



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Atezolizumab

Proprietary Product Name: Tecentriq

Sponsor: Roche Products Pty Ltd

September 2018

TGA Health Safety
Regulation

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

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- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Common abbreviations

Abbreviation	Meaning
1L	First line treatment
2L	Second line treatment
2L +	≥ Second line treatment
3L	Third line treatment
3L +	≥ Third line treatment
ACM	Advisory Committee on Medicines
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALK	Anaplastic Lymphoma Kinase (also known as ALK tyrosine kinase)
ALT	Alanine Transaminase
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate Transaminase
ATA	Anti-therapeutic antibody
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration time curve
AUC _{0-∞}	Area under the plasma concentration time curve from time zero to infinity
AUC ₀₋₂₄	Area under the curve for 24 hours
AUC ₀₋₁₂	Area under the curve for 12 hours
BCG	Bacillus Calmette-Guerin
BD	Twice daily
BOR	Best overall response
BSC	Best supportive care
BUN	Plasma blood urea nitrogen
CER	Clinical evaluation report

Abbreviation	Meaning
CI	Confidence interval
CL	Clearance
C _{max}	Maximum plasma (serum) concentration
CMI	Consumer Medicines Information
C _{min}	Minimum plasma (serum) concentration
CNS	Central nervous system
CR	Complete response
CSR	Clinical study report
CT	X-Ray Computed Tomography
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
CYP	Cytochrome P450
DCR	Disease control rate
DILI	Drug-induced liver injury
EC ₅₀	Half/50% of maximal dose
ECG	Electrocardiograph
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ER	Exposure-response
ERAUC	Exposure ratio based on AUC
ESMO	European Society of Medical Oncology
FDA	US Food and Drug Administration
GIT	Gastro intestinal tract
GLP	Good laboratory practice

Abbreviation	Meaning
hERG K	Human ether-a-go-go Related Gene potassium channel
HR	Hazard ratio
HRCT	High Resolution CT scan
IASLC	International Association for the Study of Lung Cancer
IC ₅₀	Half maximal inhibitory concentration
IC	Tumour-infiltrating immune cell
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
ICH	Immunohistochemistry
INR	International normalised ratio
IPF	Idiopathic Pulmonary Fibrosis
IRF	Independent review facility
IUO	Investigational use only
IV	Intravenous
LFTs	Liver function tests
LOQ	Limit of quantification
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NOAELs	No observable effect levels
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall Survival
PD	Pharmacodynamics
PD-1	Programmed death-1

Abbreviation	Meaning
PD-L1	Programmed death-1 ligand
PFS	Progression free survival
P-gp	P-glycoprotein
PI	Product information
PK	Pharmacokinetics
PR	Partial response
PS	Performance status
q3w	Every 3 weeks
QoL	Quality of Life
QT	QT interval (in heart rate)
RCC	Renal cell carcinoma
RECIST	Response evaluation criteria in solid tumours
RMP	Risk management plan
RTKs	Receptor tyrosine kinases
SAE	Serious adverse event
SCE	Summary of Clinical Efficacy
SCLC	Small cell lung cancer
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	Stable disease
SJS	Stevens-Johnson syndrome
SMQ	Standardised MedDRA Queries
SOC	System organ class
TCC	Transitional cell carcinoma
TEN	Toxic epidermal necrolysis
TIR	Time in response

Abbreviation	Meaning
TTOR	Time to onset of response
$t_{1/2}$	Half life
T_{max}	Time after administration when maximum plasma concentration is reached
UC	Urothelial cancer
UIP	Usual interstitial pneumonia
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
V1	Central volume of distribution
V2	Peripheral volume of distribution
Vss	Volume of distribution at steady state

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New biological entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	26 July 2017
<i>Date of entry onto ARTG:</i>	27 July 2017
<i>ARTG number:</i>	277120
<i>Active ingredient:</i>	Atezolizumab (rch)
<i>Product name:</i>	Tecentriq
<i>Sponsor's name and address:</i>	Roche Products Pty Ltd Level 8, 30-34 Hickson Road Sydney NSW 2000
<i>Dose form:</i>	Injection concentrated vial
<i>Strength:</i>	1200 mg/20 ml
<i>Approved therapeutic use:</i>	<i>Tecentriq is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, Tecentriq should be used after progression on or after targeted therapy.</i>
<i>Route of administration:</i>	Intravenous

Product background

This AusPAR describes the application by the sponsor to register a new biological entity called atezolizumab (rch) with a tradename of Tecentriq. Atezolizumab is a genetically engineered, humanised, monoclonal antibody. It targets human programmed death-ligand 1 (PD-L1) on tumour-infiltrating immune cells (ICs) and tumour cells (TCs), and inhibits the interaction of the ligand with its receptors programmed death-1 (PD-1) and B7.1, both of which can provide inhibitory signals to T cells. The pharmaco-therapeutic group (ATC code) had not yet been assigned at the time of the submission.

The submission seeks approval of two indications:

- *the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy, and*
- *the treatment of patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy.*

NSCLC is the leading cause of cancer-related mortality worldwide and represents a major health problem. Lung cancer is the fifth most commonly diagnosed invasive cancer in

Australia and causes more deaths than any other cancer in both males and females. Its high mortality rate results from both a high incidence rate and a very low survival rate. The poor survival outcome is due, at least partly, to the relatively high proportion of cases diagnosed at an advanced stage.¹ In 2013, there were 8,217 deaths from lung cancer in Australia, and 10,926 new cases were diagnosed in 2012.²

Urothelial carcinoma (also known as urothelial cell carcinoma, transitional cell carcinoma of the urinary tract, or urothelial bladder cancer) is one of the most commonly occurring genitourinary malignancies. Globally, there were an estimated 429,793 new cases of bladder cancer and 165,084 deaths in 2012.³ In Australia in 2014, bladder cancer (ICD-10 code C67) was estimated to be the eighth most commonly diagnosed cancer in men, and the eighteenth most commonly diagnosed malignancy in women with 2,060 and 675 cases respectively.⁴ Bladder cancer was estimated to have caused 1115 deaths in Australia in 2014, the majority of which occurred in men.⁵ The overall 5-year survival rate for patients diagnosed with metastatic urothelial carcinoma is approximately 5.5%.⁶

Current treatment options

Non-small cell lung cancer (NSCLC)

The sponsor states, that in the first-line setting, patients who do not harbour driver mutations such as activated EGFR or ALK rearrangement (which confer sensitivity to targeted agents) are typically treated with platinum-based chemotherapy. However, despite longer survival times and reduced disease related symptoms, nearly all patients experience disease progression. The use of second line treatment options are restricted by both limited survival gains and significant toxicities such as myelosuppression and neuropathy (docetaxel), diarrhoea (pemetrexed, erlotinib), and rash (erlotinib). At the time of the submission, TGA had recently approved nivolumab, the first PD-1 immune checkpoint inhibitor, for use as a second line treatment of metastatic NSCLC. As outcomes are poor for patients with previously treated, advanced or metastatic NSCLC additional effective and tolerable treatment options are needed.

Urothelial cancer

Australian guidelines for the treatment of advanced or metastatic urothelial carcinomas include carboplatin in combination with gemcitabine, and vinflunine.⁶ At the time of the submission, TGA had approved vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum containing regimen. The sponsor comments that while several chemotherapeutic agents have been studied in the second line setting over the last three decades the low response rates are not durable and treatment is associated with considerable toxicity. Therefore, the sponsor considers that effective and tolerable novel therapeutic options with durable responses are urgently needed for these patients where little to no therapeutic advancement has been observed for more than 30 years.

Dosage forms and strengths

Tecentriq is available in a single use vial containing 1200 mg of atezolizumab in a 20 mL concentrated solution for IV infusion.

¹ Cancer incidence projections Australia, 2011 to 2020. AIHW Cancer Series No.66.

² Australian Institute of Health and Welfare, ACIM book for lung cancer (ICD10 C33-C34), 2016.

³ Canadian Cancer Survivor Network. GLOBOCAN Bladder Cancer, 2012.

⁴ ICD-10; International Statistical Classification of Diseases and Related Health Problems, 10th revision; World Health Organization.

⁵ Australian Institute of Health and Welfare 2014. Cancer in Australia: an overview 2014. Cancer series No 90. Cat. no. CAN 88. Canberra: AIHW, 2014.

⁶ SEER. Stat Fact Sheets: Bladder Cancer.

Administration

The recommended dose of atezolizumab is 1200 mg administered by IV infusion every three weeks (q3w). The initial dose must be administered over 60 minutes. If the first infusion is tolerated all subsequent infusions may be administered over 30 minutes. Patients are treated with atezolizumab until loss of clinical benefit or unmanageable toxicity. If a planned dose is missed, it should be administered as soon as possible. The schedule of administration should then be adjusted to maintain a 3-week interval between doses. No dose reductions of atezolizumab are recommended.

Dose modifications (for example, reduced infusion rate, withholding dose, and permanent discontinuation) are recommended for specified adverse drug reactions. Atezolizumab is not indicated for children and adolescents (that is, patients aged < 18 years). No dosage modifications have been proposed for patients aged \geq 65 years, patients with renal impairment or patients with hepatic impairment. Specific instructions relating to dilution and administration have been provided in the proposed PI.

Regulatory status

The regulatory status at the time of this submission to TGA is shown in Table 1. At time of this submission, Tecentriq had been approved in the US, Canada and New Zealand, with submissions under evaluation in the EU, Switzerland and Singapore.

Table 1: Regulatory status at the time of this submission to TGA

Region	Submission status	Approval details (if applicable)
EU (Centralised procedure. Rapporteur: Denmark, Co-Rapporteur: Germany)	Submitted: 21 Apr 2016 (Filed jointly for 2L+ UC, 1L cisplatin-ineligible UC and 2L+ NSCLC)	Under evaluation
USA	Submitted: 12 Jan 2016 (2L+ UC) Submitted: 19 Feb 2016 (2L+ NSCLC) Submitted: 31 Oct 2016 (1L cisplatin-ineligible UC)	<p>2L+ UC approved 18 May 2016 2L+ NSCLC approved 18 October 2016 1L cisplatin-ineligible UC approved 17 Apr 2017</p> <p>Approved indications: <i>TECENTRIQ is a programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with:</i></p> <ul style="list-style-type: none"> • <i>Locally advanced or metastatic urothelial carcinoma who: <ul style="list-style-type: none"> ○ are not eligible for cisplatin-containing chemotherapy, or ○ have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy.</i> <p><i>This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.</i></p> <ul style="list-style-type: none"> • <i>Metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA approved therapy for these aberrations prior to receiving TECENTRIQ.</i>

Table 1 continue: Regulatory status at the time of this submission to TGA

Canada	Submitted 18 Jul 2016 (2L+ UC)	Approved 12 Apr 2017 Approved indications: <i>TECENTRIQ (atezolizumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:</i> <ul style="list-style-type: none"> • <i>Have disease progression during or following platinum-containing chemotherapy</i> • <i>Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy</i> <i>Marketing authorization with conditions was based on tumour response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established (see CLINICAL TRIALS).</i>
New Zealand	Submitted: 19 Sep 2016 (Filed jointly for 2L+ UC, 1L cisplatin-ineligible UC and 2L+ NSCLC under Provisional Consent)	Approved 6 Apr 2017 Approved indications: <i>TECENTRIQ is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.</i> <i>TECENTRIQ is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:</i> <ul style="list-style-type: none"> • <i>are considered cisplatin ineligible, or</i> • <i>have disease progression during or following platinum-containing chemotherapy, or</i> • <i>have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.</i>
Switzerland	Submitted: 9 May 2016 (Filed jointly for 2L+ UC, 1L cisplatin-ineligible UC and 2L+ NSCLC)	Under evaluation
Singapore	Submitted: 30 September 2016 (Filed jointly for 2L+ UC, 1L cisplatin-ineligible UC and 2L+ NSCLC)	Under evaluation

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Registration timeline

Table 2 shows the registration timeline.

Table 2: Registration timeline for this submission.

Description	Date
Submission dossier accepted and first round evaluation commenced	29 July 2016
First round evaluation completed	3 January 2017
Sponsor provides responses on questions raised in first round evaluation	24 February 2017
Second round evaluation completed	19 April 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	28 April 2017
Sponsor's pre-Advisory Committee response	16 May 2017
Advisory Committee meeting	2 June 2017
Registration decision (Outcome)	26 July 2017
Completion of administrative activities and registration on ARTG	27 July 2017
Number of working days from submission dossier acceptance to registration decision*	210

*Legislative timeframe is 255 working days

III. Quality findings

Structure

Atezolizumab is a humanised monoclonal antibody based on an immunoglobulin G1 (IgG1) framework that contains heavy chain VHIII and light chain VKI subgroup sequences. The recombinant antibody is produced in Chinese hamster ovary (CHO) cells and consists of two heavy chains (448 amino acid residues each) and two light chains (214 amino acid residues each).

The molecular formula of intact atezolizumab is $C_{6434}H_{9878}O_{1996}N_{1702}S_{42}$ (peptide chains only, without heavy chain C-terminal lysine residues) and has a calculated molecular mass of 144,356 Da. 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 include N- and C- terminal structural variants and post-translational modifications of amino acid side chains (include oxidation, isomerisation, succinimide intermediate, glycation and hydroxylysine) and sequence variant.

Because atezolizumab has an amino acid substitution at position 298 on the heavy chain, which is the conserved N-linked glycosylation site, it is expressed as a non-glycosylated antibody. As a result, atezolizumab lacks the glycan variants typically observed for other CHO-derived monoclonal antibodies.

Stability

The sponsor proposed a shelf life of 24 months at $\leq -20^{\circ}\text{C}$ for the drug substance. Stability data were generated under real time conditions to characterise the stability profile of the substance and to establish a shelf life. The real time data submitted support the proposed shelf life.

For the drug product, stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. The product is not photostable. The proposed shelf life is 24 months when stored at 2 to 8°C . In-use stability data have also been submitted. If not used immediately, the diluted solution can be stored for up to 24 hours at 2°C to 8°C , or 8 hours at ambient temperature ($\leq 30^{\circ}\text{C}$).

- ***Briefly describe the main degradation pathways for the product and which analytical methods are the most relevant and stability indicating tests.***

The main degradation pathway appears to be general stress treatments such as high temperature. Analytical methods for stability indicating include IE-HPLC, SE-HPLC, and CE-SDS.

