs of Grade 5 [b]	0	0

The most commonly reported AESIs (≥5% of patients in any treatment group) were dermatological reactions (rash) in both arms, nervous system disorders (peripheral neuropathy) in the docetaxel arm, and hepatic events (ALT and AST increased) in the atezolizumab arm. Grade 3 AESIs were reported for 4.6% of patients receiving atezolizumab and 2.4% of patients receiving docetaxel. Three patients in the atezolizumab arm experienced Grade 4 AESIs (hepatitis [2 patients], blood bilirubin increased [1 patient]).

No clinically relevant changes in median values for laboratory safety parameters or vital signs were observed during atezolizumab treatment. Changes in median values for haematology parameters were as expected during docetaxel treatment.

Table 95 Study OAK: Adverse Events Leading to Death within 30 Days of Last Dose of Study Drug or Prior to Initiation of Non-Protocol Therapy (Safety Evaluable Population)

MedDRA System Organ Class MedDRA Preferred Term	Docetaxel (Actual) (N=578)	Atezolizumab (Actual) (N=609)	All Patients (N=1187)
Total number of patients with at least one adverse event	14 (2.4%)	10 (1.6%)	24 (2.0%)
Overall total number of events	14	10	24
INFECTIONS AND INFESTATIONS			
Total number of patients with at least one adverse event	5 (0.9%)	4 (0.7%)	9 (0.8%)
Total number of events	5	4	9
PNEUMONIA	2 (0.3%)	1 (0.2%)	3 (0.3%)
SEPSIS	1 (0.2%)	2 (0.3%)	3 (0.3%)
RESPIRATORY TRACT INFECTION	2 (0.3%)	0	2 (0.2%)
SEPTIC SHOCK	0	1 (0.2%)	1 (<0.1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Total number of patients with at least one adverse event	6 (1.0%)	2 (0.3%)	8 (0.7%)
Total number of events	6	2	8
DYSPNOEA	1 (0.2%)	1 (0.2%)	2 (0.2%)
PULMONARY HAEMORRHAGE	1 (0.2%)	1 (0.2%)	2 (0.2%)
HAEMOPTYSIS	1 (0.2%)	0	1 (<0.1%)
PNEUMOTHORAX SPONTANEOUS	1 (0.2%)	0	1 (<0.1%)
PULMONARY EMBOLISM	1 (0.2%)	0	1 (<0.1%)
RESPIRATORY DISTRESS	1 (0.2%)	0	1 (<0.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Total number of patients with at least one adverse event	2 (0.3%)	2 (0.3%)	4 (0.3%)
Total number of events	2	2	4
SUDDEN DEATH	2 (0.3%)	1 (0.2%)	3 (0.3%)
DEATH	0	1 (0.2%)	1 (<0.1%)
CARDIAC DISORDERS			
Total number of patients with at least one adverse event	0	1 (0.2%)	1 (<0.1%)
Total number of events	0	1	1
MYOCARDIAL ISCHAEMIA	0	1 (0.2%)	1 (<0.1%)
GASTROINTESTINAL DISORDERS			
Total number of patients with at least one adverse event	1 (0.2%)	0	1 (<0.1%)
Total number of events	1	0	1
LOWER GASTROINTESTINAL HAEMORRHAGE	1 (0.2%)	0	1 (<0.1%)
RENAL AND URINARY DISORDERS			
Total number of patients with at least one adverse event	0	1 (0.2%)	1 (<0.1%)
Total number of events	0	1	1
RENAL FAILURE	0	1 (0.2%)	1 (<0.1%)

Table 96 Study OAK: Treatment-Related Adverse Events Reported in > 10% Patients in either Treatment Arm (Safety Evaluable Population)

MedDRA Preferred Term	Docetaxel (Actual) (N=578)	Atezolizumab (Actual) (N=609)	All Patients (N=1187)
ALOPECIA	198 (34.3%)	3 (0.5%)	201 (16.9%)
FATIGUE	177 (30.6%)	87 (14.3%)	264 (22.2%)
DECREASED APPETITE	116 (20.1%)	52 (8.5%)	168 (14.2%)
ANAEMIA	114 (19.7%)	24 (3.9%)	138 (11.6%)
NAUSEA	112 (19.4%)	53 (8.7%)	165 (13.9%)
DIARRHOEA	109 (18.9%)	47 (7.7%)	156 (13.1%)
ASTHENIA	96 (16.6%)	51 (8.4%)	147 (12.4%)
NEUTROPENIA	85 (14.7%)	7 (1.1%)	92 (7.8%)
MYALGIA	81 (14.0%)	21 (3.4%)	102 (8.6%)
FEBRILE NEUTROPENIA	61 (10.6%)	0	61 (5.1%)
STOMATITIS	59 (10.2%)	13 (2.1%)	72 (6.1%)
NEUROPATHY PERIPHERAL	58 (10.0%)	6 (1.0%)	64 (5.4%)

Study POPLAR

In this study, patients in the atezolizumab arm (N=142) received treatment for a median of 3.7 months as compared to patients in the docetaxel arm (N=135) who received treatment for a median of 2.1 months. Additionally, the proportion of patients receiving treatment for ≥12 months was 21.1% (atezolizumab) as compared to 3.7% (docetaxel).

Table 97 Study POPLAR: Overview of safety (cut-off date: 8 May 2015)

	Docetaxel (N=135)	Atezolizumab (N=142)	All Patients (N=277)
Total number of patients with at least one adverse event	130 (96.3%)	136 (95.8%)	266 (96.0%)
Total number of events	1325	1354	2679
Total number of patients with at least one			
Grade 5 AE	5 (3.7%)	6 (4.2%)	11 (4.0%)
Serious AE	46 (34.1%)	50 (35.2%)	96 (34.7%)
AE leading to withdrawal from treatment	30 (22.2%)	11 (7.7%)	41 (14.8%)
AE leading to dose modification/interruption	44 (32.6%)	34 (23.9%)	78 (28.2%)
Related AE	119 (88.1%)	95 (66.9%)	214 (77.3%)
Related AE leading to withdrawal from treatment	24 (17.8%)	2 (1.4%)	26 (9.4%)
Related AE leading to dose modification/interruption	32 (23.7%)	15 (10.6%)	47 (17.0%)

Grade 3 or 4 AEs occurred in 52.6% (docetaxel) and 40.1% (atezolizumab). Of these, 38.6% (docetaxel) and 11.3% (atezolizumab) were considered related to study drug. The incidence of Grade 5 AEs was low (3.7% docetaxel vs. 4.2% atezolizumab) and only in few patients (3 (2.2%) docetaxel vs. 1 (0.7%) atezolizumab) were the Grade 5 AEs considered related to study treatment. With regard to SAEs, the incidence was 34.1% (docetaxel) and 35.2% (atezolizumab). Related SAEs occurred in 17.0% (docetaxel) and 8.5% (atezolizumab).

AESIs of any Grade were observed in 29.6% (docetaxel) and 28.9% (atezolizumab). The incidence of Grade 3-4 AESIs was 3.0% (docetaxel) and 5.6% (atezolizumab). No patients in either arm experienced a Grade 5 AESI.

Table 98 Study POPLAR: All Grade Adverse Events Reported in ≥ 10% of Patients in Any of the Treatment Arms by Preferred Term (Safety-Evaluable Population)

MedDRA Preferred Term	Docetaxel (N=135)	Atezolizumab (N=142)	All Patients (N=277)
Total number of patients with at least one adverse event	130 (96.3%)	136 (95.8%)	266 (96.0%)
Total number of events	1325	1354	2679
FATIGUE	54 (40.0%)	55 (38.7%)	109 (39.4%)
DECREASED APPETITE	28 (20.7%)	49 (34.5%)	77 (27.8%)
NAUSEA	45 (33.3%)	31 (21.8%)	76 (27.4%)
COUGH	33 (24.4%)	38 (26.8%)	71 (25.6%)
DYSPNOEA	27 (20.0%)	38 (26.8%)	65 (23.5%)
DIARRHOEA	38 (28.1%)	24 (16.9%)	62 (22.4%)
CONSTIPATION	32 (23.7%)	29 (20.4%)	61 (22.0%)
ALOPECIA	52 (38.5%)	3 (2.1%)	55 (19.9%)
ANAEMIA	26 (19.3%)	23 (16.2%)	49 (17.7%)
PYREXIA	16 (11.9%)	24 (16.9%)	40 (14.4%)
ASTHENIA	22 (16.3%)	14 (9.9%)	36 (13.0%)
VOMITING	18 (13.3%)	18 (12.7%)	36 (13.0%)
ARTHRALGIA	12 (8.9%)	22 (15.5%)	34 (12.3%)
RASH	16 (11.9%)	15 (10.6%)	31 (11.2%)
INSOMNIA	11 (8.1%)	19 (13.4%)	30 (10.8%)
BACK PAIN	11 (8.1%)	16 (11.3%)	27 (9.7%)
MUSCULOSKELETAL PAIN	7 (5.2%)	19 (13.4%)	26 (9.4%)
MYALGIA	18 (13.3%)	8 (5.6%)	26 (9.4%)
NEUTROPENIA	17 (12.6%)	2 (1.4%)	19 (6.9%)
PNEUMONIA	4 (3.0%)	15 (10.6%)	19 (6.9%)
NEUROPATHY PERIPHERAL	16 (11.9%)	2 (1.4%)	18 (6.5%)

To adjust for the longer period on treatment of the atezolizumab arm compared with the docetaxel arm, adjusted analyses for patient-year at risk were performed where atezolizumab had a higher incidence than docetaxel.

Table 99 Study POPLAR: Table Adverse Events Rates Adjusted for Patient-Years at Risk for AEs with Higher Incidence in the Atezolizumab Arm (Safety-Evaluable Population)

	Docetaxel (N=135)	Atezolizumab (N=142)
Arthralgia		
Total patient-years at risk	45.9	84.2
Number of adverse events observed	16	27
AE rate per 100 patient-years	34.84	32.06
95% CI	(19.91, 56.57)	(21.13, 46.65)
Decreased Appetite		
Total patient-years at risk	45.9	84.2
Number of adverse events observed	35	58
AE rate per 100 patient-years	76.20	68.88
95% CI	(53.08, 105.98)	(52.30, 89.04)
Dyspnoea		
Total patient-years at risk	45.9	84.2
Number of adverse events observed	33	44
AE rate per 100 patient-years	71.85	52.25
95% CI	(49.46, 100.90)	(37.97, 70.15)
Insomnia		
Total patient-years at risk	45.9	84.2
Number of adverse events observed	12	20
AE rate per 100 patient-years	26.13	23.75
95% CI	(13.50, 45.64)	(14.51, 36.68)
Musculoskeletal Pain		
Total patient-years at risk	45.9	84.2
Number of adverse events observed	7	19
AE rate per 100 patient-years	15.24	22.56
95% CI	(6.13, 31.40)	(13.58, 35.24)
Pneumonia		
Total patient-years at risk	45.9	84.2
Number of adverse events observed	6	18
AE rate per 100 patient-years	13.06	21.38
95% CI	(4.79, 28.43)	(12.67, 33.78)
Pyrexia		
Total patient-years at risk	45.9	84.2
Number of adverse events observed	19	29
AE rate per 100 patient-years	41.37	34.44
95% CI	(24.91, 64.60)	(23.06, 49.46)

Atezolizumab versus chemotherapy in 2L+UC patients

Study IMvigor 211

More patients receiving chemotherapy compared with atezolizumab reported treatment related Grade 3 or 4 AEs, treatment related SAEs and treatment related AEs leading to dose withdrawal. The frequency of Grade 5 AEs (within 30 days after last dose) was comparable between treatment arms. The incidence of AESIs was higher in the atezolizumab arm than chemotherapy arm as these are specific to atezolizumab, however, in the majority of cases, these events were mild or moderate in severity. One Grade 5 AESI (with preferred term pneumonitis) was reported in the chemotherapy arm, and none in the atezolizumab arm.