- ***Provide details of the potency assay(s).***

The potency assay of atezolizumab, Reactivation of PD-1-Expressing Jurkat Cells by rhuMAb PD-L1, serves as a quantitative in vitro assay to determine the potency of both Drug Substance and Drug Product. The analytical procedure measures the ability of atezolizumab to relieve the PD-L1/PD-1-mediated inhibition of IL-2 secretion from activated T cells. It uses a Jurkat cell line engineered to express PD-1 (Jurkat PD-1 cells). In this procedure, the Jurkat PD-1 cells are incubated together with PD-L1-expressing WIL2-S B cells in the presence of a constant concentration of a T-cell-activating reagent and increasing concentrations of atezolizumab. Engagement of PD-1 with PD-L1 delivers an inhibitory signal that reduces IL-2 secretion from activated Jurkat PD-1 cells. Binding of atezolizumab to PD-L1 relieves this inhibition, resulting in increased secretion of IL-2 into the supernatant, which is detected by ELISA. The results, expressed in optical density units, are plotted against the atezolizumab concentrations, and a parallel line program is used to estimate the activity of the atezolizumab samples relative to the Reference Standard. There is no international standard for atezolizumab; therefore, the Reference Standard was assigned a specific activity of 1.00×10^4 Units/mg, and the results are reported in units/mg.

- ***Based on the stability studies conducted, what are the allowable temperature deviations (this should be noted on the CPD when it is provided)?***

The company has provided data to support the in-use stability (see above).

One batch of drug product has been subjected to temperature cycling:

- 2 to 8°C for 7 days
- -20°C for 14 days
- 2 to 8°C for 7 days
- -20°C for 14 days
- 2 to 8°C for 7 days
- $25^{\circ}\text{C}/60\% \text{ RH}$ for 10 days, and
- $30^{\circ}\text{C}/75\% \text{ RH}$ for 3 days.

After completion of the temperature excursion cycle, the vials were placed in the stability chamber at 2 to 8°C , corresponding to long-term conditions. The samples were tested for colour, clarity, physical state, pH, SE-HPLC, Non-reduced CE-SDS, IE-HPLC, potency and

protein content at the end of each interval point. The temperature excursion study still ongoing and the end of shelf life stability data is not available now.

- ***Are there any stability data specifically related to transport or temperature cycling that was available in the application?***

See above.

Biopharmaceutics

Data is not required.

Quality summary and conclusions

There are no objections on quality grounds to the approval of Tecentriq.

Proposed Conditions of Registration

Batch Release Testing and Compliance with Certified Product Details (CPD):

- It is a condition of registration that all batches of Tecentriq imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
- It is a condition of registration that each batch of Tecentriq imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

IV. Nonclinical findings

Introduction

The submitted dossier was relatively small, but was generally acceptable according to the relevant guidelines.⁷ All pivotal safety-related studies were GLP compliant. The clinical formulation was used in the pivotal repeat-dose toxicity study, while an early formulation (and drug substance manufacturing process) was used for the shorter term study in cynomolgus monkeys. A comparative pharmacology studies confirmed similar binding affinities for drug substances produced by the two manufacturing processes.

Pharmacology

Primary pharmacology

Rationale and mechanism of action

The PD-L1 (also B7-H1, CD274) protein is expressed on limited cell types of normal tissues (see *Secondary pharmacodynamics and safety pharmacology* for cell types expressing this protein). The PD-L1 protein has been shown to be expressed on the cell

⁷ ICH S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals.

surface in various human cancers, including carcinomas of the lung.⁸ PD-L1 is a binding and functional partner of PD-1 on immune cells. The PD-L1/PD-1 interaction plays a dominant role in the suppression of T cell responses in vivo, including in the tumour microenvironment.⁹ Additionally, PD-L1 interacts with B7-1 (CD80) on activated T cells to mediate an inhibitory signal. Blockade of the PD-L1/PD-1 and the PD-L1/B7-1 interactions by atezolizumab is envisaged to enhance the functional activity of tumour-infiltrating lymphocytes to induce tumour regression.

In vitro

In vitro, atezolizumab bound to human PD-L1 expressed on HEK293 cells and activated human T cells with K_D and EC_{50} values, respectively, around 0.4 nM. Atezolizumab was shown to block human PD-L1 binding to B7-1 and PD-1 with IC_{50} values 40 to 83 pM. The efficacious concentrations are well below the anticipated clinical C_{min} in patients (around 480 nM after the first cycle).

Atezolizumab had similar (< 2-fold difference in most assays) affinity for activated monkey T cells as activated human T cells and similar affinity for murine PD-L1 as human PD-L1. Atezolizumab blocked murine PD-L1/B7-1 and PD-L1/PD-1 interactions with similar potency to that observed with the human proteins. Based on these findings, cynomolgus monkeys and mice are considered appropriate animal models from a pharmacological perspective.

As atezolizumab, a humanised monoclonal antibody, induced anti-drug antibodies in a toxicity study, mouse atezolizumab analogues were used for in vivo pharmacology studies in this species. These analogues generally displayed a similar potency to atezolizumab in the set of studies described above, and therefore are considered appropriate analogues in the pharmacology studies.

In vivo

The anti-tumour efficacy of an atezolizumab analogue was assessed in mouse colorectal and melanoma cancer models. There was a greater than 75% reduction in tumour growth in all tested animal models with 10 mg/kg IP atezolizumab given three times per week for up to 3 weeks (approximately a third of the proposed clinical dose on a mg/m^2 basis).¹⁰ Complete tumour regression was observed in one colorectal cancer model. The time to tumour progression was also prolonged with each increase in treatment length.

The submitted pharmacology studies support the proposed clinical dose. No studies assessed the efficacy of atezolizumab in animal models of NSCLC or mUC, so no specific comment can be made in regard to these indications. However, as with colon cancers and melanomas, PD-L1 has been shown to be expressed in multiple lung carcinomas. Therefore, similar efficacy might have been seen in a NSCLC model.

Secondary pharmacodynamics and safety pharmacology

Atezolizumab was engineered with an amino acid substitution at position 298 resulting in a non-glycosylated antibody to impair Fc γ receptor binding and to prevent Fc-mediated depletion of cells expressing PD-L1. In vitro, atezolizumab showed minimal binding to human Fc γ receptors with EC_{50} values > 100 $\mu g/mL$ (a concentration approximately

⁸ Dong, H. *et al.* (2002) Tumor-associated B7-H1 promotes T-cell apoptosis: A potential mechanism of immune evasion. *Nat. Med.* 8: 793-800.

⁹ Reviewed in Chen, L. & X. Han. (2015) Anti-PD-1/PD-L1 therapy of human cancer: past, present, and future. *J. Clin. Invest.* 125: 3384-3391.

¹⁰ Based on a clinical dose of 1200 mg over 3 weeks and using mg/kg to mg/m^2 conversion factors of 3 and 33 for mice and humans, respectively (equating to a clinical dose of 792 mg/m^2 in patients and around 270 mg/m^2 in mice)

similar to the clinical C_{min}). Atezolizumab showed no ADCC activity at concentrations up to 10 µg/mL in a NK cell-based assay. The tested concentrations in these assays were low compared with systemic levels in patients, so interactions with these aspects of the immune system cannot be completely dismissed.

Some binding of atezolizumab to the syncytiotrophoblasts of the human placenta was observed in an ex vivo study to assess the tissue cross-reactivity of atezolizumab. This is consistent with the expression of PD-L1 in this tissue and has relevance with respect to the use of atezolizumab in pregnancy (see *Reproductive toxicity*).¹¹ Some staining was observed in the lymph node, thymus and tonsils, which may be associated with immunoreactive macrophages in these tissues.⁸ PD-L1 is also expressed on non-lymphoid cells, including vascular endothelial cells, epithelial cells, muscle cells, hepatocytes, pancreatic islet cells, astrocytes in the brain, placenta and eye.¹²

No specialised safety pharmacology studies were submitted. Effects on the cardiovascular, respiratory and central nervous systems were assessed in repeat-dose toxicity studies in cynomolgus monkeys (in accordance with ICH S6[R1]).¹³ No ECG or neurological abnormalities were observed in cynomolgus monkeys treated with ≤ 50 mg/kg IV. No effects on respiratory rate were observed at this dose. The maximum serum concentration of atezolizumab achieved at this dose was almost 7 times the clinical C_{max} at steady state. No adverse effects on the central nervous, cardiovascular or respiratory systems are predicted during clinical use.

Pharmacokinetics

The pharmacokinetics of atezolizumab was examined in cynomolgus monkeys. Exposures appeared to be dose proportional. There were no obvious sex differences in any of the parameters. Similar to that seen in human subjects, in monkeys higher exposures were observed after repeated dosing. Clearance was moderate in monkeys (around 4 mL/day/kg) with the volume of distribution at steady state similar to the whole blood volume in both species, suggesting minimal extravascular distribution. Consistent with the protein nature of the drug, the elimination half-life was long: around 11 days in monkeys and 27 days in human subjects. Given the shorter half-life in monkeys, it seems appropriate that weekly dosing (rather than the clinical dosing regimen of 3 weekly dosing) was used in the submitted toxicity studies.

No distribution, metabolism, excretion or pharmacokinetic interaction studies were submitted (in accordance with ICH S6[R1]).

Overall the pharmacokinetic profile of atezolizumab in cynomolgus monkeys support the use of this species in the toxicity studies, taking into account the shorter half-life in this species than in human subjects.

Toxicology

Acute toxicity

No single-dose toxicity studies were submitted which is considered acceptable. No treatment-related mortalities were observed in mice or cynomolgus monkeys treated with

¹¹ Petroff, M.G. *et al.* (2003) B7 family molecules are favorably positioned at the human maternal-fetal interface. *Biol. Repro.* 68: 1496-1504.

¹² Reviewed in Sharpe, A.H. *et al.* (2007) The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. *Nat. Immunol.* 8: 239-245.

¹³ ICH, S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

≤ 50 mg/kg IV atezolizumab in the repeat-dose toxicity studies. Also taking into account the minimal toxicity observed in the repeat-dose toxicity studies, atezolizumab is considered to have a moderate to low order of acute toxicity.

Repeat-dose toxicity

Repeat-dose toxicity studies in mice (15 days) and cynomolgus monkeys (up to 26 weeks) were submitted. The duration of the pivotal study is consistent with the relevant guidelines (ICH S9 and ICH S6[R1]).¹⁴ The choice of species is considered appropriate from a pharmacology and/or pharmacokinetic perspective. The clinical route (IV) was used in all studies, with the SC route also used in the 8-week toxicity study in cynomolgus monkeys. Dosing was weekly in all studies (compared with the 3 weekly clinical dosing regimen). As stated above, this is considered appropriate for the monkey studies given the shorter half-life in this species.

Anti-drug antibodies (ADAs) were detected in both species. In the monkey studies, ADAs were detected in nearly all animals, but serum drug concentrations were not significantly reduced by ADAs over the dosing period. In the mouse study, all treated animals were positive for ADAs on day 18, significantly reducing serum drug concentrations on day 17 (3 days after the last dose) by >75% compared with day 3 (3 days after the first dose). ADA production in mice reduces the utility of the toxicity study in the species. Findings in this study are only discussed briefly below.

Relative exposure

As dosing was weekly in the animal studies and three weekly in patients, the AUC_{0-7 days} in animals was multiplied by 3 for comparison with the clinical AUC. Relative exposures achieved were modest at the highest tested doses. Higher doses may have been achievable, given the limited toxicity observed in the studies.

Table 3: Relative exposure in repeat-dose toxicity studies

Species	Study duration [Study no]	Dose (mg/kg IV)	Dosing frequency	AUC _{0-7 days} (µg·day/mL)	AUC _{0-3 weeks} (µg·day/mL)	ER [#]
Monkey (Cynomolgus)	8 weeks [Study 08-1148]	5	weekly	598 [†]	1794	0.3
		15		3588 [†]	10764	2
		50		13000 [†]	39000	7
	26 weeks [Pivotal; Study NC 13-3278]	5	weekly	882 [^]	2646	0.5
		15		7817 [^]	23450	4.5
		50		19600 [^]	58800	11
Human (patients)	steady state	[1200 mg]	3 weekly	-	5253	-

[#] = 3 x animal AUC: human AUC; [†] = data are average weekly exposure over the entire dosing period (that is, AUC_{0-56 days/8}) for both sexes (data specific for the last sampling occasion were not available); [^] =

¹⁴ ICH, S9: Nonclinical Evaluation for Anticancer Pharmaceuticals; ICH, S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

AUC_{0-3 days} (378, 3350 and 8400 µg·day/mL at 5, 15 and 50 mg/kg, respectively) after the last dose normalised to AUC_{0-7 days} for the sexes combined

Major toxicities

The most notable finding in the toxicity studies with monkeys was reversible arteritis/periarteritis in multiple tissues of animals treated with 50 mg/kg IV atezolizumab in both studies (8 and 26-weeks) and one female with 15 mg/kg atezolizumab in the 26-week study (exposure ratio based on AUC (ER_{AUC}) 4.5). Increased blood leukocytes, lymphocytes (including an increase in total T cells, CD4⁺ T cells and B cells) and serum C reactive protein were seen in one female treated with 50 mg/kg for 26 weeks, and correlated with microscopic evidence of arteritis/periarteritis. This finding is consistent with the pharmacological action of atezolizumab; PD-L1 has a role in regulating T cells (including their apoptosis), minimising the potential for autoimmune reactions, either *via* its interaction with PD-1 or via a non-PD-1 pathway.¹⁵ Sciatic neuropathy (vacuolation and lymphocyte infiltration) was observed in mice treated with atezolizumab. The underlying mechanism for this finding is likely to be similar to the arteritis/periarteritis observed in monkeys.¹⁶ Given the interaction of PD-L1 with B7-1 on T cells, as well as with PD-1, a greater potential for autoimmune reactions may exist with anti-PD-L1 antibodies such as atezolizumab compared with anti-PD-1 antibodies.

One female treated with 50 mg/kg IV atezolizumab for 26 weeks had evidence of *Balantidium coli* infection in the gastrointestinal tract. It is unclear if this female had a pre-existing infection prior to treatment. This parasite is not uncommon in monkey colonies.

Two male monkeys experienced isolated incidences of infusion-related reactions (characterised by hypoactivity, staggered movement and an increased heart rate) in the pivotal study. Infusion-related reactions are a risk with this product.

Genotoxicity and carcinogenicity

No studies were submitted. Given the protein nature of the drug and the proposed indication, this is considered acceptable.

Reproductive toxicity

No dedicated reproductive or developmental toxicity studies were submitted. Parameters that may affect fertility were examined in a general toxicity study, and a discussion regarding potential effects on a developing fetus was supported by appropriate literature. This is considered acceptable, taking into account the relevant guideline, ICH S9.¹⁷

There was no effect on serum testosterone levels or sperm quality (count, motility, morphology) in male cynomolgus monkeys treated for 26 weeks with ≤50 mg/kg IV atezolizumab (ER_{AUC} 11). Male reproductive organs were not affected by atezolizumab treatment.

Female cynomolgus monkeys treated with 50 mg/kg IV atezolizumab experienced irregular menstruation during the dosing period, including an increase in mean menstrual

¹⁵ Dong, H. *et al.* (2004) B7-H1 determines accumulation and deletion of intrahepatic CD8⁺ lymphocytes. *Immunity* 20: 327-336; Menke, J. *et al.* (2007) Programmed death 1 ligand (PD-L) 1 and PD-L2 limit autoimmune kidney disease: distinct roles. *J. Immunol.* 179: 7466-7477; Nishimura, H. *et al.* (1999) Development of lupus-like autoimmune diseases by disruption of the *PD-1* gene encoding an ITIM motif-carrying immunoreceptor. *Immunity* 11: 141-151; Keir, M.E. *et al.* (2006) Tissue expression of PD-L1 mediates peripheral T cell tolerance; Herold, M. *et al.* (2015) B7-H1 selectively controls TH17 differentiation and central nervous system autoimmunity via a novel non-PD-1-mediated pathway. *J. Immunol.* 195: 3584-3595.

¹⁶ Yoshida, T. *et al.* (2008) PD-1 deficiency reveals various tissue-specific autoimmunity by H-2[b] and dose-dependent requirement of H-2[g7] for diabetes in NOD mice. *Proc Natl Acad Sci* 105: 3533-3538.

¹⁷ ICH, S9: Nonclinical Evaluation for Anticancer Pharmaceuticals.

cycle length (ER_{AUC} at the NOEL 2 to 5). The findings correlated with a lack of newly formed corpora lutea and decreased ovary weight at terminal necropsy and were considered treatment-related. Menstrual cycling returned to normal during the treatment-free period. The underlying mechanism for the effects on menstrual cycling is unclear. No effects on menstrual cycling have been reported for anti-PD-1 antibodies, but this parameter may not have been examined in studies with these compounds. Nonetheless, irregular menstrual cycling with atezolizumab treatment suggests female fertility may be affected by the drug.

PD-L1 is expressed by cytotrophoblasts and syncytiotrophoblasts in the human placenta. Administration of an anti-PD-L1 antibody to mice increased the rate of fetal resorptions (to 86%) with a consequent reduction in litter size. Similar results were observed in female PD-L1 knockout mice.¹⁸ These data suggest that PD-L1 is involved in fetomaternal tolerance by negatively regulating the maternal immune system. Given the published results with an anti-PD-L1 antibody (as well as those with PD-L1-deficient mice), atezolizumab may be expected to cause embryofetal lethality in pregnant patients.

Atezolizumab binds to the neonatal Fc receptor (FcRn) (presented in Module 3) and would be expected to cross the placental barrier. There are no studies specifically investigating teratogenicity of blocking PD-L1 or gene knockout. PD-1 or PD-L1 deficient mouse offspring develop spontaneous autoimmunity.¹⁹

Pregnancy classification

The sponsor has proposed Pregnancy Category D.²⁰ This is considered appropriate given the embryofetal lethality observed in published literature and is consistent with the pregnancy category of anti-PD-1 antibodies.

Local tolerance

In the toxicity studies, there were no notable injection site reactions following IV administration.

Immunotoxicity

Based on the pharmacological action of atezolizumab, perturbations to the immune system would be expected. Atezolizumab did not induce cytokine release from unstimulated human PBMCs at up to 250 µg/mL in vitro, but the effect on cytokine release was not tested with primed/activated lymphocytes. In a mouse model of acute lymphocytic choriomeningitis virus (LCMV) infection (CL-13), administration of an atezolizumab analogue before or at the peak of infection resulted in a very high mortality rate (up to 100%). The high mortality rate was attributed to enhanced CD8⁺ T cell function with an increase in T cell-derived cytokines, TNF-α and IFNγ, and an extremely high viral burden in multiple organs (which is atypical for a viral infection). Using this model, deaths were also observed following PD-1 blockade or administration of IL-2. Lethality was not observed in 3 other mouse models of acute viral infection or when the anti-PD-L1 antibody was administered after the acute phase of infection. While the LCMV CL-13 model is not a realistic viral model, the findings in this model suggest effects on immune

¹⁸ Guleria, I. *et al.* (2005) A critical role for the programmed death ligand 1 in fetomaternal tolerance. *J. Exp. Med.* 202: 231-237.

¹⁹ Reviewed in Okazaki, T. & Honjo, T. (2006) The PD-1-PD-L pathway in immunological tolerance. *Trends Immunol.* 27: 195-201.

²⁰ Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

function are likely with atezolizumab administration. PD-1 deficient mice with tuberculosis infection were shown to have reduced survival compared with wild-type mice associated with heightened inflammatory responses.²¹ PD-L1 blockade suppressed immunity of mice against intracellular bacterial infection by *Listeria monocytogenes*.²² The above findings suggest blocking the PL-L1/PD-1 pathway may increase the inflammatory responses and severity of some infections.

Paediatric use

Atezolizumab is not proposed for paediatric use. No specific juvenile animal studies were submitted.

Nonclinical summary and conclusions

Summary

- The submitted dossier was relatively small, but was generally acceptable according to the relevant guidelines. All pivotal safety-related studies were GLP compliant.
- In vitro, atezolizumab bound PD-L1 and blocked PD-L1 binding to PD-1 and B7-1 with subnanomolar potency. In vivo, a greater than 75% reduction in tumour growth to complete regression was observed in mouse models of colorectal carcinoma and melanoma. No animal model efficacy studies were submitted to specifically support the indications.
- No adverse effects on the function of central nervous, cardiovascular or respiratory systems are predicted during clinical use.
- The pharmacokinetics of atezolizumab in cynomolgus monkeys and human subjects was generally consistent with the protein nature of the drug: moderate clearance rates, long half-lives and limited extravascular distribution. The pharmacokinetic profile of atezolizumab was considered acceptably similar in cynomolgus monkeys and human subjects.
- Atezolizumab is considered to have a moderate to low order of acute toxicity in mice and cynomolgus monkeys.
- Repeat-dose toxicity studies by the IV route were conducted in mice (15 days) and cynomolgus monkeys (up to 26 weeks). The most notable finding were arteritis/periarteritis in multiple tissues of monkeys and neuropathy in mice, probably autoimmune reactions.
- No genotoxicity or carcinogenicity studies were submitted, which is considered acceptable.
- No dedicated reproductive toxicity studies were submitted. In repeat-dose toxicity studies, female cynomolgus monkeys that received atezolizumab experienced irregular menstruation and a prolonged menstrual cycle. Exposures at the no effect level were 2 to 5 times the clinical AUC. Based on published literature, atezolizumab may be expected to cause embryofetal lethality in pregnant patients.

²¹ Lázár-Molnár, E. *et al.* (2010) Programmed death-1 (PD-1)-deficient mice are extraordinarily sensitive to tuberculosis. *PNAS* 107: 13402–13407

²² Rowe, J.H. *et al.* (2008) PDL-1 blockade impedes T cell expansion and protective immunity primed by attenuated *Listeria monocytogenes*. *J. Immunol.* 180:7553–7557; Seo, S.K. *et al.* (2008) Blockade of endogenous B7-H1 suppresses antibacterial protection after primary *Listeria monocytogenes* infection. *Immunol.* 123:90–99.

Conclusions and recommendation

- The pharmacology studies lend support for the proposed clinical dose and marginal support for the proposed indications.
- The combined animal safety studies revealed the following findings of potential clinical relevance:
 - Autoimmune reactions
 - Effects on female fertility
 - Embryofetal lethality if used during pregnancy
- The draft PI should be amended as directed.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The sponsor provided a clinical rationale for the submission. In summary, the sponsor's clinical rationale is based on the need to for additional effective and tolerable novel options for the second line treatment of UC and NSCLC. The sponsor considers that *"the efficacy profile [for atezolizumab] observed across studies, combined with the distinct and favourable safety profile [of the medicine] compared to standard chemotherapy, supports a favourable benefit-risk profile in 2L+ NSCLC patients, regardless of PD-L1 expression. Similarly, with regard to the UC indication, the totality of the data demonstrates a [favourable] benefit-risk for the use of atezolizumab in patients with locally advanced or metastatic UC after prior chemotherapy regardless of their level of PD-L1 expression and therefore supports an indication in these patient populations"*. The sponsor's clinical rationale for the submission is considered satisfactory. The sponsor's comment regarding the favourable benefit-risk balance for atezolizumab for the proposed indications is considered in this clinical evaluation report (CER).

Guidance

Information indicated that a pre-submission meeting was held between the TGA and the sponsor. The agreed minutes indicate that the meeting focused on presenting the clinical development program and Phase II trial results to TGA, and seeking TGA comment on the proposed submission on the basis of the Phase I/II data. It is considered that all significant clinical issues raised in the *Record of discussions* have been discussed in this clinical evaluation report. The sponsor states that submission is consistent with the lodged pre-submission planning form.

Contents of the clinical dossier

The clinical dossier provided the results of a limited development program for the registration of atezolizumab (a new biological entity) for the treatment of locally advanced or metastatic UC or NSCLC in previously treated patients.

- Two patient PK and initial tolerability studies: Study PCD4989g (Study G027831), a Phase I, open-label, dose-escalation study of the safety and PK of atezolizumab in patients with locally advanced or metastatic solid tumours or haematological malignancies (including UC and NSCLC subgroups); and Study J028994, a Phase I, open-label, dose-escalation study of the safety, tolerability and PK of atezolizumab in Japanese patients with advanced solid tumours.
- Three population PK reports: Report 1066935 (based on the Phase I Studies PCD4989g and J028944); Report 1067934 (based on the Phase II Study IMvigor 210 in patients with UC); and Report 1067735 (based on the Phase II Studies BIRCH, FIR and POPLAR in patients with NSCLC).
- Four exposure-response (E-R) analysis reports: Report 1067242 (E-R analysis in patients with UC); Report 1068446 (E-R analysis in patients with previously untreated metastatic UC); Report 1068603 (E-R analysis in patients with NSCLC); Report 1068477 (E-R analysis in patients with NSCLC from POPLAR, a pivotal Phase II study).
- One human PK/PD report: Report 1066934, a modelling and simulation analysis report providing a concentration-QTc analysis for atezolizumab based on data from the Phase I Study PCD4989g.
- Two studies providing uncontrolled data supporting registration of atezolizumab for UC: Study IMvigor 210, a Phase II study nominated by the sponsor as being the pivotal UC study, with addendum, study update and supplemental results reports; and Study PCD4989g, a Phase I study including a subset of patients with UC.
- One pivotal Phase II study providing controlled data supporting registration of atezolizumab for NSCLC: the POPLAR study (Study G028754), plus an addendum and a supplemental results report.
- Three Phase I/II studies providing uncontrolled data supporting registration of atezolizumab for the treatment of NSCLC: the BIRCH study (Study G028754), a Phase II study plus a supplemental results report; the FIR study (Study G028625), a Phase II study; and Study PCD4989g, a Phase I study including a subset of patients with NSCLC.
- Literature references.

Paediatric data

No paediatric data were submitted. The sponsor states that no paediatric data have been submitted to the EU and that it has an agreed Paediatric Investigation Plan (PIP) with that jurisdiction. The sponsor states that no paediatric data have been submitted to the US FDA. The sponsor states that it has full waivers from the FDA for obligations relating to the submission of paediatric studies with atezolizumab in NSCLC (11 December 2014) and urothelial bladder cancer (30 July 2015) on the basis of “extremely limited applicability in paediatric patients”.

Good clinical practice

The submitted Phase I/II studies were undertaken in compliance with the principles of Good Clinical Practice.

Pharmacokinetics

Studies providing pharmacokinetic data

The submission included no dedicated clinical pharmacology studies. There were no clinical pharmacology studies in healthy subjects. Clinical pharmacology information (including PK and PD data) were provided in subjects with advanced or metastatic malignancies, including subjects with NSCLC and UC. The absence of clinical pharmacology data in healthy subjects is considered to be acceptable for a medicine proposed for treatment of locally advanced or metastatic NSCLC or UC after prior chemotherapy.

Pharmacokinetic (PK) and exposure response (E-R) data were provided in the six clinical studies listed below.

- Study PCD4989g (GO27831), a Phase Ia, open-label, dose-escalation study of the safety, tolerability, and PK of atezolizumab in patients with locally advanced or metastatic solid tumours or haematologic malignancies, including a UC cohort and an NSCLC cohort.
- Study J028944, a Phase I, open-label, multicentre, dose-escalation study of the safety, tolerability, and PK of atezolizumab in Japanese patients with locally advanced or metastatic solid malignancies. This study did not include efficacy data.
- Study GO29293 (hereafter referred to as IMvigor 210), a Phase II, global, multicentre, single-arm study designed to evaluate the efficacy and safety of atezolizumab in patients with locally advanced or metastatic UC.
- Study GO28754 (hereafter referred to as “BIRCH”), a Phase II, global, multicentre, single-arm study designed to evaluate the efficacy and safety of atezolizumab in patients with PD-L1 selected, locally advanced or metastatic NSCLC.
- Study GO28753 (hereafter referred to as “POPLAR”), a Phase II, global, multicentre, open-label, randomised, controlled study designed to evaluate the efficacy and safety of atezolizumab compared to docetaxel in patients with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen.
- Study GO28625 (hereafter referred to as “FIR”), a Phase II, global, multicentre, single-arm study designed to evaluate the efficacy and safety of atezolizumab in patients with PD-L1 selected, locally advanced or metastatic NSCLC.