Table 100 Overview of adverse events (safety-evaluable population): IC2/3, IC1/2/3, and All comers – IMvigor 211

a) Adverse events (within 30-day window)

	All-Comers		IC2/3		IC1/2/3	
	Chemotherapy (N=443)	Atezolizumab (N=459)	Chemotherapy (N=112)	Atezolizumab (N=114)	Chemotherapy (N=297)	Atezolizumab (N=312)
Total number of patients with at least one adverse event	435 (98.2%)	438 (95.4%)	110 (98.2%)	111 (97.4%)	293 (98.7%)	302 (96.8%)
Total number of events	4378	4091	1099	1052	2878	2801
Total number of patients with at least one						
Treatment-related AE	395 (89.2%)	319 (69.5%)	99 (88.4%)	85 (74.6%)	266 (89.6%)	215 (68.9%)
Grade 3-4 AE	249 (56.2%)	233 (50.8%)	58 (51.8%)	68 (59.6%)	159 (53.5%)	162 (51.9%)
Treatment-related Grade 3-4 AE	189 (42.7%)	91 (19.8%)	39 (34.8%)	26 (22.8%)	119 (40.1%)	64 (20.5%)
Grade 5 AE	18 (4.1%)	17 (3.7%)	4 (3.6%)	3 (2.6%)	10 (3.4%)	10 (3.2%)
Treatment-related Grade 5 AE	8 (1.8%)	3 (0.7%)	2 (1.8%)	2 (1.8%)	4 (1.3%)	2 (0.6%)
Serious Adverse Event	191 (43.1%)	188 (41.0%)	41 (36.6%)	58 (50.9%)	118 (39.7%)	135 (43.3%)
AE leading to withdrawal from treatment	78 (17.6%)	34 (7.4%)	20 (17.9%)	10 (8.8%)	51 (17.2%)	25 (8.0%)
AE leading to dose modification/interruption	210 (47.4%)	134 (29.2%)	52 (46.4%)	35 (30.7%)	136 (45.8%)	94 (30.1%)
Treatment-related AE leading to withdrawal from treatment	63 (14.2%)	16 (3.5%)	17 (15.2%)	7 (6.1%)	41 (13.8%)	13 (4.2%)

b) SAEs (treatment-related) and AESIs (without 30-day window)

	All-Comers		IC2/3		IC1/2/3	
	Chemotherapy (N=443)	Atezolizumab (N=459)	Chemotherapy (N=112)	Atezolizumab (N=114)	Chemotherapy (N=297)	Atezolizumab (N=312)
Total number of patients with at least one adverse event	436 (98.4%)	440 (95.9%)	110 (98.2%)	111 (97.4%)	294 (99.0%)	303 (97.1%)
Total number of events	4729	4425	1171	1149	3108	3063
Total number of patients with at least one						
Treatment-related Serious Adverse Event	110 (24.8%)	72 (15.7%)	22 (19.6%)	21 (18.4%)	68 (22.9%)	57 (18.3%)
Adverse Event of Special Interest of Any Grade	98 (22.1%)	139 (30.3%)	26 (23.2%)	45 (39.5%)	64 (21.5%)	106 (34.0%)
Adverse Event of Special Interest of Grade 3-4	13 (2.9%)	37 (8.1%)	3 (2.7%)	10 (8.8%)	7 (2.4%)	27 (8.7%)
Adverse Event of Special Interest of Grade 5	1 (0.2%)	0			1 (0.3%)	0
AE of Special Interest Medical Concepts: patients with at least one						
Dermatologic	34 (7.7%)	71 (15.5%)	10 (8.9%)	20 (17.5%)	22 (7.4%)	48 (15.4%)
Neurologic	57 (12.9%)	13 (2.8%)	17 (15.2%)	4 (3.5%)	37 (12.5%)	11 (3.5%)
Hepatic	19 (4.3%)	33 (7.2%)	3 (2.7%)	11 (9.6%)	10 (3.4%)	25 (8.0%)
Endocrine	2 (0.5%)	32 (7.0%)	0	8 (7.0%)	2 (0.7%)	25 (8.0%)
Gastrointestinal	1 (0.2%)	8 (1.7%)	1 (0.9%)	4 (3.5%)	1 (0.3%)	8 (2.6%)
Pulmonary	2 (0.5%)	7 (1.5%)	1 (0.9%)	4 (3.5%)	2 (0.7%)	7 (2.2%)
Musculoskeletal and Joint	0	3 (0.7%)	0	3 (2.6%)	0	3 (1.0%)
Cardiac	1 (0.2%)	1 (0.2%)			1 (0.3%)	1 (0.3%)
Other Non-specific Immune	0	1 (0.2%)			0	1 (0.3%)

Table 101 Overview of adverse events (safety-evaluable population): vinflunine versus taxanes subgroups (within 30-day window)

	Atezolizumab (N=459)	Vinflunine (N=242)	Taxane (N=201)	All Patients (N=902)
Total number of patients with at least one adverse event	438 (95.4%)	238 (98.3%)	197 (98.0%)	873 (96.8%)
Total number of events	4091	2570	1808	8469
Total number of patients with at least one				
Treatment-related AE	319 (69.5%)	219 (90.5%)	176 (87.6%)	714 (79.2%)
Grade 3-4 AE	233 (50.8%)	154 (63.6%)	95 (47.3%)	482 (53.4%)
Treatment-related Grade 3-4 AE	91 (19.8%)	124 (51.2%)	65 (32.3%)	280 (31.0%)
Grade 5 AE	17 (3.7%)	10 (4.1%)	8 (4.0%)	35 (3.9%)
Treatment-related Grade 5 AE	3 (0.7%)	7 (2.9%)	1 (0.5%)	11 (1.2%)
Serious Adverse Event	188 (41.0%)	130 (53.7%)	61 (30.3%)	379 (42.0%)
AE leading to withdrawal from treatment	34 (7.4%)	38 (15.7%)	40 (19.9%)	112 (12.4%)
AE leading to dose modification/interruption	134 (29.2%)	131 (54.1%)	79 (39.3%)	344 (38.1%)
Treatment-related AE leading to withdrawal from treatment	16 (3.5%)	29 (12.0%)	34 (16.9%)	79 (8.8%)

Safety in special populations

Age

Overall, in the All Patients Population, there was no noteworthy difference in the safety profile of atezolizumab based on age (< 65 years vs ≥ 65 years). However numerical differences were observed between the age groups for AEs leading to dose interruption (23.7% for < 65 vs. 27.2% for ≥ 65).

No data are available with regard to the safety profile of Tecentriq in children and adolescents aged below 18 years.

Table 102 Adverse events by age group in the All patient population

	<65 Years n=1053	65–74 Years n=757	75–84 Years n=333	≥85 Years n=17
Total AEs, n	9968	7959	3620	140
Total number of patients with at least one AE, n (%)	1002 (95.2%)	719 (95.0%)	323 (97.0%)	17 (100.0%)
Serious adverse events—total, n (%)	394 (37.4%)	290 (38.3%)	138 (41.4%)	10 (58.8%)
Fatal	28 (2.7%)	17 (2.2%)	7 (2.1%)	0
Hospitalization/prolong existing hospitalization	379 (36.0%)	278 (36.7%)	135 (40.5%)	10 (58.8%)
Life-threatening	34 (3.2%)	19 (2.5%)	9 (2.7%)	0
Disability/incapacity	13 (1.2%)	10 (1.3%)	6 (1.8%)	0
Other (medically significant)	15 (1.4%)	12 (1.6%)	4 (1.2%)	0
AEs leading to dropout, n (%)	73 (6.9%)	44 (5.8%)	25 (7.5%)	1 (5.9%)
Psychiatric disorders, n (%)	196 (18.6%)	151 (19.9%)	69 (20.7%)	2 (11.8%)
Nervous system disorders, n (%)	316 (30.0%)	262 (34.6%)	89 (26.7%)	6 (35.3%)
Accidents and injuries, n (%)	42 (4.0%)	59 (7.8%)	34 (10.2%)	4 (23.5%)
Cardiac disorders, n (%)	92 (8.7%)	52 (6.9%)	30 (9.0%)	0
Vascular disorders, n (%)	137 (13.0%)	110 (14.5%)	44 (13.2%)	4 (23.5%)
Cerebrovascular disorders, n (%)	7 (0.7%)	14 (1.8%)	5 (1.5%)	0
Infections and infestations, n (%)	418 (39.7%)	320 (42.3%)	155 (46.5%)	5 (29.4%)
Anticholinergic syndrome, n (%)	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures, n (%)	94 (8.9%)	101 (13.3%)	47 (14.1%)	4 (23.5%)

AE=adverse event.

Notes: The All Patients population comprises atezolizumab-treated urothelial carcinoma and NSCLC patients from the following studies with the following clinical cutoff dates: OAK (7 July 2016), BIRCH and POPLAR (1 December 2015), IMvigor 210 (4 July 2016), Study PCD4989g (31 March 2016), and FIR (7 January 2015).

Multiple occurrences of the same adverse event in the same individual were counted once.

Gender

Nearly twice as many male as female study participants were included in the All Patients population. The total number of patients experiencing an AE was approximately 95% with an incidence slightly lower in the female All UC subgroup and slightly higher in the female All NSCLC subgroup. The incidence of Grade 5 AEs was low in all subgroups. With regard to SAEs, AEs leading to dose interruption and AEs leading to study treatment discontinuation, the incidences were systematically higher among the male subgroups. However there was no difference regarding the SOCs of the reported events.

Race

Caucasians accounted for 84.8% of the All Patients population, as compared to 2.2% of Blacks, 7.7% of Asians and 5.3% of other races).

Histology

Based on NSCLC histology, the safety profile of atezolizumab was similar between subgroups and comparable to the 2L+NSCLC All Patients population. The total number of patients experiencing AEs was 92.0% (Squamous) vs. 95.9% (Non-squamous). There were no major differences between the squamous and non-squamous subpopulations.

Table 103 Overview of Safety by Histology (2L+NSCLC Safety-Evaluable Patients)

	2L+ NSCLC Squamous N=452	2L+ NSCLC Non-squamous N=1184	2L+ NSCLC All Patients N=1636
Total number of patients with at least one AE	416 (92.0%)	1135 (95.9%)	1551 (94.8%)
Total number of patients with			
Grade 3-4 AE	189 (41.8%)	471 (39.8%)	660 (40.3%)
Grade 5 AE	23 (5.1%)	21 (1.8%)	44 (2.7%)
SAE	180 (39.8%)	418 (35.3%)	598 (36.6%)
AE leading to treatment withdrawal	44 (9.7%)	74 (6.3%)	118 (7.2%)
AE leading to dose interruption	119 (26.3%)	314 (26.5%)	433 (26.5%)
AESI of Any Grade	123 (27.2%)	360 (30.4%)	483 (29.5%)
AESI of Grade 3-4	22 (4.9%)	63 (5.3%)	85 (5.2%)
AESI of Grade 5	1 (0.2%)	0	1 (<0.1%)

Note: All AEs collected after first treatment dose and within 30 days from last treatment dose, start of a non-protocol cancer therapy, or discontinuation from study are included, except for AESIs where no 30 day-time window was applied.

Sources: t_ae_aet01_N_NSCP_SQM, t_ae_aet01_N_NSCP_NSQM, t_ae_aet04_3cat_N_NSCP_SQM, t_ae_aet01_N_NSCP, t_ae_aet04_3cat_N_NSCP, t_ae_aet04_3cat_trtem_N_NSCP_aegrp01fl.

Summaries of AEs by Grade by histology (SOC and PT): Squamous, and Non-squamous.

Summaries of AEs leading to discontinuation of atezolizumab by Grade by histology (SOC and PT): Squamous, and Non-squamous.

Summaries of AEs leading to dose interruption by Grade by histology (SOC and PT): Squamous, and Non-squamous .

Summaries of AESIs by Grade by histology (SOC and PT): Squamous, and Non-squamous.

Level of PD-L1 expression

- All NSCLC Population

Based on PD-L1 expression, the total number of the All NSCLC population experiencing AEs was 94.8%. Grade 3 or 4 AEs occurred in 40.3% while the incidence of Grade 5 AEs was low (2.7%). The incidence of SAEs was 36.6%. The incidence of AEs leading to dose interruption was 26.5%% while the incidence of AEs leading to treatment discontinuation was 7.2%. The incidence of AESIs of any Grade was 29.5%. The incidence of Grade 3 to 4 AESIs was 5.2% and one (<0.1%) Grade 5 AESI was observed in the 2L+NSCLC All Patients population.

There were no major or clinically relevant differences between TC1/2/3 or IC1/2/3 and TC2/3 or IC2/3.

Table 104 Overview of Safety by PD-L1 Expression Status (NSCLC Safety-Evaluable Patients)

	All NSCLC N=1636	2L+ NSCLC All Patients N=1452	2L+ NSCLC TC1/2/3 or IC1/2/3 N=488 *	2L+ NSCLC TC2/3 or IC2/3 N=882
Total number of patients with at least one AE	1551 (94.8%)	1379 (95.0%)	462 (94.7%)	844 (95.7%)
Total number of patients with:				
Grade 3-4 AE	660 (40.3%)	587 (40.4%)	190 (38.9%)	372 (42.2%)
Grade 5 AE	44 (2.7%)	40 (2.8%)	7 (1.4%)	26 (2.9%)
SAE	598 (36.6%)	530 (36.5%)	174 (35.7%)	338 (38.3%)
AE leading to treatment withdrawal	118 (7.2%)	108 (7.4%)	38 (7.8%)	67 (7.6%)
AE leading to dose interruption	433 (26.5%)	381 (26.2%)	140 (28.7%)	251 (28.5%)
AESI of Any Grade	483 (29.5%)	434 (29.9%)	160 (32.8%)	273 (31.0%)
AESI of Grade 3-4	85 (5.2%)	78 (5.4%)	26 (5.3%)	53 (6.0%)
AESI of Grade 5	1 (<0.1%)	1 (<0.1%)	0	1 (0.1%)

Note: All AEs collected after first treatment dose and within 30 days from last treatment dose, start of a non-protocol cancer therapy, or discontinuation from study are included, except for AESIs where no 30 day-time window was applied.

Furthermore, when analysing safety data of patients expressing TC0 or IC0 for the docetaxel and atezolizumab treated patients of the OAK and POPLAR studies (see below table), the incidence of the various types of AEs is generally comparable to the ITT population meaning that quite consistently the incidence of the various types of AEs was lower in the atezolizumab arm as compared to the docetaxel arm. Overall, atezolizumab had a favourable safety profile compared to docetaxel in this subgroup of NSCLC patients.

Table 105 Overview of safety by TC0 and IC0 PD-L1 expression status (OAK and POPLAR safety-evaluable patients)

	POPLAR		OAK	
	Docetaxel N=36	Atezolizumab N=51	Docetaxel N=256	Atezolizumab N=258
Total number of patients with at least one AE	36 (100.0%)	50 (98.0%)	246 (96.1%)	242 (93.8%)
Total number of patients with:				
Grade 3-4 AE	19 (52.8%)	19 (37.3%)	139 (54.3%)	94 (36.4%)
Grade 5 AE	1 (2.8%)	3 (5.9%)	7 (2.7%)	6 (2.3%)
SAE	13 (36.1%)	17 (33.3%)	83 (32.4%)	71 (27.5%)
AE leading to treatment withdrawal	8 (22.2%)	3 (5.9%)	52 (20.3%)	18 (7.0%)
AE leading to dose modification/interruption	15 (41.7%)	11 (21.6%)	96 (37.5%)	48 (18.6%)
AESI of Any Grade	11 (30.6%)	14 (27.5%)	55 (21.5%)	71 (27.5%)
AESI of Grade 3-4	0	1 (2.0%)	7 (2.7%)	14 (5.4%)
AESI of Grade 5	0	0	0	0

Note: All AEs collected after first treatment dose and within 30 days from last treatment dose, start of a non-protocol cancer therapy, or discontinuation from study are included, except for AESIs where no 30 day-time window was applied.

- All UC Population

1L UC All Comers population

Based on PD-L1 expression, the total number of the 1L UC All Comers population experiencing AEs was 96.6%, with Grade 3 or 4 AEs occurring in 42.9% and Grade 5 AEs in 3.4%. The incidence of SAEs was 35.3% and the incidence of AEs leading to dose interruption was 32.8% while the incidence of AEs leading to treatment discontinuation was 5.9%. The incidence of AESIs of any Grade was 26.9%. The incidence of Grade 3 to 4 AESIs was 5.0% and no Grade 5 AESIs were observed in the 1L UC All Comers population.

When dividing patients into subgroups based on IC0, IC1, IC1/2/3 or IC2/3 numerical differences were observed but the sample size was small in several of the subgroups and the differences were not considered clinically meaningful.

2L+UC All Comers population

Based on PD-L1 expression, the total number of 2L+UC All Comers population experiencing AEs was 95.8%. Grade 3 or 4 AEs occurred in 47.4% while the incidence of Grade 5 AEs was low (1.0%). The incidence of SAEs were 44.7%. The incidence of AEs leading to dose interruption was 25.1% while the incidence of AEs leading to treatment discontinuation was 3.2%. The incidence of AESIs of any Grade was 26.8%. The incidence of Grade 3 to 4 AESIs was 4.7% and no Grade 5 AESIs were observed in the UC 1L All Comers population.

When dividing patients into subgroups based on IC0, IC1, IC1/2/3 or IC2/3 once again numerical differences were observed. However, albeit the sample size in the subgroups was larger compared to the 1L UC population, it is still not considered clinically meaningful to draw conclusions based on the observed differences.

Table 106 Overview of Safety by PD-L1 Expression Status: 1L cisplatin ineligible UC Patients (UC Safety-Evaluable Patients)

	All UC N=524	1L cisplatin ineligible UC All Comers N=119	1L cisplatin ineligible UC IC0 N=39	1L cisplatin ineligible UC IC1 N=48	1L cisplatin ineligible UC IC1/2/3 N=80	1L cisplatin ineligible UC IC2/3 N=32
Total number of patients with at least one AE	510 (97.3%)	114 (95.8%)	39 (100.0%)	45 (93.8%)	75 (93.8%)	30 (93.8%)
Total number of patients with:						
Grade 3-4 AE	288 (55.0%)	54 (45.4%)	19 (48.7%)	19 (39.6%)	35 (43.8%)	16 (50.0%)
Grade 5 AE	8 (1.5%)	4 (3.4%)	1 (2.6%)	1 (2.1%)	3 (3.8%)	2 (6.3%)
SAE	234 (44.7%)	45 (37.8%)	12 (30.8%)	18 (37.5%)	33 (41.3%)	15 (46.9%)
AE leading to treatment withdrawal	25 (4.8%)	9 (7.6%)	3 (7.7%)	2 (4.2%)	6 (7.5%)	4 (12.5%)
AE leading to dose interruption	164 (31.3%)	41 (34.5%)	11 (28.2%)	15 (31.3%)	30 (37.5%)	15 (46.9%)
AESI of Any Grade	165 (31.5%)	37 (31.1%)	14 (35.9%)	14 (29.2%)	23 (28.8%)	9 (28.1%)
AESI of Grade 3-4	37 (7.1%)	9 (7.6%)	3 (7.7%)	4 (8.3%)	6 (7.5%)	2 (6.3%)
AESI of Grade 5	0	0	0	0	0	0

Hepatic and renal function

Safety data for patients with organ dysfunction is limited (e.g., kidney and liver dysfunction). Based on a popPK analysis, no dose adjustment is required in patients with renal impairment or in patients with mild hepatic impairment.

There are no data in patients with moderate or severe hepatic impairment and data in patients with severe renal impairment are limited.

Use in pregnancy and lactation

No data regarding pregnancies in the clinical studies were available at the cut-off date.

Overdose

No data regarding overdose with atezolizumab are available. The highest tested dose in the clinical development programme was 20 mg/kg every 3 weeks.

Region

The incidence of adverse events across regions is described in the below table:

Table 107 Safety by region (safety evaluable patients)

	All Patients n = 2160				All UC n = 524				All NSCLC n = 1636			
No. of Patients	Asia n = 211	Europe n = 877	North America n = 1058	Other n = 14	Asia n = 0	Europe n = 137	North America n = 387	Other n = 0	Asia n = 211	Europe n = 740	North America n = 671	Other n = 14
At least one AE	202 (95.7%)	809 (92.2%)	1036 (97.9%)	14 (100.0%)	0	131 (95.6%)	379 (97.9%)	0	202 (95.7%)	678 (91.6%)	657 (97.9%)	14 (100.0%)
Grade 3–4 AEs	61 (28.9%)	372 (42.4%)	512 (48.4%)	3 (21.4%)	0	71 (51.8%)	217 (56.1%)	0	61 (28.9%)	301 (40.7%)	295 (44.0%)	3 (41.2%)
Grade 5 AEs	2 (0.9%)	35 (4.0%)	14 (1.3%)	1 (7.1%)	0	5 (3.6%)	3 (0.8%)	0	2 (0.9%)	30 (4.1%)	11 (1.6%)	1 (7.1%)
SAEs	63 (29.9%)	369 (42.1%)	397 (37.5%)	3 (21.4%)	0	69 (50.4%)	165 (42.6%)	0	63 (29.9%)	300 (40.5%)	232 (34.6%)	3 (21.4%)
AEs leading to treatment withdrawal	16 (7.6%)	68 (7.8%)	58 (5.5%)	1 (7.1%)	0	10 (7.3%)	15 (3.9%)	0	16 (7.6%)	58 (7.8%)	43 (6.4%)	1 (7.1%)
AEs leading to dose interruption	51 (24.2%)	235 (26.8%)	308 (29.1%)	3 (21.4%)	0	46 (33.6%)	118 (30.5%)	0	51 (24.2%)	189 (25.5%)	190 (28.3%)	3 (21.4%)

AE = adverse event; NSCLC = non–small cell lung cancer; SAE = serious adverse event; UC = urothelial carcinoma.

Notes: All adverse events collected after the first treatment dose and within 30 days from last treatment dose, start of a non-protocol cancer therapy, or discontinuation from study were included.

Europe includes AUT, BEL, BGR, BIH, CHE, DEU, ESP, FIN, FRA, GBR, GEO, GRC, HUN, ITA, NLD, NOR, POL, PRT, RUS, SRB, SVN, TUR, UKR. North America includes USA and CAN. Asia includes AUS, HKG, JPN, KOR, NZL, SGP, THA, TWN. Other includes BRA, CHL, GTM.