Cumulatively, the studies investigated and characterised the single- and multiple-dose PK of atezolizumab, the potential effect of atezolizumab serum concentration on change from baseline in QTc interval (QTcF), and the immunogenicity of atezolizumab.

Non-compartmental (NCA) and population pharmacokinetic (popPK) analyses were conducted to quantitatively describe the PK of atezolizumab and to evaluate the effects of relevant covariates (for example, demographics, laboratory baseline values, disease status) that may contribute to variability in atezolizumab exposure in individual patients. The popPK of atezolizumab was first assessed based on Phase I data from the two clinical Studies PCD4989g and J028944 and resulted in the “Phase I popPK Model” being developed. The “Phase I popPK Model” subsequently underwent external validation for each indication separately, using PK data collected in the Phase II clinical Study IMvigor 210 for UC, and in BIRCH, POPLAR, and FIR for NSCLC.

E-R analyses were conducted to assess possible relationships between selected clinical efficacy and safety endpoints and atezolizumab exposure for patient populations in each indication separately. The E-R analyses for UC were based on data from Study PCD4989g and IMvigor 210, and the E-R analyses for NSCLC were based on data from Study PCD4989g, BIRCH, POPLAR, and FIR.

Analyses of the immunogenicity of atezolizumab (incidence of anti-therapeutic antibodies (ATA)) and the effect of these ATAs on atezolizumab PK and efficacy were also conducted.

Biopharmaceutic and bioavailability studies

No dedicated clinical biopharmaceutic or bioavailability studies for atezolizumab were undertaken. This issue is discussed below in the Bioavailability section of this CER.

Bioanalysis

Serum samples were analysed for atezolizumab with the use of an enzyme-linked immunosorbent assay (ELISA). This assay was validated and run at two sites (Genentech and ICON). The validation performance parameters of the ELISA from the two sites are summarised below.

Table 4: Validation performance parameters for pharmacokinetic assays.

PK Assay Validation and Sample Analysis Site, Method Number	Validation Report No.	Standard Curve Reporting Range (ng/mL)	MQC (ng/mL)	Accuracy (%Recovery)	Intra-Assay Precision (%CV)	Inter-Assay Precision (%CV)	Clinical Study No.
Genentech, Inc., BA.MET.MPDL.005	MPDL.005.AVR_1	0.6 to 24	60	81 to 112	2 to 5	2 to 11	PCD4989g
ICON Laboratory Services, Inc., M08.MPDL3280A.huse.1	MPDL.005.AVR_1	0.6 to 20	60	93.2 to 125.0	1.57 to 4.12	2.21 to 4.59	PCD4989g, JO28944, IMvigor 210, FIR, POPLAR, BIRCH

CV = coefficient of variation; MQC = minimum quantifiable concentration; PK = pharmacokinetic.

Evaluator's conclusions on pharmacokinetics

- The PK of atezolizumab have been adequately characterised in two Phase I studies in patients with advanced malignancy, four Phase II studies in patients with UC or NSCLC, and a popPK analysis based on data from the two Phase I studies. The popPK model based on the two Phase I studies was validated using the PK data from the Phase II study in patients with UC (IMvigor 210) and the three Phase II studies in patients with NSCLC (POPLAR, BIRCH, FIR). Therefore, the data from the popPK analysis Report 106693 can be extrapolated to patients with UC and NSCLC. There were no studies exploring the PK of atezolizumab in healthy subjects. All PK data were based on studies in patients with cancer.
- Atezolizumab is a genetically engineered, humanised, monoclonal antibody that binds to PD-L1 and blocks interactions with both PD-1 and B7.1 receptors. It is a non-glycosylated IgG1 kappa immunoglobulin that has a calculated molecular mass of approximately 144 kDa. It is composed of two light chains consisting of 214 amino acid residues and two heavy chains consisting of 448 amino acid residues.
- The popPK analysis established that a linear two-compartment disposition model with first-order elimination adequately described atezolizumab concentration-time data following administration of 1 to 20 mg/kg of atezolizumab q3w, or the 1200 mg fixed-dose q3w (Report 106693).
- In patients with advanced malignancies, atezolizumab demonstrated linear PK over the dose range 1-20 mg/kg based on dose normalised C_{max} , C_{min} , and AUC_{0-21} (PCD4989g). The popPK model estimated geometric mean accumulation ratios for C_{min} , C_{max} , and AUC were 2.75, 1.46, and 1.91-fold, respectively, following multiple dose administration of atezolizumab q3w (Report 106693). Based on simulations, the popPK model estimates that 90% of steady-state is reached after 2 to 3 cycles of repeated q3w dosing (that is, 6 to 9 weeks).
- Based on popPK modelling for atezolizumab for a typical patient, the V_{ss} is 6.91 L, the CL is 0.2 L/day, and the $t_{1/2}$ is 27 days (Report 106693). The volume of distribution is small and less than the volume of total body water of approximately 42 L.

- In the final popPK model (Report 106693), body weight, albumin, tumour burden, and ATA were statistically significant covariates for CL, body weight and albumin were statistically significant covariates for V1, and gender was a statistically significant covariate for both V1 and V2. However, the effects of these covariates on the PK of atezolizumab are considered to be clinically insignificant and no dose adjustments based on the covariates are required. The results from the popPK analysis suggest the unexplained inter-individual (IIV) is moderate for CL (that is, 29%), V1 (that is, 18%), and V2 (that is, 34%). There were no data relating to intra-subject PK variability.
- There were no data on the metabolism of atezolizumab. However, as the drug is a monoclonal antibody (IgG) it can be reasonably inferred that it will undergo catabolism via proteolytic degradation in a similar manner to endogenous IgG. Atezolizumab is unlikely to be a substrate for CYP450 enzymes. There were no data on renal elimination. However, as the molecular weight of atezolizumab is large (approximately 144 kDa) it can be predicted that it will not undergo renal clearance. There were no mass balance studies, but such studies are considered to be not necessary for therapeutic proteins.
- The C_{max} and C_{min} values in Cycle 1 following the proposed atezolizumab dose of 1200 mg q3w administered by IV infusion to patients with advanced malignant disease were consistent across the 5 Phase I/II clinical studies. In particular, the C_{max} and C_{min} values were consistent in the Phase II clinical studies in patients with UC (IMvigor 210) and NSCLC (POLAR, BIRCH, FIR).
- In the clinical studies, exposure parameters (C_{max} , C_{min}) were lower in patients who were positive for ATA compared to patients who were negative for ATA. However, in the Phase I study, patients who received ≥ 10 mg/kg atezolizumab (including fixed-dose 1200 mg) maintained geometric mean steady-state trough serum concentrations above the target level of 6 $\mu\text{g/mL}$, irrespective of ATA status (PCD4989g). Similarly, in the Phase II studies in patients with UC and NSCLC treated with 1200 mg q3w, steady-state trough serum concentrations were consistently above the target level of 6 $\mu\text{g/mg}$ in all patients, irrespective of ATA status. The popPK analysis (Report 1066935) predicted that CL would be 16% greater in ATA-positive patients compared to ATA-negative patients, but steady state exposure parameters would be no greater than 19% lower in a typical ATA-positive patient compared to a typical ATA-negative patient.
- There were no dedicated PK studies assessing the effects of age, renal impairment, hepatic impairment or gender on the PK of atezolizumab. However, the popPK *post-hoc* analyses indicates that there are no significant difference in atezolizumab CL normalised on other significant covariates based on age (< 65, 65 to 75, ≥ 75 years), renal impairment (normal renal function, mild, moderate, severe renal impairment) or hepatic impairment (normal hepatic function, mild hepatic impairment). There were no popPK data in patients with moderate or severe hepatic impairment, while popPK data in patients with severe renal impairment were limited ($n = 8$). Based on the popPK analysis, no atezolizumab dose adjustment appears to be indicated based on age, gender, mild or moderate renal impairment, or mild hepatic impairment.
- In summary, the popPK analysis showed that age, body weight, gender, positive ATA status, serum albumin levels, tumour burden, region or race, mild, moderate or severe renal impairment, mild hepatic impairment, level of PD-L1 expression on ICs and TCs, or ECOG status had no clinically significant effects on the PK of atezolizumab.
- There were no data assessing drug-drug interactions (DDIs) involving atezolizumab. In general, PK DDIs between therapeutic monoclonal antibodies and conventional small-molecule drugs are not expected, since these drugs are primarily eliminated by

catabolism. In addition, monoclonal antibodies are unlikely to be substrates for CYP450 enzymes or protein transporter systems that can be modified by small-molecule drugs.

Pharmacodynamics

Studies providing pharmacodynamic data

The submission included the following studies with pharmacodynamic information.

Exposure-Efficacy Relationships

- UC (IMvigor 210): Exposure-efficacy analyses were conducted with data from patients with urothelial carcinoma enrolled in IMvigor 210. The objectives of these analyses were: (1) to explore exposure-response (ER) relationships with objective response rate (ORR) as assessed by an independent review facility (IRF) using RECIST v1.1 following atezolizumab 1200 mg q3w; and (2) to evaluate the need for dose adjustment in patient subgroups.
- NSCLC: Exposure-efficacy analyses were conducted with data from patients with NSCLC enrolled in BIRCH and POPLAR. The objectives of these analyses were: (1) to explore ER relationships with ORR as assessed by an IRF (BIRCH) and investigator (POPLAR) using RECIST v1.1 and OS (POPLAR) following atezolizumab 1200 mg q3w; and (2) to evaluate the need for dose adjustment in patient subgroups.

Exposure-Safety Relationships

- UC (IMvigor 210): Exposure-safety analyses were conducted with data from patients with urothelial carcinoma enrolled in IMvigor 210. The objectives of these analyses were: (1) to explore exposure-safety relationships for adverse events Grade 3 to 5 (AEG35) and adverse events of special interest (AESI) following atezolizumab 15 mg/kg and 1200 mg q3w; and (2) to evaluate the need for dose adjustment in patient subgroups.
- NSCLC (PCD4989g, BIRCH, POPLAR, FIR): Exposure-safety analyses were conducted with data from atezolizumab treated patients with NSCLC enrolled in Studies PCD4989g, BIRCH, POPLAR and FIR. The objectives of these analyses were: (1) to explore exposure-safety relationships for AEG35 and AESI following atezolizumab 15 mg/kg and 1200 mg q3w; and (2) to evaluate the need for dose adjustment in patient subgroups. An integrated exposure-safety analysis was performed in all atezolizumab-treated patients from the four Phase II studies (Report 1068603).

QTc Assessment

- No dedicated thorough QT/QTc study was undertaken. However, in *study PCD4989g* a concentration-QTc (C-QTc) analysis was conducted using triplicate ECGs collected from patients (n = 417) receiving atezolizumab 10, 15, 20 mg/kg, and 1200 mg, under controlled conditions during the dose expansion phase of the study, to construct a quantitative model describing the relationship between observed atezolizumab concentrations and the change from baseline QTc interval (Δ QTc).

Immunogenicity

- The immunogenicity of atezolizumab was investigated in six Phase I/II studies (PCD4989g, JO28944, IMvigor 210, BIRCH, POPLAR, and FIR).

Evaluator's conclusions on pharmacodynamics

- The exposure-efficacy (ORR) data showed no relationship in patients with UC, while in patients with NSCLC the data were inconsistent. Overall, it is considered that no firm conclusions can be made about the exposure-efficacy relationship in the submitted data. The key results for the assessment of the atezolizumab exposure-efficacy relationships were as follows: (a) in patients with UC (IMvigor 210), there was no statistically significant relationship between the probability of response and AUC, C_{max} and C_{min} in Cycle 1 and AUC_{ss}; (b) in patients with NSCLC (BIRCH), there was a statistically significant ($p = 0.0005$) positive relationship between the proportion of patients with a response (CR + PR) and the AUC_{ss}, but not with AUC, C_{max}, or C_{min} in Cycle 1; (c) in patients with NSCLC (BIRCH), the simulations of expected ORRs versus AUC_{ss} in patients from Cohorts 2 plus 3 were similar using fixed-dose 1200 mg and weight-based dose 15 mg/kg, supporting the proposed fixed-dose treatment regimen; (d) in patients with NSCLC (POPLAR), there were no statistically significant positive relationships between the proportion of responders (CR + PR) and AUC, C_{max} and C_{min} in Cycle 1 and AUC_{ss}; (e) in patients with NSCLC (POPLAR), OS probability increased with exposure based on AUC Cycle 1, C_{min} Cycle 1, and AUC_{ss}; $p < 0.001$ by Cox regression analysis; and (f) in patients with NSCLC (POPLAR), OS in patients treated with atezolizumab relative to OS in patients treated docetaxel improved with increasing exposure (AUC_{ss}) to atezolizumab.
- The exposure-safety (AEG35, AESI) response data suggested no clinically significant relationships for patients with UC and NSCLC. The key results for the assessment of the atezolizumab exposure-safety relationships were as follows: (a) in patients with UC (pooled analysis, Report 1067242), there were no statistically significant relationships between exposure (AUC, C_{max}, C_{min} in Cycle 1, and AUC_{ss}) and safety outcomes of AEG35 or AESI; (b) in patients with NSCLC (pooled analysis, Report 1068603), there were no statistically significant relationships between increasing exposure (AUC, C_{max}, C_{min} in Cycle 1, and AUC_{ss}) and the incidence of AEG35; (c) in patients with NSCLC (pooled analysis, Report 1068603), there was a statistically significant relationship between both C_{min} (Cycle 1) and AUC_{ss} and the incidence of AESI; and (d) in the patients with NSCLC (pooled analysis, Report 1068603), there were no statistically significant relationships between exposure (AUC, C_{max}, and C_{min} in Cycle 1, and AUC_{ss}) and the most commonly reported AESI occurring in ≥ 15 patients (that is, rash, AST increased, hypothyroidism, pneumonitis, ALT increased, maculo-papular rash).
- The atezolizumab C-QTc analysis in patients with advanced cancers from *study PCD4989g* suggests that clinically meaningful changes in the QTcF interval are unlikely at the proposed dose of atezolizumab (1200 mg q3w) in patients with UC or NSCLC (Report 1066934).
- The overall incidence of treatment-emergent ATAs was high in the six Phase I/II studies, with rates ranging from 16.7% to 54.5%. The popPK analysis determined that ATA-positive patients had an atezolizumab clearance that was approximately 16% higher than ATA-negative patients. This difference accounts for the trend observed across the studies for lower atezolizumab exposure metrics (C_{max}, C_{min}, AUC) in ATA-positive patients compared to ATA-negative patients. However, in all studies in which atezolizumab was administered at doses ≥ 10 mg/kg serum atezolizumab concentrations remained well above the target concentration of 6 $\mu\text{g/mL}$ irrespective of ATA-status. ATA-status had no clinically meaningful impact on efficacy based on ORR assessment in patients with UC or NSCLC. ATA status had no clinically meaningful impact on safety in patients with UC or NSCLC. However, the incidence of Grade 3-4 AEs and SAEs was higher in ATA-positive patients compared to ATA-negative patients in the total population treated with atezolizumab. In the all patients population, the

incidence of hypersensitivity and infusion related reactions (MedDRA AE PTs) was low and was similar for ATA-positive and ATA-negative patients.