The clinical cutoff dates for the studies are OAK (7 July 2016), BIRCH and POPLAR (1 December 2015), IMvigor 210 (4 July 2016), Study PCD4989g (31 March 2016), and FIR (7 January 2015).

Sources: t_ae_aet01_UBNPreg, t_ae_aet01_NSCPreg, t_ae_aet01_UBCPreg, t_ae_aet04_UBNPreg, t_ae_aet04_UBCPreg, t_ae_aet04_NSCPreg.

While differences by regions were noted, no individual SOCs or PTs were noted to account for these regional differences and these findings were not considered clinically significant.

Overall, the safety profile of atezolizumab remained consistent across regions.

Smoking status

Patients who had never smoked accounted for 21.4% (462 of 2160 patients) of the All Patients population, and the remaining 78.6% (1698 of 2160 patients) were current or previous smokers. Increased toxicity was seen in the current or previous smoker group, especially grade 5 AEs in the NSCLC group.

In the UC population, the increased incidence of serious adverse events were related to infections and infestations SOC (16.0% vs. 11.4%) and respiratory, thoracic, and mediastinal disorders SOC (8.0% vs. 4.0%).

In the NSCLC group, grade 3-4 adverse events, grade 5 adverse events, serious adverse events, adverse events leading to treatment withdrawal, and adverse events leading to dose interruption were

similar in the All Patients population and the All NSCLC population regardless of smoking status (see below table).

Table 108 Safety by Smoking Status (Safety-Evaluable Patients)

	All Patients n = 2160		All UC n = 524		All NSCLC n = 1636	
No. of Patients	Never n = 462	Current or Previous n = 1698	Never n = 175	Current or Previous n = 349	Never n = 287	Current or Previous n = 1349
At least one AE	438 (94.8%)	1623 (95.6%)	171 (97.7%)	339 (97.1%)	267 (93.0%)	1284 (95.2%)
Grade 3–4 AEs	211 (45.7%)	737 (43.4%)	94 (53.7%)	194 (55.6%)	117 (40.8%)	543 (40.3%)
Grade 5 AEs	6 (1.3%)	46 (2.7%)	2 (1.1%)	6 (1.7%)	4 (1.4%)	40 (3.0%)
SAEs	163 (35.3%)	669 (39.4%)	67 (38.3%)	167 (47.9%)	96 (33.4%)	502 (37.2%)
AEs leading to treatment withdrawal	24 (5.2%)	119 (7.0%)	6 (3.4%)	19 (5.4%)	18 (6.3%)	100 (7.4%)
AEs leading to dose interruption	112 (24.2%)	485 (28.6%)	46 (26.3%)	118 (33.8%)	66 (23.0%)	367 (27.2%)

Safety related to drug-drug interactions and other interactions

No formal studies investigating possible drug-drug interactions with atezolizumab have been conducted and thus no data are available. Atezolizumab is an antibody and is thus cleared principally by catabolism. Thus, atezolizumab is not expected to show pharmacokinetic interactions with other drugs.

Atezolizumab enhances the immune response and concomitant administration of immuno-modulatory agents could result in pharmacodynamic interactions. Patients were excluded from atezolizumab clinical trials if they were administered immuno-modulatory products within 4 weeks prior to enrolment.

Discontinuation due to adverse events

Overall, 148 (6.9%) of the All Patients Population experienced AEs leading to study treatment discontinuation, with a higher incidence in the All NSCLC Population (7.2%) compared to the All UC Population (5.7%). By SOC, the most common AEs occurred within *Respiratory, thoracic and mediastinal disorders* (1.5%), *Infections and infestations* (1.3%).

Table 109 Overview of frequency and reasons for study treatment discontinuation (safety-evaluable patients)

Patient Disposition - Treatment
UC and NSCLC Safety Evaluable Patients
Protocols: GO27831 (UC and NSCLC Cohort), GO28625, GO28753, GO28754, GO29293, GO28915

	All Patients (N=2160)	All UC (N=524)	All NSCLC (N=1636)
Discontinued treatment	1797 (83.2%)	447 (85.3%)	1350 (82.5%)
Adverse Event	148 (6.9%)	30 (5.7%)	118 (7.2%)
Completed	21 (1.0%)	6 (1.1%)	15 (0.9%)
Death	14 (0.6%)	0	14 (0.9%)
Lost To Follow-Up	2 (<0.1%)	1 (0.2%)	1 (<0.1%)
Non-Compliance	7 (0.3%)	3 (0.6%)	4 (0.2%)
Other	9 (0.4%)	4 (0.8%)	5 (0.3%)
Physician Decision	21 (1.0%)	6 (1.1%)	15 (0.9%)
Progressive Disease	1493 (69.1%)	371 (70.8%)	1122 (68.6%)
Protocol Violation	13 (0.6%)	0	13 (0.8%)
Withdrawal By Subject	69 (3.2%)	26 (5.0%)	43 (2.6%)

GO27831=PCD4989g; GO28625=FIR; GO28753=POPLAR; GO28754=BIRCH; GO29293=IMvigor 210; GO28915=OAK.
Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO29293:04JUL2016, GO28915:07JUL2016.

Program: /opt/BIOSTAT/prod/cdt7692b/p27831j/t_ds_dst01_trt.sas
Output: /opt/BIOSTAT/prod/cdt7692b/p27831j/reports/t_ds_dst01_trt_UBNP.out
17OCT2016 19:59

Note: Data were collected from the treatment discontinuation CRF.

2.7.1. Discussion on clinical safety

The safety of Tecentriq is based on pooled data in 2,160 patients with metastatic UC (N=524) and NSCLC (N=1636). The number of patients included in the Pooled All Patients population (N=2160) and in each population based on malignancy is considered sufficient to evaluate the overall safety of atezolizumab in the population covered by the applied indications.

Based on line of therapy, TC/IC status and/or cisplatin ineligibility/non-response, further sub-populations were defined. As defining sub-populations divides the patients into multiple groups, some of these groups contain limited numbers of patients, making analyses of safety profiles in specific sub-populations somewhat uncertain. The safety profiles in these sub-populations are thus primarily regarded as exploratory.

All patients in the pivotal studies IMvigor 210, OAK, POPLAR, BIRCH, FIR and were exposed to the proposed dose. In the supportive study PCD4989g only 6 UC patients and no NSCLC patients were exposed to the proposed dose, albeit that a larger proportion may have been dosed close to the proposed dose. 86 patients from the UC Cohort and 26 patients from the NSCLC Cohort were dosed 15 mg/kg every 3 weeks, equivalent to 1200 mg in patients weighing 80 kg. Further, 5 patients from the NSCLC Cohort were dosed 20 mg/kg every 3 weeks. Overall, it is considered that a sufficient number of patients were exposed to the proposed dose to document safety in the posology applied for.

The median duration of exposure to atezolizumab at the proposed dose in the All Patients population was 3.5 months. The median duration of safety follow-up in the All Patients population was 4.5 months. At the time of data cut-off for each study, 63.6% of study participants in the All Patients had withdrawn from the study. The majority, representing 69.1%, discontinued due to progressive disease. The reasons for study withdrawal were consistent between the All UC and All NSCLC safety populations. From a safety perspective this is considered acceptable.

Safety profile

By SOC, the most frequently reported AEs (≥20% of patients) belonged to General disorders and administration site conditions, GI-disorders, Respiratory, thoracic and mediastinal disorders, Musculoskeletal and connective tissue disorders, Metabolism and nutrition disorders, Infections and infestation, Skin and subcutaneous tissue disorders, Nervous system disorders, Investigations, Blood and lymphatic system disorders and Renal and urinary tract disorders. Incidences varied slightly between studies.

The incidence of fatigue, urinary tract infection (UTI), oedema peripheral, abdominal pain, and haematuria was higher in the All UC population, whereas dyspnoea and cough were more frequent in the All NSCLC population, which are consistent with the underlying diseases.

Overall, 66.5% of the patients in the All Patients Population had at least one AE that was considered by the investigator to be related to atezolizumab treatment. The most common adverse reactions (any grade) were fatigue (35.4%), decreased appetite (25.5%), nausea (22.9%), dyspnoea (21.8%), diarrhoea (18.6%), rash (18.6%), pyrexia (18.3%), vomiting (15.0%), arthralgia (14.2%), asthenia (13.8%) and pruritus (11.3%).

SAEs occurred in 38.5% of patients (All patients); 44.7% in the All UC and 36.6% in the All NSCLC populations. The most common SAEs were pneumonia, dyspnoea and pyrexia in the All NSCLC, while in the All UC population the most common SAEs were urinary tract infection, sepsis and haematuria. Treatment-related SAEs reported in 4 or more patients (≥0.3%) were pneumonitis (1.0%), pyrexia (0.8%), diarrhoea (0.6%), colitis, nausea, AST increased (0.4% each), pneumonia, ALT increased, hypothyroidism and muscular weakness (0.3% each). Treatment-related SAEs were reported in 9.4% of patients in the 'All Patients population'.

The majority of deaths occurred beyond 30 days after last dose (80.7% [1007/1248]). The most common reason for death was progression of the underlying disease, which accounted for 85.1% (1062/1248) of all deaths.

AEs leading to study treatment discontinuation were experienced by 6.9% of the All Patients Population experienced. By Population, AEs leading to study treatment discontinuation occurred with higher incidence in the All NSCLC Population (7.2%) compared to the All UC Population (5.7%). This was primarily driven by AEs of pneumonitis, dyspnoea, pneumonia aspiration and pneumonia. However, based on the provided safety data there is no indication of increased risk of NSCLC patients having to discontinue treatment due to pulmonary adverse events caused by atezolizumab, as most events could be attributed to the underlying disease.

Treatment with atezolizumab should continue until the patient no longer experiences clinical benefit or until development of unacceptable toxicity. Long-term use is considered as missing information in the RMP and will be further investigated post-marketing in previously treated NSCLC patients and in patients with locally advance or metastatic urothelial or non-urothelial carcinoma of the urinary tract.

Immune-related events

Immune-related AEs are considered the key risk with the class of immune checkpoint inhibitors that target the PD-1/PD-L1 or cytotoxic T-lymphocyte antigen signalling pathway. Accordingly, a subset of important immune-related events of particular clinical relevance were identified as important ADRs, which include hypothyroidism, diabetes mellitus, pneumonitis, colitis, hyperthyroidism, pancreatitis, hepatitis, non-infectious meningoencephalitis, adrenal insufficiency, myasthenic syndrome and Guillain-Barré syndrome and hypophysitis. Of these, the majority was Grade 1 or 2, and the most commonly observed immune-related events were hypothyroidism and pneumonitis. At the clinical cut-

off dates for all studies included in the pooled analysis, no patients had AEs in the myasthenic syndrome SMQ, however, these events were observed in other clinical studies in the atezolizumab clinical development program.

It was observed that the incidence of immune-related pneumonitis was systematically higher in the All NSCLC Population, with AEs of higher Grade as compared to the All UC Population. This may partly be explained by an increased baseline risk in NSCLC due to atezolizumab induced immunologic response to tumour and surroundings. This seems to be in line with the observed safety profile of other immune checkpoint inhibitors, where a difference is also observed in lung vs. non-lung patients. As the incidences were relatively small and comparable with other studies of similar immune therapies, the provided data is considered acceptable. Most immune-related adverse reactions occurring during treatment with atezolizumab were reversible with interruptions of atezolizumab and initiation of corticosteroids and/or supportive care. In total 78/549 patients (14.2%) were in need of systemic corticosteroids. Only a minor fraction of the patients (28 (1.3%)) had to discontinue treatment due to immune-related reactions, and approximately 101 (4.7%) patients had to have a dose interruption. Median time to onset differed from ADR to ADR and likewise with median time to resolution.

Patients should be monitored for clinical signs and symptoms of the above listed immune-related events (Increase in ALT, AST or bilirubin levels, thyroid function, motor and sensory neuropathy, increase in serum amylase or lipase levels). For suspected immune-related adverse reactions, thorough evaluation to confirm aetiology or exclude other causes should be performed. Based on the severity of the adverse reaction, atezolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with systemic corticosteroid use, administration of other systemic immunosuppressants may be considered. Atezolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reactions, except for endocrinopathies that are controlled with replacement hormones (see sections 4.2, 4.4 and 4.8 of the SmPC).

Treatment with atezolizumab should also be permanently discontinued if a treatment-related toxicity does not resolve to Grade 0 or Grade 1 within 12 weeks after adverse reaction onset date, or if a corticosteroid dose of > 10 mg prednisone or equivalent per day is required for treatment-related toxicity beyond 12 weeks after adverse reaction onset date (see section 4.2 and 4.4 of the SmPC).

In the All Patients population, 308 patients (14.3%) treated with atezolizumab infusion-related reactions (IRRs)/hypersensitivity (type I). Signs and symptoms of IRRs overlap with several very common atezolizumab ADRs, including chills, dyspnoea, hypotension, influenza-like illness, pyrexia, and rash. The rate of all grade IRR AEs was similar between UC (13.0%) and NSCLC (14.7%) patients. These events were mild and seldomly required systemic treatment. Hence, pre-treatment is not deemed necessary. The rate of infusion should be reduced or treatment should be interrupted in patients with Grade 1 or 2 infusion related reactions. Atezolizumab should be permanently discontinued in patients with Grade 3 or 4 infusion related reactions. Patients with Grade 1 or 2 infusion-related reactions may continue to receive atezolizumab with close monitoring.

All the above listed immune-related events are listed as important identified risk in the RMP. In order to increase awareness and provide information concerning their signs and symptoms and how to manage them, an educational programme has been developed for healthcare professionals and patients, including Physician Information and Management Guidelines and a Patient Alert Card.

Other important pharmacological class effects for immune checkpoint inhibitors include immune-related myositis, immune-related nephritis, immune-related severe cutaneous adverse reactions and immune-related vasculitis as well as ocular inflammatory toxicity. Currently there is insufficient evidence to confirm a causal association with atezolizumab use and these events and these remain important potential risk.

Among the safety-evaluable patients with available post-treatment anti-therapeutic antibody status, 39.1% (785/2007) developed ATA. Irrespective of the population, the incidences of Grade 5 AEs and AEs leading to treatment discontinuation were very low and comparable. With regard to Grade 3-4 AEs, slightly more SAEs are observed in ATA-positive patients. Some numerical differences were observed in Grade 3-4 AEs (40.7% in ATA negative vs. 47.0% in ATA-positive patients), which was mainly driven by AEs reported in the *Metabolism and nutrition disorders* SOC and the decreased appetite within the *Metabolism and nutrition disorders* SOC in ATA-positive patients. The incidence of SAEs was also slightly higher in ATA-positive patients (40.5%) compared with ATA-negative patients (34.0%), but this difference was not driven by any specific SOC or individual AE preferred term. The development of ATA is considered a potential important risk in the risk management plan and is being further investigated in Study OAK and Study IMvigor 211 (see Risk Management Plan).

Subgroup analysis

- **NSCLC**

With regard to histology in NSCLC, there are no major differences between the squamous and non-squamous subpopulations. Also, there were no major or clinically relevant differences between TC1/2/3 or IC1/2/3 and TC2/3 or IC2/3. Furthermore, when analysing safety data of patients expressing TC0 or IC0 for the docetaxel and atezolizumab treated patients of the OAK and POPLAR studies, the incidence of the various types of AEs was generally comparable to the ITT population meaning that quite consistently the incidence of the various types of AEs was lower in the atezolizumab arm as compared to the docetaxel arm.

In study POPLAR, by adjusting for person-years at risk the applicant has demonstrated no increased incidence among the atezolizumab-treated patients for the majority of AEs. However, musculoskeletal pain and pneumonia occurred with a higher incidence among the atezolizumab-treated patients as compared to the docetaxel-treated patients. Low grade musculoskeletal pain has been considered an expected event with atezolizumab as part of a cluster of symptoms associated with influenza-like illness and is probably related to the mechanism of action of atezolizumab, which causes activation of the immune system, and subsequent release of inflammatory cytokines. Musculoskeletal pain is reported as commonly with other immunotherapy drugs such as nivolumab and pembrolizumab. The observed musculoskeletal pain in the studies of atezolizumab is acceptable and do not represent a new safety signal. Regarding the increased incidence of pneumonia in the docetaxel arm (10.6 vs 3.6%), there was no evidence showing that this was related to the also increased frequency of neutropenia in the same arm (12.6 vs 1.4%). There were no significant difference between the treatment arms in the OAK trial, hence, this finding is not of any major concern.

Overall, atezolizumab had a favourable safety profile as compared to docetaxel in NSCLC patients.

- **UC**

Based on PD-L1 expression, the total number of the 1L UC All Comers population experiencing AEs was 96.6% and the total number of 2L+UC All Comers population experiencing AEs was 95.8%. When dividing patients into subgroups based on IC0, IC1, IC1/2/3 or IC2/3 numerical differences were observed but the sample size was small in several of the subgroups and the differences were not considered clinically meaningful to draw conclusions based on the observed differences.

Based on top-line results, the overall safety experience in the atezolizumab arm of the ongoing Study IMvigor 211 study was consistent with its known safety profile in a single-agent setting and was similar across the PD-L1 expression subgroups. No new safety signals were identified. The safety results provided also demonstrated that atezolizumab was better tolerated than chemotherapy, with an incidence of AEs leading to treatment discontinuation or modification/interruption, treatment related Grade 3 or 4 AEs and treatment related SAEs lower in the atezolizumab treatment arm compared to chemotherapy and each subgroups of chemotherapy regimen (vinflunine or taxanes). Subgroup analyses of safety by chemotherapy regimen (vinflunine vs. taxanes) showed a better toxicity profile of taxanes compared to vinflunine. This is considered relevant in the context of the different OS results according to the chemotherapy subgroup (OS HR 0.75 [95%CI: 0.60, 0.94] for atezolizumab compared with taxanes; HR 0.92 [0.75, 1.13] for the comparison of atezolizumab with vinflunine).

The baseline and prognostic disease characteristics of the IMvigor210 Cohort 1 study population were overall comparable to patients in the clinic who would be considered cisplatin ineligible but would be eligible for a carboplatin-based combination chemotherapy. There are insufficient data for the subgroup of patients that would be unfit for any chemotherapy; therefore atezolizumab should be used with caution in these patients, after careful consideration of the potential balance of risks and benefits on an individual basis. Use of atezolizumab in previously untreated patients with urothelial carcinoma who are considered unfit for chemotherapy are also considered missing information and will be further investigated post-marketing.

Safety in special populations

Overall, in the All Patients Population, there was no noteworthy difference in the safety profile of atezolizumab based on age (< 65 years vs ≥ 65 years). No data are available with regard to the safety profile of Tecentriq in children and adolescents aged below 18 years. A Phase I/II, open-label study in paediatric and young adult patients with previously treated solid tumors is ongoing to evaluate the safety and tolerability of atezolizumab in this patient population.

Nearly twice as many male as female study participants were included in the All Patients population. Nevertheless, the total number included in each gender subgroup is considered sufficient to provide for meaningful analyses. The total number of patients experiencing an AE was approximately 95% depending on subgroup although the incidence was slightly lower in the female All UC subgroup and slightly higher in the female All NSCLC subgroup. With regard to SAEs, AEs leading to dose interruption and AEs leading to study treatment discontinuation, the incidences were systematically higher among the male subgroups. However no difference was noted regarding the SOC.

The majority of study participants were Caucasian. Due to the imbalance in race, no meaningful conclusions could be drawn from the analyses of safety by race. The majority of the patients were from North America and Europe. While differences in the incidence of adverse events across regions were noted, with lower Grade 3-4 and SAEs in Asian patients, no individual SOCs or PTs were noted to account for these regional differences and these findings were not considered clinically significant.

No data are available in patients with moderate or severe hepatic impairment and data in patients with severe renal impairment are limited.

No data are available regarding the safety profile with regard to overdose, drug abuse, withdrawal and rebound or effects on ability to operate machinery or impairment of mental ability.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted (see section 4.9 of the SmPC).

Patients experiencing fatigue should be advised not to drive and use machines until symptoms abate (see sections 4.7 and 4.8 of the SmPC)

Also, no data regarding pregnancy or lactation were available at the cut-off date. However preclinical data suggest that PD-L1 has a role in establishing maternal/foetal tolerance. Therefore, women of childbearing potential have to use effective contraception during and for 5 months after treatment with atezolizumab, and atezolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with atezolizumab. No data regarding possible excretion of atezolizumab in human milk are available and a risk to newborns/infants cannot be excluded (see Section 4.6 of the SmPC). No clinical data are either available on the possible effects of atezolizumab on fertility. No reproductive and development toxicity studies have been conducted with atezolizumab.

Hypersensitivity to atezolizumab or to any of the excipients was an exclusion criterion in atezolizumab clinical trial programme. Atezolizumab is contraindicated in patients with a known hypersensitivity to atezolizumab or to any of the excipients. Other exclusion criteria included history of active autoimmune disease, concomitant use with other immuno-modulatory agents, concomitant treatment with systemic corticosteroids or other immunosuppressive medications, patients with history of severe reactions to immune checkpoint inhibitors, pre-existing viral or bacterial infection, concomitant administration of live attenuated vaccine, all of which are listed as missing information in the RMP.

No data are available on concomitant or sequential use of atezolizumab with intra-vesical bacillus Calmette-Guérin vaccine for the treatment of urothelial carcinoma. Safety of atezolizumab administered with BCG will be investigated post-marketing. This is reflected in the RMP.

2.7.2. Conclusions on the clinical safety

Based on the assessment of the currently submitted data, the size of the All Patients Population as well as the size of the All UC Population and All NSCLC Population, respectively, is considered sufficient to evaluate the safety profile. The majority of patients were exposed to the proposed dose and follow-up time is regarded sufficient.

The ADRs reported for patients being treated with atezolizumab appear to be mostly of low grade and manageable, and the overall safety profile of atezolizumab is similar to that of other immune checkpoint inhibitors targeting the PD-1/PD-L1 signalling pathway.

It was noted that immunological ADRs include hepatitis, pneumonitis, colitis, pancreatitis, endocrinopathies, neuropathies, and meningoencephalitis. These are managed appropriately with the recommendations as stated in the SmPC section 4.2, 4.4 and 4.8 and are also addressed in the RMP. However, in order to raise awareness of health care professionals, patients and/or their caregivers about the potential for immune-related adverse events and infusion-related reactions, which are considered important identified risks, the CHMP has imposed an educational programme for both healthcare professionals and patients to help on the identification and detection of the signs and symptoms relevant to the early recognition/identification of those ADRs.

In conclusion, the CHMP considers that the safety and tolerability of atezolizumab has been described appropriately and is acceptable.