- No conclusions can be drawn about the incidence of NAb in ATA-positive patients treated with atezolizumab, due to the high number of post-treatment ATA positive samples that were indeterminate in the NAb assay. The sponsor is requested to comment on the reasons for the large number of indeterminate results.

Dosage selection for the pivotal studies

Study PCD4989g (Phase I) was the first-in-human study. The primary objectives of this study were to: (1) evaluate the safety and tolerability of atezolizumab administered by IV infusion q3w to patients with locally advanced or metastatic solid tumours or haematological malignancies; (2) determine the maximum tolerated dose (MTD) and to evaluate the dose-limiting toxicities (DLTs) of atezolizumab when administered as a single agent to patients by IV infusion q3w; and (3) identify a recommended Phase II dose of atezolizumab.

The clinical starting dose and the associated safety factor for Study PCD4989g were based on the results from the 8-week toxicology study in cynomolgus monkeys, which supported a no observed adverse effect level (NOAEL) of 5 mg/kg (Study 08-1148). Based on a NOAEL of 5 mg/kg and an estimated human CL value of 1.98 mL/day/kg projected from the cynomolgus monkey data, the exposure (AUC) based safety factor was 268-fold. The single-dose, body weight-normalised, dose-based safety factor calculated on body surface (BSA) at the proposed Phase I starting dose of 0.01 mg/kg was 500-fold.

The escalating dose levels of atezolizumab in the Phase I formulation tested in Study PCD4989g included 0.01, 0.03, 0.1, 0.3, 1, 3, 10, and 20 mg/kg administered by IV infusion q3w (21 ± 2 days). Additional intermediate dose levels and/or different schedules of atezolizumab could be tested on the basis of new nonclinical efficacy, clinical safety, and clinical pharmacokinetic data available at the time, and after discussion with the investigators.

The atezolizumab target trough concentration (C_{trough}) was projected to be 6 µg/mL based on several assumptions, including a tumour-interstitial concentration to plasma ratio of 0.30 derived from tissue distribution data in tumour bearing mice, target-receptor tumour occupancy data indicating that 95% tumour-receptor saturation is needed for efficacy, and the observed atezolizumab interim PK results in humans from the dose escalation phase of Study PCD4989g.

In Study PCD4989g, no DLTs were observed at any levels during the dose escalation phase and no MTD was established. PK data from Study PCD4989g suggested that, while a subset of ATA-positive patients receiving 0.3 to 3 mg/kg atezolizumab q3w experienced a reduction of C_{min} to below limit of quantification (LOQ), patients receiving 10 to 20 mg/kg atezolizumab maintained geometric mean C_{min} levels that was in excess of both the LOQ of 0.06 µg/mL and the target serum concentration of 6 µg/mL. These data suggested that the 15 mg/kg atezolizumab q3w regimen (or fixed-dose equivalent of 1200 mg q3w) would be sufficient to maintain C_{min} levels at or above the target level of 6 µg/mL, irrespective of ATA-status.

The 15 mg/kg atezolizumab q3w regimen (or fixed-dose equivalent) was 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). Subsequent PK simulations using a preliminary popPK model based on PK data obtained in Study PCD4989g did not suggest any clinically meaningful differences in exposure following fixed-dose or weight-based regimens. On the basis of this initial preliminary

analysis, a fixed-dose regimen of 1200 mg q3w (equivalent to an average body weight-based dose of 15 mg/kg) was selected for the Phase II and III studies, the Phase II study in patients with UC.

The rationale for the dose selection in the pivotal and supportive Phase II studies is acceptable.

Efficacy

Studies providing efficacy data

UC

The evaluable data provided to support the application to register atezolizumab for the treatment of UC were:

- **IMvigor 210 study (nominated by the sponsor as a pivotal study):** This was a Phase II, global, multicentre, single-arm study designed to evaluate the efficacy and safety of atezolizumab in patients with locally advanced or metastatic UC. A total of 438 patients were enrolled into two separate cohorts (Cohort 1 (n = 122) and Cohort 2 (n = 316)). Cohort 1 (n = 118 treated patients) included 1L atezolizumab-treated patients with locally advanced or metastatic UC who were treatment naïve for inoperable locally advanced or metastatic or recurrent UC and cisplatin-ineligible (1L cis-ineligible UC population). For patients in Cohort 1 who had received prior adjuvant/neoadjuvant chemotherapy for UC, a treatment-free interval of greater than 12 months between the last treatment administration and the date of recurrence was required in order to be considered treatment-naïve in the metastatic setting. Prior local intravesical chemotherapy or immunotherapy was allowed if completed at least 4 weeks prior to initiation of study treatment. Cohort 2 (n = 311 treated patients) included 2L+ atezolizumab-treated patients with locally advanced or metastatic UC who had progressed on prior platinum-containing chemotherapy regimens in the metastatic setting or who had progressed within 12 months of treatment with a platinum-containing adjuvant/neoadjuvant regimen (2L+ UC population). The efficacy data from Cohort 2, involving patients who received second line or beyond treatment with atezolizumab are considered to be the population directly relevant to the proposed indication. The results for Cohort 2 from *IMvigor 210* have recently been published in the *Lancet*.²³
- **Study PCD4989g UC Cohort (nominated by the sponsor as a supportive study):** This was a Phase Ia, multicentre, first-in-human, open-label, dose-escalation study of the safety and PK of atezolizumab administered IV as a single agent to patients with locally advanced or metastatic solid tumors or haematological malignancies, including 93 patients with UC (2L+ UC cohort) who were OR-evaluable with at least a 24-week follow-up as of the 7 August 2015 clinical cutoff date. Efficacy was a secondary objective of this study.
- **Pooled efficacy data by PD-L1 IC status** including patients with UC (n = 378) administered atezolizumab as second line or beyond treatment (2L+ UC patients) from Study PCD4989g UC Cohort (clinical cut-off of 2 December 2014) and *IMvigor 210* Cohort 2 (primary analysis clinical cut-off of 5 May 2015). No pooled analyses were performed for 1L cisplatin-ineligible UC patients since study *IMvigor 210* was the only study with atezolizumab in this patient population.

²³ Rosenberg JE, Hofmann-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy; a single-arm, multicentre, Phase II-trial. *Lancet* 2016; 387: 1909-20.

NSCLC

Efficacy data supporting the submission to register atezolizumab for the treatment of NSCLC are derived from two studies nominated by the sponsor as being pivotal (BIRCH and POPLAR) and two studies nominated by the sponsor as being supportive (FIR and PCD4989g). Most of the patients in these studies with locally advanced or metastatic NSCLC were treated with atezolizumab in the second-line or beyond setting (that is, 2L+) and had varying levels of PD-L1 expression on both tumour cells (TCs) and tumour-infiltrating immune cells (ICs). The four studies are outlined below.

- Study G028753 (POPLAR) was a randomised Phase II, global, multicentre, open-label clinical trial designed to compare the overall survival (OS) benefit of atezolizumab against standard of care chemotherapy (docetaxel) in patients with locally advanced or metastatic NSCLC who had progressed during or following a platinum-containing regimen regardless of their PD-L1 expression level. This study has been recently published in *Lancet*.²⁴
- Study G028754 (BIRCH) was a Phase II, global, multicentre, single-arm clinical trial of atezolizumab across multiples lines of therapy in patients with locally advanced or metastatic NSCLC who were selected by PD-L1 status (TC2/3 or IC2/3), and who were evaluated according to pre-specified analyses compared to historical controls as measured by the objective response rate (ORR).
- Study G028625 (FIR) was a Phase II, global, multicentre, single-arm clinical study designed to evaluate the efficacy and safety of atezolizumab as a single agent in patients with locally advanced or metastatic NSCLC who had PD-L1 expression level of TC2/3 or IC2/3.
- Study PCD4989g is an ongoing Phase Ia, multicentre, first-in-human, open-label, dose-escalation clinical trial of the safety and PK of atezolizumab administered IV as a single agent to patients with locally advanced or metastatic solid tumours or haematologic malignancies, including NSCLC (PCD4989g NSCLC Cohort). The secondary objectives of this study included a preliminary assessment of the anti-tumour activity of atezolizumab and the exploratory objectives included an evaluation of overall survival (OS).

Evaluator's conclusions on efficacy

UC

The efficacy data for atezolizumab 1200 mg q3w for the treatment of locally advanced or metastatic UC after prior chemotherapy are derived from one Phase II study nominated by the sponsor as being pivotal (IMvigor 210 Cohort 2 (2L+ UC)) and one Phase I study in the UC Cohort (2L+ UC) nominated by the sponsor as being supportive (Study PCD4989g).

IMvigor 210 also included patients (Cohort 1) with locally advanced or metastatic UC who were treatment naive and ineligible for treatment with cisplatin who received first-line treatment with atezolizumab. However, the patients in Cohort 1 are unrepresentative of the proposed treatment group for the UC indication. Consequently, the data from this cohort have not been reviewed in this section.

The efficacy data from each study were provided separately and pooled efficacy data were submitted for selected endpoints (that is, ORR, BOR, and DOR in the IC0, IC1, and IC2/3 subgroups). The results for the pooled efficacy analysis were consistent with the separate efficacy analysis from IMvigor 210. This finding is not unexpected, given that the majority

²⁴ Fehrenbacher L et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, Phase II randomised controlled trial. *Lancet* 2016; 387: 1837-46.

of patients in the pooled efficacy population were derived from IMvigor 210 (that is, 82.3% (311/378) from IMvigor 210 Cohort 2 and 17.7% (67/378) from Study PCD4989g UC Cohort).

Both IMvigor 210 and Study PCD4989g were open-label and uncontrolled studies, with the primary efficacy endpoint being ORR. While both studies included PFS and OS data neither of these two endpoints was pre-specified as a primary efficacy endpoint, which is considered to be inconsistent with the TGA adopted EMA guidelines relating to the evaluation of medicines for the treatment of cancer (CHMP/EWP/205/95/Rev.4/Corr).

The sponsor compared the ORR outcome in the IMvigor 201 Cohort 2 with a historical response rate of 10% derived from published literature relating to second-line systemic treatments for patients with advanced transitional-cell carcinoma of the urothelium. However, this comparison is considered to be supportive rather than confirmatory, due to the biases associated with cross-study comparisons.

There were no data comparing atezolizumab with vinflunine, which is approved in Australia for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of prior platinum therapy. The absence of comparative efficacy data from a controlled treatment arm is a significant deficiency in the submission and is considered to preclude adequate assessment of the efficacy of atezolizumab for the proposed UC indication.

IMvigor 210 Cohort 2 primary efficacy analysis

Efficacy data for IMvigor 210 Cohort 2 were provided for three cut-off dates, which were 5 May 2015 (primary analysis), 14 September 2015 (updated analysis) and 27 November 2015 (supplementary analysis).

The efficacy results for Cohort 2 at the data cut-off date of 5 May 2015 were the protocol-defined primary analysis for this cohort. The data at this cut-off date allowed for at least 24 weeks of follow-up for the last enrolled patient, and the median length of follow-up for the enrolled patients was 7.1 months. Tumour specimens from all enrolled patients were prospectively tested for PD-L1 expression by a central laboratory. The three pre-defined treatment populations of interest were the IC2/3 subgroup (PD-L1 staining of tumour-infiltrating immune cells $\geq 5\%$), the IC1/2/3 subgroup (PD-L1 staining of tumour-infiltrating immune cells $\geq 1\%$) and the all-comers group (irrespective of PD-L1 staining).

There were two co-primary efficacy endpoints comprising the ORR (IRF-assessed; RECIST v1.1.) and the ORR (INV-assessed; mRECIST). The pre-specified statistical analysis method for the efficacy endpoints was based on a hierarchical fixed-sequence testing procedure in which the first test in the hierarchy for Cohort 2 compared ORR (IRF-assessed; RECIST v1.1) in the IC2/3 subgroup with a historical control rate of 10%. Formal testing of subsequent comparisons in the hierarchy was dependent on statistical significance being demonstrated for the preceding test. The study met its co-primary endpoints in all pre-specified treatment groups (that is, IC2/3, IC1/2/3, all-comers), and demonstrated statistically significant ORRs by IRF-assessed RECIST v1.1 and by INV-assessed mRECIST compared to a historical control response rate of 10%. In general, ORRs assessed by INV per mRECIST were higher than ORRs assessed by IRF per RECIST v1.1, but the results of the two assessments were consistent. The following discussion of the results from Cohort 2 will focus on the primary and secondary efficacy endpoints determined by IRF per RECIST v1.1. The IRF assessment per RECIST v1.1 method is considered to be a more conservative assessment method than INV assessment per mRECIST or RECIST v1.1, and represents the general approach for regulatory assessment of medicines used to treat cancer.

In the IC2/3 subgroup (n = 100), the ORR (IRF-assessed; RECIST v1.1) was 27.0%, which was statistically significantly greater than the 10% historical control response rate ($p <$

0.0001). In the IC1/2/3 subgroup (n = 208), the ORR (IRF-assessed; RECIST v1.1) was 18.3%, which was statistically significantly greater than the 10% historical control response rate (p<0.0004). In the all-comers group (n = 311), the ORR (IRF-assessed; RECIST v1.1) was 15.1%, which was statistically significantly greater than the 10% historical control response rate (p < 0.0058).