2.8. Risk Management Plan

Safety concerns

Table 110 Summary of the 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 • Hypophysitis Immune-related neuropathies: • Guillain-Barré syndrome • Myasthenic syndrome / myasthenia gravis Immune related meningoencephalitis Infusion-related reactions
Important potential risks	Embryofetal toxicity Anti-therapeutic antibodies Immune-related myositis Ocular inflammatory toxicity Immune-related nephritis Immune-related severe cutaneous adverse reactions Immune-related vasculitis
Missing information	Use in patients with history of active autoimmune disease Use in patients with pre-existing viral or bacterial infection Use in patients with history of severe reactions to immune check point inhibitors Concomitant use with other immuno-modulatory drugs Potential pharmacodynamic interaction with systemic immunosuppressants including corticosteroids Concomitant administration of live attenuated vaccine Use in patients with severe organ impairment Use in pediatric patients Use during lactation Long term use Use of atezolizumab in previously untreated patients with urothelial carcinoma who are considered unfit for chemotherapy. Concomitant or sequential use of atezolizumab with intra-vesical

	bacillus Calmette-Guérin vaccine for the treatment of urothelial carcinoma

Pharmacovigilance plan

Table 111 Ongoing and planned studies in the post-authorisation pharmacovigilance plan

Study/Activity Type and Title/ Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for submission of interim or final reports
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 (Category 3)	To determine if atezolizumab treatment results in an improved OS compared with docetaxel To evaluate safety and tolerability of atezolizumab compared with docetaxel To evaluate incidence of ATAs against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy	Anti-therapeutic antibodies	Ongoing	Final CSR: Q1 2019
GO29664: A Phase I/II, Multicenter, Open-Label Study of the Safety and Pharmacokinetics of atezolizumab (MPDL3280A) in Pediatric and Young Adult Patients with Previously Treated Solid Tumors (Category 3)	To evaluate the safety and tolerability of atezolizumab, focusing on the nature, frequency, and severity of serious and non-serious adverse events, as well as effects on laboratory values, vital signs, or other safety biomarkers	Use in pediatric patients	Ongoing	Final CSR: December 2018
GO29322: A Phase IB Study of the Safety and Pharmacology of atezolizumab Administered with Ipilimumab or Interferon-Alpha in	To evaluate the safety and tolerability of atezolizumab and ipilimumab in combination in patients with advanced or metastatic NSCLC or	Use of atezolizumab with other immunomodulatory drugs	Ongoing	Final CSR: July 2018

Study/Activity Type and Title/ Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for submission of interim or final reports
Patients with Locally Advanced or Metastatic Solid Tumors (Category 3)	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 (Category 3)	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	Ongoing	Final CSR: June 2022
MO39171: Single-Arm Long-Term Safety and Efficacy Study of atezolizumab in previously treated NSCLC Patients (Category 3)	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 serious and non-serious immune-related adverse events (irAEs) related to atezolizumab treatment.	Long-term atezolizumab use	Planned	Final CSR: May 2022
MO29983: An Open-Label, Single Arm, Multicenter, Safety Study of atezolizumab in Locally Advanced or Metastatic Urothelial or Non-Urothelial Carcinoma of the Urinary Tract (Category 3)	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	Long-term atezolizumab use	Ongoing	Final CSR: Q1 2023

Study/Activity Type and Title/ Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for submission of interim or final reports
	during and following atezolizumab administration.			
TBD/Observational Study/TBD Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, and infusion-related reactions (Category 3)	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 adverse events	Planned	Protocol submission: December 2017 Interim report: December 2020 Final Report: December 2022

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Table 112 Summary table of Risk Minimisation Measures

Safety concern	**Routine Risk Minimization measures**	**Additional Risk Minimization measures**
Immune-Related Hepatitis	SmPC wording in sections 4.2, 4.4 and 4.8	Educational materials for HCPs and patient alert cards
Immune-Related Pneumonitis	SmPC wording in sections 4.2, 4.4 and 4.8	Educational materials for HCPs and patient alert cards.
Immune-Related Colitis	SmPC wording in sections 4.2, 4.4 and 4.8	Educational materials for HCPs and patient alert card.
Immune-Related Pancreatitis	SmPC wording in sections 4.2, 4.4 and 4.8	Educational materials for HCPs and patient alert card.
Immune-Related Endocrinopathies • Diabetes Mellitus • Hypothyroidism • Hyperthyroidism • Adrenal Insufficiency • Hypophysitis	SmPC wording in sections 4.2, 4.4 and 4.8	Educational material for HCPs and patient alert card
Immune-Related Neuropathies • Guillain-Barre Syndrome • Myasthenic Syndrome / Myasthenia Gravis	SmPC wording in sections 4.2, 4.4 and 4.8	Educational material for HCPs and patient alert card
Immune-Related Meningoencephalitis	SmPC wording in sections 4.2, 4.4 and 4.8	Educational material for HCPs and patient alert card
Infusion-Related Reactions	SmPC wording in sections 4.2, 4.4 and 4.8	Educational material for HCPs and Patient alert card
Embryofetal Toxicity	SmPC wording in sections 4.6 and 5.3	None
Anti-Therapeutic Antibodies	SmPC wording in section 4.8	None
Immune-Related Myositis	No text in SmPC	None
Immune-Related Ocular Inflammatory Toxicity	No text in SmPC	None
Immune-Related Nephritis	No text in SmPC	None
Immune-Related Severe Cutaneous Adverse Reactions	SmPC wording in sections 4.2and 4.8	None
Immune-Related Vasculitis	No text in SmPC	None
Use in patients with history of active autoimmune disease	SmPC wording in section 4.4	None
Use in patients with pre-existing	No text in SmPC	None

Safety concern	Routine Risk Minimization measures	Additional Risk Minimization measures
viral or bacterial infection		
Use in patients with history of severe reactions to immune checkpoint inhibitors	No text in SmPC	None
Concomitant use with other immuno-modulatory agents	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.	None
Potential pharmacodynamic interaction with systemic immunosuppressants including corticosteroids	This safety concern considered as missing information is included in section 4.5 Interaction with other medicinal products and other forms of interaction and as one of the exclusion criteria within the Warnings and Precautions and the description of studies included in the E.U. SmPC.	None
Concomitant administration of live attenuated vaccine	This safety concern considered as missing information is mentioned as one of the exclusion criteria within the Warnings and Precautions and the description of studies included in the E.U. SmPC.	None
Use in patients with severe organ impairment	SmPC wording in sections 4.2 and5.2	None
Use in pediatric patients	SmPC wording in sections 4.2 and5.2	None
Use in pregnancy and lactation	SmPC wording in section 4.6	None
Long-term use	No text in SmPC	None
Use of atezolizumab in previously untreated patients with urothelial carcinoma who are considered unfit for chemotherapy	SmPC wording in section 4.4	None
Concomitant or sequential use of atezolizumab with intra-vesical bacillus Calmette-Guérin vaccine for the treatment of urothelial carcinoma.	No specific text in SmPC	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.5.1 is acceptable.

2.9. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant 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 Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 18.05.2016. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.10. New Active Substance

The applicant declared that atezolizumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers atezolizumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.11. Product information

2.11.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.11.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tecentriq (atezolizumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance NSCLC indication

3.1. Therapeutic Context

3.1.1. Disease or condition

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving Tecentriq.

The aim of the therapy with atezolizumab is to prolong survival in patients with NSCLC that have failed on prior chemotherapy.

3.1.2. Available therapies and unmet medical need

Lung cancer remains the leading cause of cancer deaths worldwide in men and the second leading cause of cancer deaths worldwide in women. More than half of the patients with NSCLC are diagnosed with distant metastatic disease, which directly contributes to poor survival prospects. Thus, there is an unmet medical need for these patients, which are otherwise faced with a dismal prognosis.

3.1.3. Main clinical studies

Data to support the application for atezolizumab monotherapy in patients with locally advanced or metastatic NSCLC after prior chemotherapy are derived from the pivotal Study OAK and four supportive Studies POPLAR, BIRCH, FIR and PCD4989g NSCLC Cohort. During the procedure the Applicant provided results from the OAK study.

3.2. Favourable effects

Atezolizumab exerts direct anti-tumour activity in patients with NSCLC as demonstrated by OS rates in controlled Phase II and III studies POPLAR and OAK. Both studies met their primary endpoint. Statistically significant and clinically relevant results were demonstrated. The curves start separating at 3 months and continue to stay separated throughout the follow-up period. The pivotal study OAK showed a median OS for atezolizumab of 13.8 months vs. 9.6 months for docetaxel and a HR of 0.73 (95%CI: 0.62, 0.87, p<0.0003) for the overall population.

The study POPLAR showed a median OS for atezolizumab of 12.6 months vs. 9.7 months for docetaxel and a HR of 0.73 (95%CI: 0.56, 0.80, p<0.0404) for the overall population. In the OAK study, both squamous and non-squamous histology subgroups, the TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3, and TC0 and IC0 subgroups treated with atezolizumab showed OS improvement compared with patients treated with docetaxel. Across all PD-L1 expression subgroups defined by different TC or IC cut-offs, the point estimates of the HRs for OS were equal to or below 0.82**.**

In the POPLAR study HRs for OS favoured atezolizumab, ranging from 0.49 (TC3 or IC3) to 0.54 (TC2/3 or IC2/3) to 0.59 (TC1/2/3 or IC1/2/3). In the TC0 and IC0 subgroup, OS was similar between atezolizumab and docetaxel (HR 1.04; 95% CI: [0.62, 1.75]). In the OAK study, both squamous and

non-squamous histology subgroups, the TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3, and TC0 and IC0 subgroups treated with atezolizumab showed OS improvement compared with patients treated with docetaxel. Across all PD-L1 expression subgroups defined by different TC or IC cut-offs, the point estimates of the HRs for OS were equal to or below 0.82**.**

Response rates in the range of 17% to 27% are observed in cohort 2 and 3 (2L and 3L respectively) in the BIRCH study. Having in mind that previous studies with docetaxel in 2L setting have resulted in response rates of 7-11 %, the observed ORR with atezolizumab may be considered clinically meaningful. Compared to historical control rates, the results are also statistically highly significant.

Atezolizumab demonstrated a prolonged duration of response (DOR) relative to docetaxel for subjects in the ITT population, consistent with the superior OS of atezolizumab relative to docetaxel. The median DOR (per RECIST v1.1) in responders was nearly doubled in the atezolizumab arm compared with the docetaxel arm (14.3 months atezolizumab, 95% CI: 11.6, NE, versus 7.2 months docetaxel; 95% CI 5.6, 12.5).

3.3. Uncertainties and limitations about favourable effects

N/A

3.4. Unfavourable effects

In general, atezolizumab had a favourable safety profile compared to docetaxel. Atezolizumab was overall well tolerated in a fragile patient population. However, increased incidences of musculoskeletal pain was observed in the atezolizumab arm of the OAK and POPLAR studies as compared to the docetaxel arm.

Common AEs included hypersensitivity, immune-related AEs, decreased appetite, hypokalaemia, hyponatremia, hypotension, dyspnpnoea, nausea, vomiting, diarrhea, abdominal pain, colitis[j] , dysphagia, AST increased , ALT increased, arthralgia, musculoskeletal pain, pyrexia, fatigue, asthenia, infusion related reaction, influenza like illness, and chills.

AEs leading to study treatment discontinuation were more frequent in the All NSCLC Population as compared to the All UC Population and this was primarily driven by AEs of pneumonitis, dyspnea, pneumonia aspiration and pneumonia, but these seems to related to the underlying disease and not atezolizumab.

3.5. Uncertainties and limitations about unfavourable effects

A range of immune-related AEs occur at a very low incidence among the All Patients Population. The safety profile of other compounds of the same class indicates that the underlying frequency of these AEs is expected to be low. However, due to the limited number of patients included in the five atezolizumab registration studies, it is considered difficult to draw solid conclusions regarding the exact frequency of the respective immune-related AEs. Hence, educational materials for health care professionals are proposed which aims to facilitate early recognition and intervention of the important immune-related risks. A study will be conducted in order to evaluate the effectiveness of HCP educational materials. Data from HCP surveys and reporting rates for the important identified immune related risks will be collected and analysed to evaluate effectiveness of the HCP brochure (see RMP section).

The post-baseline incidence of treatment emergent ATA was 31.3% in the All Patients population. The overall incidences of Grade 3-4 AEs, SAEs and AEs leading to dose interruptions were higher in the ATA-positive population compared to the ATA-negative population (differences pronounced in the UC population). The development of ATA is considered a potential important risk in the risk management plan and is being further investigated in Study OAK (see Risk Management Plan).

Nonetheless, in the OAK and POPLAR studies the overall safety profile of atezolizumab compares favourably with docetaxel.

3.6. Effects Table

Table 113 Effects Table for atezolizumab POPLAR and OAK (data cut-offs: 1 December 2015 and 7 July 2016, respectively)

Effect	Short Description	Unit	Treatment Atezolizumab	Control Docetaxel	Uncertainties/ Strength of evidence	References
Favourable Effects						
mOS	Median Overall Survival	months	13.8	9.6	HR = 0.73 (95%CI: 0.62, 0.87).	OAK CSR
mOS	Median Overall Survival	months	12.6	9.7	HR = 0.73 (95%CI: 0.56, 0.80)	Poplar CSR
Unfavourable Effects (OAK)						
Musculoskeletal pain		N/total (%)	64/609 (10.5)	25/578 (4.3)		
Immune-mediated AEs		N/total (%)	77/609 (12.6)	55/578 (9.5)	Uncertainty regarding the exact frequency	
Grade 3-4		N/total (%)	227/609 (37.3)	310/578 (53.6)		
Unfavourable Effects (Poplar)						
Musculoskeletal pain		N/total (%)	19/142 (13)	19/135 (14)		
Immune-mediated AEs		N/total (%)	11/142 (7.7)	10/135 (7.4)		
Grade 3-4		N/total (%)	19/51 (37.3)	19/36 (52.8)		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Median OS is improved by 2.9 and 4.3 months in the POPLAR and OAK studies respectively, which is

clinically significant.

With regard to safety, immune-related AEs are considered the key risk with the class of immune checkpoint inhibitors that target the PD-1/PD-L1 or cytotoxic T-lymphocyte antigen signaling pathway. A range of immune-related AEs occur at a very low incidence among the All Patients Population. The safety profile of other compounds of the same class indicates that the underlying frequency of these AEs is expected to be low. Direct comparison of safety in the POPLAR and OAK studies compares favourable for atezolizumab compared to docetaxel.

3.7.2. Balance of benefits and risks

A high unmet medical need for locally advanced and metastatic patients with non-small cell lung cancer is acknowledged. Statistically significant and clinically meaningfull results have been demonstrated. The safety profile is considered acceptable, despite some uncertainty about immune-related AEs occurring at a very low incidence among the All Patients Population. Overall, the balance of benefits and risks is considered favourable.

The overall treatment effect is consistently observed across TC and IC subgroups. The effect of atezolizumab in the so-called PD-L1 negative patients (TC0 or IC0) is considered clinically relevant based on the direct comparison with docetaxel in the POPLAR and OAK studies. Taken together the overall results of the OAK, BIRCH and POPLAR studies are clinically meaningful and welcomed in this patient population with a dismal prognosis. These results are further supported by two supportive studies.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The benefit-risk balance of Tecentriq in 2nd line NSLCC **is considered positive**.

4. Benefit-Risk Balance - UC indication

4.1. Therapeutic Context

4.1.1. Disease or condition

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy or who are considered cisplatin ineligible.

4.1.2. Available therapies and unmet medical need

The overall 5-year survival rate for patients diagnosed with metastatic UC is approximately 5.5% (Surveillance, Epidemiology, and End Results [SEER] 2015). Poor prognostic factors for survival in

patients with metastatic UC include advanced stage of disease at the time of initial diagnosis, Karnofsky Performance Status (KPS) <80%, and visceral metastasis (i.e., lung, liver, or bone; Bajorin et al. 1999).

First-line Treatment for Metastatic Urothelial Carcinoma

Cisplatin-based chemotherapy is the preferred 1L therapy and has been shown to improve survival in patients with previously untreated metastatic UC (Loehrer et al. 1992; von der Maase et al. 2005). Cisplatin and gemcitabine (in combination with cisplatin; European Union only) are approved for 1L therapy; however, there are currently no approved 1L therapies for patients who have a contraindication to cisplatin or who are otherwise medically unfit for a cisplatin-based regimen.

The ESMO guidelines (Bellmunt et al. 2014) recommend use of carboplatin-based regimens or single agents (taxane, gemcitabine) for cisplatin ineligible patients and BSC or inclusion in a clinical study for patients with PS >=2 and poor renal function. The National Comprehensive Cancer Network (NCCN) guidelines (2015) recommend participation in clinical studies or carboplatin- or taxane-based regimens, based on 2B level of evidence.

Second-Line Treatment for Metastatic Urothelial Carcinoma

Despite the efficacy of 1L regimens for patients treated with cisplatin-based regimens, responses showed limited durability, with nearly all patients experiencing disease progression. There is currently only one approved 2L therapy in the European Union (vinflunine). The approval of vinflunine was based on data from a single randomized Phase III study that compared vinflunine plus BSC with BSC alone in 370 patients with advanced UC progressing after a platinum-containing therapy. Taxanes (paclitaxel and docetaxel) are commonly used as 2L therapy in patients with locally advanced or metastatic UC.

4.1.3. Main clinical studies

Data to support the application for atezolizumab monotherapy in patients with locally advanced or metastatic UC or who are considered cisplatin ineligible are derived primarily from two studies: Pivotal Phase II Study IMvigor 210 and a supportive Phase Ia Study (PCD4989g). During the procedure the applicant also provided topline results from the phase III IMvigor 211 study.

4.2. Favourable effects

Study IMvigor 210 and 211 showed durable responses supported by OS data in 2L patients. Durable responses are also shown in 1L cisplatin-ineligible patients, please see effects table.

4.3. Uncertainties and limitations about favourable effects

Cohort 1: 1L cisplatin ineligible:

The evidence for the benefit of atezolizumab for patients with previously untreated cisplatin-ineligible metastatic urothelial carcinoma is based on a single non-randomized study that enrolled 119 patients with ORR as primary endpoint. The non-randomized trial design in this submission is considered a large drawback, since comparisons of time-related endpoints and prognostic characteristics of study populations are associated with uncertainties. In order to further evaluate the efficacy of Tecentriq and provide further confirmation of the efficacy assumptions in 1L UC patients, the applicant should submit the results of IMvigor 130, a Phase III randomized study to evaluate the safety and efficacy of

Atezolizumab monotherapy vs. Atezolizumab and carboplatin/gemcitabine or cisplatin/gemcitabine in cisplatin-ineligible and –eligible patients.

Cohort 2: 2L+

Study IMvigor 211 did not demonstrate statistical significance in the primary OS analysis (which is partly attributed to hierarchical testing order with first test in the IC2/3 subgroup and the fact that PD-L1 expression proved to be rather of prognostic than of predictive value in this data set). OS data for atezolizumab were numerically superior to SOC. "Explorative" p-value for the overall population was 0.0378, meaning that a different study design with a primary testing in the overall study population would have led to a statistically significant outcome. The Kaplan-Meier OS curves showed a separation after approximately 7 months in favour of the atezolizumab arm, which was maintained thereafter.

Subgroup analyses suggest a different treatment effect according to chemotherapy subgroups (OS HR 0.75 [95%CI: 0.60, 0.94] for atezolizumab compared with taxanes; HR 0.92 [0.75, 1.13] for the comparison of atezolizumab with vinflunine). However OS for atezolizumab was not inferior compared to vinflunine (the only approved drug in this disease setting) and for the BR-balance with regards to vinflunine the unfavourable toxicity profile of vinflunine has to be taken into account that provides an even larger advantage of atezolizumab from the safety perspective.

Confirmed ORRs are 13.4% in both treatment arms, but a higher proportion of patients had stable disease in the chemotherapy arm compared with the atezolizumab arm (35.1% vs. 19.9%). This suggests that the proportion of patients that clearly benefit from atezolizumab monotherapy is small in 2L UC. The Kaplan-Meier OS curves initially showed a favourable treatment effect for the control arm. Retrospective analyses could not identify characteristics to select a patient population with lower likelihood to benefit from atezolizumab.

Study IMvigor 211 resolved the concerns of a lower treatment effect of atezolizumab in subjects with lower PD-L1 expression subgroups (HR for OS 0.85 for all comers and 0.82 - 0.87 across all IC subgroups). Higher PD-L1 expression was associated with better efficacy results for atezolizumab. However the same association was also demonstrated for the control arm.

In order to further evaluate the efficacy of Tecentriq and provide further confirmation of the efficacy assumptions in 1L and 2L UC, the applicant should submit the final results of study IMvigor 211 and study IMvigor 210.

Finally, the applicant is recommended to provide a "biomarker analysis plan" with timelines and should submit the results of all ongoing and planned biomarker analyses post-approval.

4.4. Unfavourable effects

Atezolizumab was overall well tolerated in a fragile patient population. Increased incidences of urinary tract infection and haematuria are observed in the All UC Cohort as compared to the All NSCLC Cohort, but this related to the underlying disease.

AEs leading to study treatment discontinuation were more frequent in the All NSCLC Population as compared to the All UC Population and this was primarily driven by AEs of pneumonitis, dyspnea, pneumonia aspiration and pneumonia.

Immune-related pneumonitis occurred with systematically higher incidence in the All NSCLC Population as compared to the All UC Population. Further, the events were generally of higher Grades. This may partly be explained by an increased baseline risk in NSCLC due to atezolizumab induced immunologic response to tumour and surroundings. This seems to be in line with the observed safety profile of other immune check point inhibitors, where a difference is also observed in lung vs. non-lung patients.

4.5. Uncertainties and limitations about unfavourable effects

A range of immune-related AEs occur at a very low incidence among the All Patients Population. The safety profile of other compounds of the same class indicates that the underlying frequency of these AEs is expected to be low. However, due to the limited number of patients included in the five atezolizumab registration studies, it is not possible to draw solid conclusions regarding the exact frequency of the respective immune-related AEs. Hence, educational materials for health care professionals are proposed which aims to facilitate early recognition and intervention of the important immune-related risks. A study will be conducted in order to evaluate the effectiveness of HCP educational materials. Data from HCP surveys and reporting rates for the important identified immune related risks will be collected and analysed to evaluate effectiveness of the HCP brochure.

The post-baseline incidence of treatment emergent ATA was 31.3% in the All Patients population. The overall incidences of Grade 3-4 AEs, SAEs and AEs leading to dose interruptions were higher in the ATA-positive population compared to the ATA-negative population (differences pronounced in the UC population). The development of ATA is considered a potential important risk in the risk management plan and is being further investigated in Study IMvigor 211 (see Risk Management Plan).