Two exploratory subgroups of particular interest included the IC0 subgroup (no discernible PD-L1 staining or < 1% PD-LI staining) and the IC1 subgroup (PD-LI staining \geq 1% to < 5%). The ORR (IRF-assessed; RECIST v1.1) was 8.7% in the IC0 subgroup (n = 103) and 10.2% in the IC1 (n = 108) subgroup. The ORRs in the IC0 and IC1 subgroups were not notably different from the 10% historical control response rate. Based on the multivariate logistic regression model, the odds ratio of having a confirmed response by IRF per RECIST V1.1 was 3.98 (95% CI: 1.72, 9.17) for the IC2/3 group compared to the IC0 group, and 1.21 (95% CI: 0.47, 3.10) for the IC1 group compared to IC0 group, when Bellmunt risk score is controlled. The logistic regression results for the IC0, IC1, and IC1/2/3 subgroups were consistent with the results for the ORR subgroup analyses. The results demonstrate that the ORR increases with increasing PD-L1 expression on ICs.

The 10% historical control response rate was based on published literature relating to second-line systemic treatments for patients with advanced transitional-cell carcinoma of the urothelium. In the relevant publication,²⁵ the authors comment that:

many chemotherapy drugs and target agents show poor or no activity in Phase II trials in the second-line setting, and few yield modest responses rates of 10-20%, median [PFS] of 2-3 months; and median [OS] 6-9 months.

In relation to the results for vinflunine, although the ITT analysis in the key registration study did not show a significant overall survival advantage compared to best supportive care (6.9 months (vinflunine) versus 4.6 months (BSC); HR = 0.88 (95% CI: 0.69, 1.12)), there was a significant improvement in the ORR (8.6% (vinflunine) versus 0% (BSC), Δ =8.6% 95% CI: 5.0, 13.7)) and median PFS (3.0 months (vinflunine) versus 1.5 months (BSC), p = 0.0012). Overall, it is considered that the historical control response rate of 10% (which is the lower boundary of the modest 10% to 20% response range suggested by the literature) is of limited utility for regulatory purposes. In the regulatory context, the comparisons between the ORRs for atezolizumab and the historical control response rate are considered to be supportive rather than confirmatory and cannot replace comparison between atezolizumab and a randomised controlled treatment arm.

The key secondary efficacy endpoints at the data cut-off of 5 May 2015 are considered to be DOR, PFS, and OS. The median DOR (IRF-assessed; RECIST v1.1) in the OR response evaluable population had not been reached in the IC2/3 or IC1/2/3 subgroups or in the all-comers group. The proportion of responders who were still in response at the cut-off date was 85.2% (n = 23), 89.5% (n = 34) and 91.5% (n = 43) in the IC2/3, IC1/2/3 and all-comers treatment groups, respectively. The median PFS (IRF-assessed; RECIST v1.1) in the ITT population had not been reached in the IC2/3 or IC1/2/3 subgroups or in the all-comers group. The median OS (IRF-assessed; RECIST v1.1) in the ITT population had not been reached in the IC2/3 or IC1/2/3 subgroups or in the all-comers group. The OS data were too immature to calculate the land-mark 1-year survival rate.

In the subgroup analyses, the majority showed ORRs \geq 10%, based on IRF-assessment per RECIST v1.1. In particular, the ORR was \geq 10% in patients aged < 65 years and \geq 65 years; male patients (but not female patients); patients with ECOG PS 0 (but not patients with ECOG PS 1); patients with primary bladder tumour (but not patients with primary sites in

²⁵ Sonpavde G, Sternberg CN, Rosenberg JE, et al. Second-line systemic therapy and emerging drugs for metastatic transitional cell carcinoma of the urothelium. *Lancet Oncol* 2010; 11: 861-70.

the renal pelvis, ureter, or urethra); patients with no liver metastases (but not patients with liver metastases); patients with no visceral metastases (but not patients with visceral metastases); patients with haemoglobin ≥ 10 g/dL (but not patients with haemoglobin < 10 g/dL); patients with baseline creatinine clearance < 60 mL/min and ≥ 60 mL/min; patients with Bellmunt risk factors 0 and 1 (but not patients with Bellmunt risk factors 2 or 3); patients with initial transitional cell carcinoma (but not patients with initial transitional cell carcinoma with mixed histology); patients with prior systemic treatment, prior carboplatin based regimens, or ≤ 3 prior systemic regimens in the metastatic setting (but not patients with ≥ 4 regimens); patients with prior systemic regimen settings including adjuvant or neoadjuvant with first PD beyond or within 12 months and patients in the metastatic setting; patients with ≤ 3 lines of prior therapy (but not patients with ≥ 4 lines of prior therapy); patients with > 3 months and with ≤ 3 months from prior chemotherapy; patients with no prior BCG therapy (but not patients with prior BCG therapy); and patients with diagnosis based on resection or TURBT (but not patients with diagnosis based on biopsy).

IMvigor 210 – updated and supplementary efficacy analyses

The updated efficacy data for *IMvigor 210* Cohort 2 at the cut-off of 14 September 2015 (median duration of follow-up of 11.7 months), was consistent with primary analysis of the efficacy data at the earlier cut-off of 5 May 2015, based on a median duration of follow-up of 7.1 months.

The supplementary report provided efficacy data for *IMvigor* Cohort 2 at the cut-off of 27 November 2015, with a minimum follow-up of 1 year for the last enrolled patient and a median duration of follow-up of 14.4 months for all enrolled patients. The ORR (IRF-assessed; RECIST v1.1) was 26.0% (26/100), 18.4% (38/207) and 14.8% (46/310) in the IC2/3, IC1/2/3 and all-comers populations, respectively. The ORR results were notably greater than the historical control response rate of 10% for the IC2/3 and the IC1/2/3 subgroups. However, it appears that the results for the IC1/2/3 subgroup were primarily driven by the results for the IC2/3 subgroup.

The median DOR (IRF-assessed; RECIST v1.1) at the data cut-off of 27 November 2015 had not yet been reached for the IC2/3, IC1/2/3 and all-comers populations. The proportions of patients who were on-going responders were 84.6% (22/26), 86.8% (33/38) and 80.4% (37/46) in the IC2/3, IC1/2/3 and all-comers populations, respectively. The estimated land-mark 1 year DOR (IRF-assessed; RECIST v1.1) event-free rates were 84.6%, 86.2%, and 81.7% for the IC2/3, IC1/2/3 and all-comers populations, respectively. The percentage of responders remaining on treatment was 76.9% (20/26), 76.3% (29/38) and 76.1% (35/46) in the IC2/3, IC1/2/3 and all-comers populations, respectively.

The median OS in the ITT population was 11.9, 9.0 and 7.9 months in the IC2/3 (n=100), IC1/2/3 (n = 207), and all-comers (n = 310) populations, respectively. The estimated rates for the land-mark 1 year survival analysis were 49.9%, 40.2% and 36.9% in the IC2/3, IC1/2/3 and all-comers populations, respectively. The OS survival results in the ITT population were notably superior in the IC2/3 subgroup compared to the IC1/2/3 subgroup, suggesting a positive relationship between PD-L1 expression and survival.

The sponsor commented (covering letter) that the survival outcomes conferred by atezolizumab in the updated analysis (data cut-off of 27 November 2015) are “clinically meaningful” when compared to published data for vinflunine (median OS of 6.9 months), docetaxel (median OS of 7.0 months) and pemetrexed (median OS of 6.7 months). However, it is considered that meaningful clinical interpretation of the OS data from *IMvigor 210* Cohort 2 is limited due to the absence of a control arm. Comparing overall survival data across studies should be interpreted cautiously due to the likelihood of bias. It is considered that, for regulatory purposes, the descriptive cross-study comparisons of

OS referred to by the sponsor should be considered to be supportive rather than confirmatory.

The sponsor also commented (covering letter) that atezolizumab provided sustained and durable responses, which were observed across all IC subgroups and represent clinical benefit compared to vinflunine with a median DOR of 7.4 months (range 4.5 to 17.0 months), docetaxel with a reported median DOR of 4 months (range 3.0 to 8.0 months) and pemetrexed with a median DOR of 8 months (range 6.0 to 18.0 months). As noted above, the median DOR (IRF-assessed; RECIST v1.1) at the data cut-off date of 27 November 2015 had not yet been reached for the IC2/3, IC1/2/3 and all-comers populations, with a median duration of follow-up of 14.4 months. Comparing median DOR across studies should be interpreted cautiously due to the likelihood of bias. It is considered that, for regulatory purposes, the descriptive cross-study comparisons of median DOR referred to by the sponsor should be considered to be supportive rather than confirmatory.

Study PCD4989g UC Cohort (2L+ UC)

In the supportive study (PCD4989g UC cohort), the confirmed ORR (IRF-assessed; RECIST v1.1) in the primary analysis at the cut-off of 2 December 2014 was 36.8% (7/19), 18.8% (11/48), 23.3% (7/30), and 11.1% (2/18) in the IC2/3, IC0/1, IC1, and IC0 subgroups respectively. The primary analysis included 87 OR evaluable patients with poor prognostic factors and a minimum of 12 weeks of follow-up.

The submission included a supplemental report for Study PCD4989g, which provided updated efficacy data for the OR-evaluable patients (n = 93) with a minimum of 24 weeks of follow-up. The updated data with a cut-off date of 7 August 2015 represents an additional 8 months of follow-up beyond the earlier cut-off date of 2 December 2014 for the primary analysis. The median duration of survival follow-up at the 7 August 2015 cut-off was 20.0 months.

At the 7 August 2015 cut-off date, 80.6% of the patients in the UC cohort (75/93) were no longer receiving atezolizumab, compared to 75.0% (69/92) of patients at the earlier cut-off date of 2 December 2014. The primary reason for discontinuation from treatment in the updated analysis was progression of disease (64.5% (60/93) at the 7 August 2015 cut-off compared to 53.3% (49/92) at the 2 December 2014 cut-off).

In the updated analysis at the 7 August 2015 cut-off, the ORRs (IRF-assessed; RECIST v1.1) were 33.3% (7/21), 20.8% (10/48), 26.7% (8/30) and 11.1% (2/18) for the IC2/3, IC0/1, IC1, and IC0 subgroups, respectively. The updated ORR results for these four subgroups were consistent with the ORR results in the primary analysis. In the updated analysis, the median DOR (IRF-assessed; RECIST v1.1) had not been yet been reached in the IC2/3 or IC0 subgroups and was 9.63 months in the IC1 subgroup. The numbers of responders without events at 7 August 2015 for the updated data were 5/7 (71.4%), 4/8 (50.0%), and 2/2 (100%) in the IC2/3, IC1, and IC0 subgroups, respectively. Supplementary DOR data for the IC0/1 subgroup were not provided.

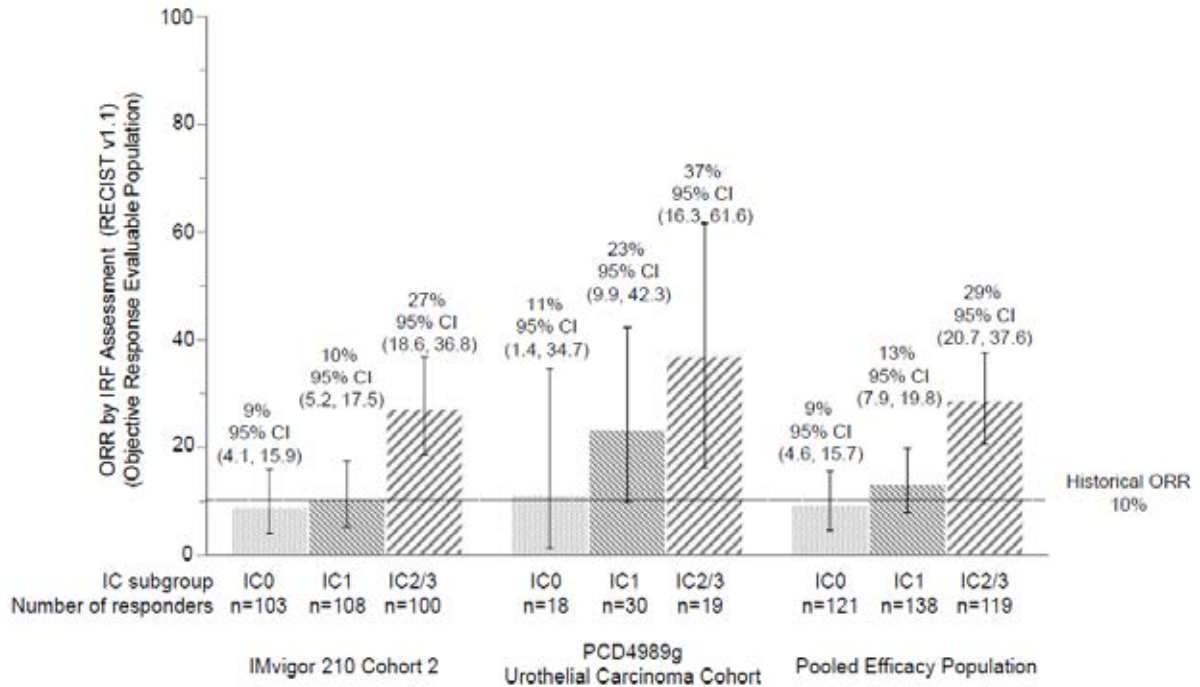
Overall, it is considered that the Phase I efficacy data from Study PCD4989g are exploratory for atezolizumab for the treatment of UC.

ORR comparison between IMvigor 210 and PCD4989g

The results for the ORR (primary analyses) assessed by the IRF per RECIST v1.1 for the OR-evaluable population in IMvigor 210 Cohort 2, Study PCD4989g UC Cohort and the pooled population for the IC0, IC1 and IC2/3 subgroups are summarised below. The IRF-assessed ORR per RECIST v1.1 was one of the co-primary endpoints in IMvigor 210 Cohort 2 and a co-primary efficacy endpoint in Study PCD4989g UC Cohort. Of particular note is the higher ORR in PCD4989g compared to IMvigor 210 in each of the IC subgroups. This is an unexpected finding as it could be predicted that the generally more heavily pre-treated

patients with more advanced disease in Study PCD4989g would be less likely to respond to treatment than the generally less heavily pre-treated patients with less advanced disease in IMvigor 210. The sponsor is requested to comment on this finding.