4.6. Effects Table

Table 114 Effects Table IMvigor 210 and IMvigor 211

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
IMvigor 210						
ORR by IRF in cohort 1 update	Response rate in 1L cisplatin-ineligible	%	All comers: 22.7 (95%CI 15.5, 31.3)		CR 9.2 (95%CI 4.7, 15.9) Median duration of response NE (95%CI 14.1, NE)	
ORR by IRF in cohort 2	Response rate in 2L UC	%	IC 2/3 = 27% IC 1/2/3=18.3% All comers=15.1% Exploratory: IC0=8.7% IC1=10.2%		IC2/3: p<0.0001 IC 1/2/3: p=0.0004 All comers: p=0.00058	
mOS – cohort 1	Median overall survival	months	IC 2/3 = 10.58 IC 1/2/3=10.58 All comers=10.58 Exploratory: IC0= NE IC1=10.41		IC 2/3 = (6.01, NE) IC 1/2/3= (8.08, NE) All comers=(8.08, NE) Exploratory: IC0= (6.74, NE) IC1= (7.72, NE)	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
mOS – cohort 1 update	Median overall survival	months	IC2/3 = 12.3 (6.0, NE) IC 1/2/3 = 14.1 (9.2, NE) All comers=15.9 (95%CI 10.4, NE)			
mOS – cohort 2 (updated analysis. Data cutoff 27 Nov 2015)	Median overall survival	Months	IC 2/3 = 11.93 IC 1/2/3=9.00 All comers= 7.89 Exploratory: IC0= 6.54 IC1= 6.70		IC 2/3 = (9.00, NE) IC 1/2/3= (7.06, 10.87) All comers= (6.70, 9.26) Exploratory: IC0= (4.37, 8.25) IC1= (5.39, 9.23)	
IMvigor 211						
mOS	Median overall survival	Months	All comers = 8.6 HR= 0.85 (0.73, 0.99) P= 0.0378	8.0	Provided for descriptive purposes only; according to the pre specified analysis hierarchy, the p-value for the OS analysis in the all comer population cannot be considered statistically significant.	
Unfavourable Effects						
Musculoskeletal pain		N/tot (%)	32/524 (6.1%)	-	Number of events observed in the All UC population.	SCS
Immune-mediated AEs Cohort 1	Immune-mediated AEs	N/total (%)	18/118 (15.3%)	-	Number of events observed	IMvigor 210 CSR
Immune-mediated AEs Cohort 2	Immune-mediated AEs	N/total (%)	57/311 (18.3%)	-	Number of events observed	IMvigor 210 CSR
Grade 3-4 AEs		N/total (%)	288/524 (55.0%)		Number of events observed in the All UC population.	

Abbreviations:
Notes: Historical control rate set at 10%

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

2L+:

Response rates in the same range as for chemotherapy have been demonstrated consistently in 767 2L UC patients across IMvigor 210 and IMvigor 211. Duration of responses was substantially longer for treatment with atezolizumab in study IMvigor 211 (median DOR 21.7 vs. 7.4 months in the atezolizumab vs. control arm). OS data for atezolizumab were numerically superior to SOC for the overall study population and across all IC subgroups. The Kaplan-Meier OS curves showed a separation after approximately 7 months in favour of the atezolizumab arm, which was maintained thereafter suggesting a non-negligible clinical benefit for those patients achieving a response. IMvigor 211 confirmed the safety data of IMvigor 210 and demonstrated a better toxicity profile of atezolizumab compared to SOC chemotherapy. Thus given the efficacy considered at least non-inferior and the superior safety profile, atezolizumab could be considered an acceptable alternative treatment option in view of the unmet medical need in this setting.

1L cisplatin ineligible:

Although overall response rates of atezolizumab compare less favourably to the best historical comparator of CarboGem (22.7% vs. 36.1%), responses were ongoing in 70% of patients with a median follow-up of 17.2 months (compared to 5.3 months for Carbo/Gem). Considering the totality of evidence from different lines of therapy and in different diseases, the efficacy of atezolizumab in 1L cisplatin ineligible patients is considered established.

The safety profile of atezolizumab in Cohort 1 was consistent with that derived from 2L UC and 2L NSCLC (including over 2500 patients).

With regard to safety immune-related AEs are considered the key risk with the class of immune checkpoint inhibitors that target the PD-1/PD-L1 or cytotoxic T-lymphocyte antigen signaling pathway. A range of immune-related AEs occur at a very low incidence among the All Patients Population.

The safety data as provided in two large randomized phase III trials (OAK and IMvigor 211) demonstrated a more favourable profile for atezolizumab compared to SOC chemotherapy in UC.

4.7.2. Balance of benefits and risks

Considering the sustained responses, the overall numerically favourable OS results in IMvigor 211 and the better safety profile of atezolizumab compared to SOC chemotherapy, atezolizumab is considered an acceptable alternative treatment option in the 2L+ setting.

Additionally it is of importance that Study IMvigor 211 results are interpreted in context with data from other checkpoint inhibitors in the same indication, namely for nivolumab (single arm study CA209275: ORR 20%, median duration of response 10.4 months, median PFS 2.0 and median OS 8.6 months, J. Bellmunt et al, NEJM, February 17, 2017) and pembrolizumab (KN-045: ORR 21.1% vs. 11.4% for pembrolizumab vs. chemotherapy control, median OS 10.3 vs. 7.4 months [HR 0.73; p=0.002], median PFS 2.1 vs. 3.3 months). The results of all 2L UC studies with PD1/PDL1 checkpoint inhibitors are to a greater or lesser extent comparable.

With regard to the 1L setting, the benefit-risk profile of atezolizumab in 1L UC is also considered positive. Durable responses, promising OS data and a favourable safety profile has been demonstrated also in the 1L UC setting. Considering the totality of evidence from different lines of therapy and in different diseases, a positive B/R balance is confirmed.

4.7.3. Additional considerations on the benefit-risk balance

Not applicable.

4.8. Conclusions

Based on the totality of the evidence, the benefit-risk balance of Tecentriq in 2nd line UC and in 1st line cisplatin-ineligible UC **is considered positive.**

Divergent positions are appended to this report.

5. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Tecentric is favourable in the following indications:

- Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy or who are considered cisplatin ineligible.
- Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving Tecentriq.

The CHMP therefore recommends the granting of the marketing authorisation 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).

Other 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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
    - 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 I Diabetes Mellitus, Hypothyroidism, Hyperthyroidism, Adrenal Insufficiency and Hypophysitis)
  - Immune-Related Neuropathies (Guillain-Barre Syndrome, Myasthenic Syndrome / Myasthenia Gravis)
  - Immune-Related Meningoencephalitis
  - 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): 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 IMvigor 210.	Submission of study results: 30 June 2019
Post-authorisation efficacy study (PAES): In order to further evaluate the efficacy of atezolizumab compared with chemotherapy for the second/third line treatment of patients with locally advanced or metastatic urothelial cancer, the MAH should submit the final CSR of study IMvigor 211.	Submission of study results: 31 May 2019
Post-authorisation efficacy study (PAES): In order to evaluate the efficacy of atezolizumab monotherapy vs. atezolizumab plus carboplatin/gemcitabine vs placebo plus cisplatin/gemcitabine in patients with locally advanced or metastatic urothelial cancer who are platinum-ineligible and –eligible, the MAH should submit the final CSR of study IMvigor 130	Submission of study results: 31 July 2021

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that atezolizumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

6. Appendix

Divergent Position

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the granting of a Marketing Authorisation for Tecentriq.

The reasons for divergent opinion were as follows:

Current evidence on efficacy and safety in first-line cisplatin-ineligible patients only comprises a single-arm study (cohort 1 in study IMvigor210), where the response rate may be considered low. Comparison is made indirectly to CarboGem and does not allow concluding on an advantage for Tecentriq over CarboGem due to limitations related to indirect cross-trial comparison. Furthermore, efficacy outcomes of ORR and PFS are considered inferior to CarboGem. Although OS appears to be longer for Tecentriq compared to CarboGem and historical data, there are presently no available data from the ongoing, randomised comparative phase 3 study, IMvigor 130, in the first-line setting. The lack of direct comparative efficacy data with first line agents precludes a determination of the extent of any potential "loss of chance". This is of particular importance as no biomarker or other factors to predict which patients may respond to Tecentriq in this setting have been identified. It is however acknowledged that responses to Tecentriq are more durable than what is seen with chemotherapy. Without data from the ongoing 1L phase 3 study (IMvigor130), the fate of those who do not respond to Tecentriq is not known.

It is acknowledged that safety seems to be more favourable when compared to chemotherapy.

In conclusion, the uncertainties in current data outweigh the favourable safety profile, and do not support approval in the overall cisplatin-ineligible population and an approval in this setting could deprive patients of an effective treatment option. Taken together, the benefit-risk balance is considered to be negative for this population.

With regard to the second-line setting, currently evidence is based on a phase 2 single-arm study (cohort 2 in IMvigor210) and the phase 3 study IMvigor 211. The design of study IMvigor 210 was based on several assumptions that were not confirmed by the phase 3 data. The observed response rates in IC2/3 in cohort 2 in study IMvigor 210 are not translated into a statistically significant difference in terms of OS in study IMvigor 211. The favourable safety profile of atezolizumab does not outweigh the uncertainties related to the efficacy in this patient population.

In conclusion, the effect of atezolizumab is demonstrated in the second-line setting in NSCLC, however, there are substantial uncertainties regarding the efficacy of atezolizumab for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy or who are considered cisplatin ineligible, which are not outweighed by the likely favourable safety profile compared to available treatment options.

London, 20 July 2017

CHMP Members expressing a divergent position:

Alar Irs	20 July 2017	Signature: ……..
Alexandre Moreau	20 July 2017	Signature: ……..
Daniela Melchiorri	20 July 2017	Signature: ……..
Johann Lodewijk Hillege	20 July 2017	Signature: ……..
Natalja Karpova	20 July 2017	Signature: ……..
Sinan Bardackci Sarac	20 July 2017	Signature: ……..

Divergent Position – Tecentriq (EMEA/H/C/4143/0000)

The undersigned member of CHMP did not agree with the CHMP's opinion recommending the granting of a Marketing Authorisation for Tecentriq.

The reasons for divergent opinion were as follows:

Current evidence on efficacy and safety in first-line cisplatin-ineligible patients only comprises a single-arm study (cohort 1 in study IMvigor210), where the response rate may be considered low. Comparison is made indirectly to CarboGem and does not allow concluding on an advantage for Tecentriq over CarboGem due to limitations related to indirect cross-trial comparison. Furthermore, efficacy outcomes of ORR and PFS are considered inferior to CarboGem. Although OS appears to be longer for Tecentriq compared to CarboGem and historical data, there are presently no available data from the ongoing, randomised comparative phase 3 study, IMvigor 130, in the first-line setting. The lack of direct comparative efficacy data with first line agents precludes a determination of the extent of any potential "loss of chance". This is of particular importance as no biomarker or other factors to predict which patients may respond to Tecentriq in this setting have been identified. It is however acknowledged that responses to Tecentriq are more durable than what is seen with chemotherapy. Without data from the ongoing 1L phase 3 study (IMvigor130), the fate of those who do not respond to Tecentriq is not known.

It is acknowledged that safety seems to be more favourable when compared to chemotherapy.

In conclusion, the uncertainties in current data outweigh the favourable safety profile, and do not support approval in the overall cisplatin-ineligible population and an approval in this setting could deprive patients of an effective treatment option. Taken together, the benefit-risk balance is considered to be negative for this population.

London, 20 July 2017

CHMP Member expressing a divergent position:

Svein Rune Anderson	20 July 2017	Signature: ……..