Figure 1: Objective response rate by IER-assessment per RECIST v1.1, OR-evaluable population.



NSCLC

The submission included four studies nominated by the sponsor as supporting the application to register atezolizumab for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy. The sponsor nominated two studies as pivotal (POPLAR (Phase II) and BIRCH (Phase II)) and two studies as supportive (FIR (Phase II) and PCD4989g (Phase I)). The patient population in the submitted studies are considered to be representative of an Australian population with locally advanced or metastatic NSCLC with prior treatment.

Overall, it is considered that data from the four submitted studies provide promising evidence supporting the efficacy of atezolizumab for the proposed indication in patients with NSCLC. However, the major limitation of the submitted efficacy data relates to the absence of a confirmatory Phase III study establishing that atezolizumab can meaningfully increase OS and/or PFS or reduce tumour burden in the proposed NSCLC patient population. Therefore, it is considered that the submission does not meet the TGA adopted EMA clinical guidelines relating to the evaluation of anticancer medications (EMA/CHMP/205/95/Rev.4).²⁶ While compliance with the guidelines is not mandatory, it is considered that the requirement in the guidelines relating to the need for a confirmatory Phase III study should not be waived, based on the limitations of the submitted Phase I/II efficacy data.

There is currently an ongoing Phase III study open-label study (OAK) comparing atezolizumab to docetaxel in 2L and 3L patients with OS as the primary endpoints. The primary analysis of this study was recently reported at the European Society for Medical Oncology (ESMO) Congress in October 2016, and the efficacy data from the study have been included in the recently updated US label for atezolizumab. The sponsor is requested

²⁶ Guideline on the evaluation of anticancer medicinal products in man.

to provide the available efficacy and safety data to the TGA for evaluation as part of its s31 Response to the first round clinical evaluation report. The efficacy data from this Phase III study might address the limitations of the submitted efficacy data from the Phase I/II studies relating to patients with the proposed NSCLC indication treated with atezolizumab in the 2L+ setting.

POPLAR

POPLAR was nominated by the sponsor as the pivotal study supporting the registration of atezolizumab for the treatment of NSCLC. It is considered that, while this relatively small Phase II study can be considered to be a pivotal study, the efficacy results from the study require confirmation by a larger pivotal Phase III study (for example, OAK).

The pivotal Phase II study (POPLAR) included open-label, efficacy data comparing atezolizumab (1200 mg q3w IV) with docetaxel (75 mg/m² q3w) until disease progression or unacceptable toxicity in PD-L1 selected patients with locally advanced or metastatic NSCLC who had progressed during or following a platinum-containing regimen. Patients were stratified on the basis of PD-L1 expression (IC0, IC1, IC2, and IC3), prior chemotherapy regimens (1 versus 2) and tumour histology (squamous versus non-squamous) and then randomised 1:1 to either atezolizumab or docetaxel. Efficacy was assessed in the total ITT population, which included all patients irrespective of PD-L1 expression, and in subgroups based on PD-L1 expression (TCs and ICs).

OS in the ITT (all-comers) population was the primary efficacy endpoint. The submitted data included a primary analysis undertaken when 173 deaths had occurred (that is, 60% event/patient ratio) at the clinical cut-off date of 8 May 2015 and an updated analysis undertaken when 200 deaths had occurred (that is, 70% event/patient ratio) at the clinical cut-off date of 1 December 2015. The key secondary efficacy endpoints were PFS, ORR, and DOR in the ITT population (INV-assessed; RECIST v1.1). At the time of the clinical cut-off date for the primary analysis, the median duration of follow-up was approximately 15 months in both treatment arms.

There was a clinically meaningful and statistically significant improvement in OS of 2.9 months observed in the primary analysis for patients in the ITT population in the atezolizumab arm (n = 143) compared to the docetaxel arm (n = 144): median OS 12.6 versus 9.7 months, respectively; stratified HR = 0.73 (95% CI: 0.53, 0.99), p = 0.0404, stratified log-rank test. The number of deaths was 78 (54.2%) in the atezolizumab arm and 95 (66.4%) in the docetaxel arm.

In the updated post-hoc OS analysis, which provided an additional 7 months of follow-up, the median duration of OS in the ITT population remained 2.9 months longer in the atezolizumab arm (n = 144) compared to the docetaxel arm (n = 143): median OS 12.6 versus 9.7 months, respectively; stratified HR = 0.69 (95% CI: 0.52, 0.92), p = 0.0106 (provided for descriptive purposes).

The median duration of PFS (INV-assessed; RECIST v1.1) in the ITT population was similar in both treatment arms, with the majority of patients in both arms experiencing an event. In the atezolizumab and docetaxel arms, the median duration of PFS was 2.7 and 3.0 months, respectively (stratified HR = 0.94 (0.72, 1.23)), and the proportion of patients with an event (death or PD) was 86.1% (124/144) and 84.6% (121/143), respectively.

The ORR (INV-assessed; RECIST v1.1) in the ITT population was modest and numerically similar in both treatment arms, being 14.6% (21/144) in the atezolizumab arm and 14.7% (21/143) in the docetaxel arm. The median DOR (INV-assessed; RECIST v1.1) was notably longer in the atezolizumab arm than in the docetaxel arm (14.3 versus 7.2 months, respectively), with a stratified HR of 0.41 (95% CI: 0.18, 0.96). The median DOR (INV-assessed; RECIST v1.1) in the updated analysis continued to favour atezolizumab

compared to docetaxel (18.6 versus 7.2 months, respectively), and showed an increase in the median DOR in the atezolizumab arm of 4.3 months compared to the primary analysis.

Efficacy was also assessed in POPLAR in PD-L1 TC and IC subgroups. The total patient numbers in the TC/IC subgroups were 47 in the *TC3 or IC3 subgroup*, 105 in the *TC2/3 or IC2/3 subgroup*, 195 in the *TC1/2/3 or IC1/2/3 subgroup*, and 92 in the *TC0 and IC0 subgroup*. Patient numbers for the atezolizumab and docetaxel arms were well balanced in each of the subgroups.

PD-L1 expression subgroup analysis showed a consistent OS benefit in favour of atezolizumab compared to docetaxel for patients with PD-L1 expression on TCs and ICs of $\geq 1\%$ (that is, *TC3 or IC3, TC2/3 or IC2/3, or TC1/2/3 or IC1/2/3 subgroups*), while no difference in OS between the two treatment arms was observed in patients with PD-L1 expression on TCs and ICs of $< 1\%$ (that is, *TC0 and IC0 subgroup*). The results for the PD-L1 expression subgroup analyses on PFS (INV-assessed; RECIST v.1.1) and ORR (INV-assessed; RECIST v1.1) were consistent with the results for the OS analysis. The results for OS, PFS and ORR showed that higher levels of PD-L1 expression on TCs or ICs increased the benefits in atezolizumab treated patients.

In a mutually exclusive subgroup analysis of OS (*TC2/3 or IC2/3 versus TC2/3 or IC2/3 excluding TC3 or IC3*), the exclusion of TC3 or IC3 marginally increased the HR from 0.54 to 0.59. In a mutually exclusive subgroup analysis of OS (*TC1/2/3 or IC1/2/3 versus TC1/2/3 or IC1/2/3 excluding TC2/3 or IC2/3*), the exclusion of TC2/3 or IC2/3 increased the HR from 0.59 to 0.65. The results suggest that each PD-L1 expression level contributes independently to OS in atezolizumab treated patients.

In the analysis of OS in the *TC1/2/3 and IC0 subgroup*, the median duration of survival was 11.2 months in the docetaxel arm and had not been reached in the atezolizumab arm (HR = 0.37 (95% CI: 0.12, 1.13)). In the analysis of OS in the *IC1/2/3 and TC0 subgroup*, the median duration of OS was 12.2 months in the docetaxel arm versus 15.6 months in the atezolizumab arm (HR = 0.63 (95% CI: 0.36, 1.12)). The analyses indicate that PD-L1 expression on both TCs and ICs independently contribute to increased OS in the atezolizumab arm compared to the docetaxel arm.

In general, the results of the subgroup analysis of OS in the ITT population based on baseline demographics and other characteristics were consistent with the primary analysis of OS. The median duration of OS was longer in the atezolizumab arm than in the docetaxel arm for both stratification factors relating to tumour histology (that is, non-squamous cell HR = 0.69 (95% CI: 0.47, 1.01); 15.5 versus 10.9 months) versus squamous cell HR = 0.80 (95% CI: 0.49, 1.30); 10.1 versus 8.6 months). The median duration of OS based on the stratification factor of number of prior therapies (1 versus 2) was longer in the atezolizumab arm than in the docetaxel arm for patients receiving 1 prior therapy (HR = 0.62 (0.42, 0.91); 16.4 versus 9.5 months), and similar in the two treatment arms for patients receiving 2 prior therapies (HR = 0.98 (95% CI: 0.60, 1.61); 9.8 versus 9.7 months).

Exploratory PRO data relating to global health status/quality of life, functioning, and lung cancer symptoms (cough, dyspnoea, chest pain, arm/shoulder pain) were assessed during the study by the EORTC QLQ-C30 and LC13. No clinically meaningful change (improvement or decline) from baseline was observed for patients in the atezolizumab arm during the study period in global health status, functioning (physical, role, emotional, cognitive, and social) or any of the symptom subscales, indicating that atezolizumab did not have a detrimental impact on health related quality of life (HRQoL). The PRO results for docetaxel were consistent with those for atezolizumab, apart from an increase in alopecia reported in the docetaxel arm. Time to deterioration (TTD) was defined as a ≥ 10 -point increase above baseline. There was no difference between the two arms in TTD of lung cancer symptoms (cough, dyspnea, chest pain, or arm/shoulder pain).

Overall, it is considered that POPLAR provides promising evidence for the efficacy of atezolizumab at the proposed dose for the proposed indication. The primary strengths of the study relate to the use of docetaxel as an active control and OS as the primary efficacy endpoint. The main limitations of the study relate to the modest improvement in overall survival in the atezolizumab arm compared to the docetaxel arm, the relatively small number of patients in both treatment arms, and the use of investigator assessed RECIST v1.1 rather than centrally (IRF) assessed RECIST v1.1 to determine best response.

BIRCH

BIRCH was nominated by the sponsor as a pivotal study supporting the registration of atezolizumab for the treatment of NSCLC. However, it is considered that this study is more appropriately considered to be supportive rather than pivotal for the following reasons. The study was a Phase II, single-arm study, with a primary efficacy endpoint of ORR (rather than OS or PFS) assessed using historical response rates which appear to be at the lower end of wide response spectrum. The absence of a randomised control arm limits the interpretation of the efficacy results.

BIRCH was a single-arm Phase II study assessing the efficacy of atezolizumab (1200 mg IV q3w) in patients with locally advanced or metastatic NSCLC based on PD-L1 expression on TCs and ICs. The study evaluated atezolizumab as first-line, second-line and third-line and beyond treatment.

The primary efficacy endpoint was ORR (IRF-assessed; RECIST v1.1) in seven pre-specified subgroups based on PD-L1 expression levels on TCs and ICs compared to historical response rates. The primary analysis was at the clinical cut-off date of 28 May 2015. The study met its primary objective of demonstrating a statistically significant and clinically meaningful improvement in ORR (IRF-assessed; RECIST v1.1) in the seven pre-specified subgroups compared to historical controls, following a hierarchical fixed-sequence testing procedure ($p < 0.0001$).

The ORRs (IRF-assessed; RECIST v1.1) ranged from 27.0% (31/115) in the TC3 or IC3 subgroup in Cohort 3 (3L+) to 17.3% (90/520) in the TC2/3 or IC2/3 subgroup in Cohorts 2+3 (2L+), with the respective historical control rates being 5% and 7%.

Cohorts 2+3 (2L+) were of key regulatory interest, as patients in these two pooled cohorts ($n = 520$) received atezolizumab as second line or beyond (2L+) treatment for locally advanced or metastatic NSCLC. In Cohorts 2+3 (2L+), higher PD-L1 expression levels (25% (60/237) in the TC3 or IC3 subgroup) was associated with higher ORR assessed by IRF per RECIST v1.1 compared to lower PD-L1 expression levels (17.3% (90/520) in the TC2/3 or IC2/3 subgroup).

The key secondary efficacy endpoints are considered to be OS, PFS (IRF-assessed; RECIST v1.1) and DOR (IRF-assessed; RECIST v1.1) in Cohorts 2+3 (2L+) in the TC3 or IC3 subgroup and the TC2/3 or IC2/3 subgroup. In Cohorts 2+3 (2L+) the key secondary efficacy endpoint results were:

- In the TC2/3 or IC2/3 subgroup, the median DOR was 8.4 months (95% CI: 6.9, NE), with 36.7% of responders (33/90) experiencing PD or death. In the TC3 or IC3 subgroup, the median DOR was 7.2 months (95% CI: 5.7, NE), with 38.3% of responders (23/60) experiencing PD or death.
- In the TC2/3 or IC2/3 subgroup, median PFS was 2.8 months (95% CI: 2.7, 2.9), with 77.1% (401/520) of patients experiencing PD or death. The 6-month and 12-month estimated PFS rates were 30.0% and 11.9%, respectively. In the TC3 or IC3 subgroup, median PFS was 4.1 months (95% CI: 2.8, 5.4), with 70.5% (167/237) of patients experiencing PD or death. The 6-month and 12-month estimated PFS rates were 36.7% and 16.8%, respectively.

- In the TC2/3 or IC2/3 subgroup, the data were too immature to satisfactorily characterise OS, with the median duration of survival not being reached. At the time of analysis, 36.0% (187/520) of patients in the TC2/3 or IC2/3 subgroup had died, and the 6-month and 12-month estimated OS rates were 73.4% and 55.3%, respectively. In the TC3 or IC3 subgroup, the data were also too immature to satisfactorily characterise OS, with the median duration of survival not being reached. At the time of analysis, 31.2% (74/237) of patients in the TC3 or IC3 subgroup had died, and the 6-month and 12-month estimated OS rates were 77.4% and 61.3%, respectively.
- Updated data at the clinical cut-off date of 1 October 2015 were provided for the ORR and DOR in patients in Cohorts 2+3 (2L+). The updated analysis data represented an additional 4 months of follow-up from the primary analysis data. The ORR (IRF-assessed; RECIST v1.1) was 27.4% in the TC3 or IC3 subgroup and 18.7% in the TC2/3 or IC2/3 subgroup. These updated results were consistent with the corresponding results at the clinical cut-off date of 28 May 2015. The median DOR (IRF-assessed; RECIST v1.1) was 9.8 months in the TC3 or IC3 subgroup and 11.3 months in the TC2/3 or IC2/3 subgroup, which were 2.6 and 2.9 months longer, respectively, than the corresponding results at the clinical cut-off date of 28 May 2015.
- Exploratory PRO data, based on EORTC QLQ-C30 and LC13, showed no evidence of negative effects of atezolizumab on health-related quality of life or functioning. There was no meaningful change from baseline in any of the domains of the EORTC QLQ-C30 and QLQ-LC13. Among treated patients (TC2/3 or IC2/3), the median time to meaningful deterioration of physical function (≥ 10 point decrease) in both Cohorts 2 and 3 occurred at 4.4 months, while the median PFS for both of these cohorts was 2.8 months.

FIR

FIR was a Phase II study nominated by the sponsor as a supporting study for the application to register atezolizumab for the treatment of NSCLC. It is agreed that this is a supporting study. In FIR, the key study cohort for regulatory purposes was Cohort 2 (2L+), which included patients with locally advanced or metastatic NSCLC with PD-L1 expression levels of TC2/3 or IC2/3 treated with atezolizumab as second-line and beyond therapy.

The primary efficacy endpoint for this study was investigator-assessed ORR per mRECIST in the efficacy-evaluable population. In Cohort 2 (2L+), the ORR (INV-assessed; mRECIST) was 17.2% (16/93) (95% CI: 10.17, 26.43) in the TC2/3 or IC2/3 subgroup, and 26.3% (10/38) (95% CI: 13.4, 43.1) in the TC3 or IC3 subgroup. The ORR results in the two subgroups INV-assessed per mRECIST were consistent with the ORR results INV-assessed per RECIST v1.1. No historical control response rates were defined for FIR, but the observed ORRs for both the TC2/3 or IC2/3 and TC3 or IC3 subgroups were greater than the historical control response rates provided in BIRCH. There were no response data in FIR assessed by an IRF using either RECIST v1.1 or mRECIST.

The key secondary efficacy endpoints in Cohort (2L+) are considered to be ORR (INV-assessed; RECIST v1.1), DOR (INV-assessed; RECIST v1.1), PFS (INV-assessed; RECIST v1.1), and OS. The results for the key efficacy endpoints in Cohort 2 (2L+) subgroups TC3 or IC3 and TC2/3 or IC2/3 are reviewed below:

- The ORR (INV-assessed; RECIST v1.1) was 16.1% (15/93) in the TC2/3 or IC2/3 subgroup and 23.7% (9/38) in the TC3 or IC3 subgroup. The results in both subgroups were consistent with the results for the ORR investigator-assessed per mRECIST.
- The DOR (INV-assessed; RECIST v1.1) data were immature at the clinical cut-off date, with the median DOR not being reached in either the TC2/3 or IC2/3 or the TC3 or IC3 subgroup.

- The median PFS (INV-assessed; RECIST v1.1) was 2.7 months in the TC2/3 or IC2/3 subgroup and 4.1 months in the TC3 or IC3 subgroup, with 74.2% (69/93) and 65.8% (25/38) experiencing an event (PD or death) in the two subgroups, respectively. In the TC2/3 or IC2/3 subgroup, the estimated 6-month and 12-month PFS rates were 32.3% and 21.5%, respectively. In the TC3 or IC3 subgroup, the estimated 6-month and 12-month PFS rates were 42.4% and 34.1%, respectively.
- The median duration of OS was 10.6 months (95% CI: 5.7, NE) in the TC2/3 or IC2/3 subgroup (46.2% (43/93) patients with an event), and had not been reached in the TC3 or IC3 subgroup. In the TC2/3 or IC2/3 subgroup, the estimated 6-month and 12-month OS rates were 58.6% and 48.3%, respectively. In the TC3 or IC3 subgroup, the estimated 6-month and 12-month OS rates were 63.0% and 60.0%, respectively.

Exploratory PRO data, based on EORTC QLQ-C30 and LC13, showed no evidence of negative effects of atezolizumab on health-related quality of life or functioning.

Overall, FIR is considered to provide supportive data for atezolizumab for the proposed indication. The limitations of the data include the absence of a control arm, the primary efficacy endpoint being ORR (INV-assessed; mRECIST) rather than OS or PFS, and no independent assessment of tumour response data based on RECIST criteria.

Study PCD4989g

Study PCD4989g was nominated by the sponsor as a supportive efficacy study. However, the study is considered to provide exploratory rather than supportive efficacy data for the following reasons. The study was a Phase I, first-in humans, dose-escalation study in patients with locally advanced or metastatic solid tumours or haematological malignancies, including a small cohort of heavily pretreated patients with NSCLC (n = 88) administered atezolizumab at doses of 1, 10, 15, and 20 mg/kg q3w, rather than the proposed fixed-dose 1200 mg q3w. The primary objectives of the study related to evaluation of safety and tolerability, determination of MTD and DLTs, and recommendation of Phase II dose rather than efficacy. The secondary objectives included a preliminary assessment of anti-tumour activity based on ORR, while evaluation of OS was only an exploratory objective.

Safety

Studies providing safety data

The submission included safety data on 1547 patients, including 521 (33.7%) patients with UC and 1026 (66.3%) patients with NSCLC. Each of the five submitted clinical studies included atezolizumab-treated patients with safety data.

- IMvigor 210, the sponsor-nominated pivotal Phase II study in patients with UC, included safety data at the time of the primary efficacy analysis (clinical cut-off date of 5 May 2015) for 429 atezolizumab-treated patients. These 429 patients included, primary efficacy safety data for 311 patients (Cohort 2) who failed a prior platinum-containing chemotherapy regimen or progressed within 12 months of a platinum-based treatment administered in the adjuvant/neo-adjuvant setting, and interim safety data for 118 patients (Cohort 1) who were cisplatin-ineligible patients. Updated safety data Cohort 1 were provided at the clinical cut-off date of 14 September 2015 (primary analysis for Cohort 1).
- BIRCH, a sponsor-nominated pivotal Phase II study in patients with NSCLC, included safety data for 659 atezolizumab-treated patients at the time of the primary efficacy analysis (clinical cut-off date of 28 May 2015).

- POPLAR, a sponsor-nominated pivotal Phase II study in patients with NSCLC, included safety data for 142 atezolizumab-treated patients and 135 docetaxel-treated at the time of the primary efficacy analysis (clinical cut-off date of 8 May 2015).
- FIR, a sponsor-nominated supporting Phase II study in patients with NSCLC, included safety data for 137 atezolizumab-treated patients at the time of the primary analysis (clinical cut-off date of 7 January 2015).
- PCD4989g, a sponsor-nominated supporting Phase I study for patients with UC and NSCLC, included safety data for 481 atezolizumab-treated patients with solid tumours or haematological malignancies, including 92 patients with UC and 88 patients with NSCLC at the clinical cut-off date of 2 December 2014.

Post-marketing data

Not applicable.

Evaluator's conclusions on safety

Safety data from the All Patients population, IMvigor Cohort 2 (UC) and POPLAR (NSCLC) have been evaluated. The only study providing comparative data for atezolizumab-treated patients (atezolizumab versus docetaxel) was POPLAR (NSCLC).

Conclusions relating to the safety data from the All Patients population for all atezolizumab-treated patients are provided below, while conclusions relating to the safety data for atezolizumab-treated patients from IMvigor 210 Cohort 2 (UC) and the comparative safety data for atezolizumab versus docetaxel from POPLAR (NSCLC) are presented in the *First Round assessment of risks* section.

Patient characteristics

The All Patients population included safety data on 1547 atezolizumab-treated patients, including 521 (33.7%) patients with UC (All UC population) and 1026 (66.3%) patients with NSCLC (All NSCLC population). Based on the 'rule of threes' it can be reasonably predicted that a population of 1547 atezolizumab treated patients is sufficient to detect adverse drug reactions associated with atezolizumab occurring with an incidence of at least 0.2%. The baseline demographic and disease characteristics of the UC and NSCLC safety populations are considered to be representative of patients in Australian clinical practice with locally advanced or metastatic UC or NSCLC disease.

The All UC population included 521 patients, comprising 118 patients in the IL cisplatin ineligible population (all comers) and 403 patients in the 2L+ (all-comers). In the All UC population (n = 521), the median age of the safety evaluable population was 67 years (range: 32, 92 years), with 64.5% (n = 326) being aged ≥ 65 years and 23.2% (n = 121) being aged ≥ 75 years. The majority of patients were male (77.9%, n = 406), and 'White' (88.9%, n = 463). The primary tumour site in the majority of patients was the bladder (73.1%, n = 381). The majority of patients had not received prior treatment with intravesical therapy of any kind (69.5%, n = 298) and in particular prior intravesical treatment with BCG (70.7%, n = 323). The histology of the tumour was predominantly transitional cell carcinoma (91.7%, n = 478). All patients had received prior chemotherapy, with 7.1% (n = 24) having received 1 line, 45.3% (n = 153) having received 2 lines and 47.6% (n = 161) having received ≥ 3 lines. The majority of patients had visceral metastases at baseline (75.4%, n = 393), while in contrast the majority of patients had no liver metastases at baseline (70.4%, n = 367).

In the All NSCLC population (n = 1026), the median age of the safety evaluable population was 64 years (range: 24, 88 years), with 48.1% (n = 494) being aged > 65 years and 14.9% (n = 153) being aged ≥ 75 years. The majority of patients were male (59.5%, n = 610), and

'White' (82.7%, n = 849). The majority of tumours were non-squamous cell (71.4%, n = 733). The majority of patients (81.9%, n = 840) had received prior chemotherapy, with similar proportions of patients having received 1 line (42.3%; n = 434) or ≥ 2 lines (39.6%, n = 406). The majority of patients had a history of previous tobacco used (70.9%, n = 727) and 12.0% (n = 123) of patients were current tobacco users. Overall, 892 of 1026 NSCLC patients (86.9%) had PD-L1 expression levels of TC2/3 or IC2/3 (BIRCH, POPLAR, FIR and NSCLC Cohort of PCD4989g), while 153 of 230 patients (66.5%) from POPLAR and the NSCLC Cohort of PCD4989g had PD-L1 expression levels of TC1/2/3 or IC1/2/3.

Exposure

The median duration of safety follow-up in the All Patients population (n = 1547) was 4.5 months (range: 0.5, 32.9 months). The majority of patients in the All Patients population received atezolizumab at a fixed-dose of 1200 mg q3w (88.8%; (1373/1547)), and the remaining 174 patients received atezolizumab at weight-based doses of 1-20 mg/kg q3w. The median duration of exposure to atezolizumab in the All Patients population was 3.5 months (range: 0, 19.4 months), with 45.7% (n = 625) of patients being exposed for ≤ 3 months, 18.6% (n = 256) for > 3 to 6 months, 31.0% (n = 425) for > 6 to 12 months, and 4.7% (n = 65) for >12 to 24 months. The median number of 21-day treatment cycles received by patients in the All Patients population was 6 (range: 1, 28). The median number of 21-day atezolizumab treatment cycles is relatively small as is the number of patients treated with atezolizumab for > 12 months.

The main limitation of the exposure data related to the small number of patients exposed to atezolizumab for > 12 months. The absence of long-term safety data is a deficiency in the submitted clinical dossier, given that the sponsor proposes that atezolizumab be administered for as long as it continues to demonstrate clinical benefit or until toxicity occurs. Adequate long-term safety data for atezolizumab is only likely to emerge during routine post-marketing surveillance.

In the All Patients population (n = 1547), 72.9% (n = 1128) of patients discontinued study treatment, with the most common reasons being disease progression (59.1%, n = 915) and AEs (4.8%, n = 75). In the All Patients population (n = 1547), at the time of data cut-off for each study contributing data, 47.5% (n = 735) of patients had withdrawn from the study, and this percentage was similar in the All UC and All NSCLC populations (48.0% and 47.3%, respectively). The most common reasons for study withdrawal were death (39.8%, n = 615), withdrawal by subject (3.0%, n = 47), lost-to-follow up (1.7%, n = 26) and progressive disease (1.2%, n = 18).

Commonly reported adverse events

AEs in atezolizumab-treated patients (irrespective of relationship to treatments) reported in $\geq 10\%$ of patients in the All Patients population (n = 1547), in decreasing order of frequency, were fatigue (35.9%), decreased appetite (24.2%), nausea (22.4%), dyspnoea (20.5%), cough (19.7%), diarrhoea (17.6%), pyrexia (17.1%), constipation (17.0%), vomiting (14.3%), back pain (13.0%), arthralgia (12.5%), anaemia (12.2%), pruritus (10.9%), and asthenia (10.3%). The majority of AEs were Grade 1 or 2 in maximum intensity (81.1%; (817/1008)).

AEs considered to be related to treatment with atezolizumab reported in $\geq 10\%$ of patients in the All Patients population (n = 1547), in decreasing order of frequency, were fatigue (21.4%), nausea (11.2%) and decreased appetite (10.2%). The majority of treatment-related AEs were Grade 1 or 2 in maximum intensity (79.9%; (266/333)).

Deaths

At the time of data cut-off dates for each study, a total of 615 (39.8%) patients had died in the All Patients population, comprising 207 (39.7%) patients in the All UC population and 408 (39.7%) patients in the All NSCLC population. The majority of deaths in the All

Patients population occurred > 30 days after the last dose of atezolizumab (73.7%, (453/615)), with similar results being observed for the All UC and All NSCLC populations (71.5%, (148/207) and 74.8%, (305/408), respectively). The most common reason for death in these patients was disease progression, which accounted for 82.4% (507/615) of all deaths in the All Patients population.

Overall, 54 deaths were attributed to AEs (42 of which occurred \leq 30 days after the last dose of atezolizumab or prior to initiation of non-protocol anti-cancer therapy). An additional 55 deaths were attributed to the cause of 'other'. Grade 5 AEs (that is, death attributed to AE) occurring \leq 30 days after the last dose of atezolizumab or prior to initiation of non-protocol therapy were reported in 42 (2.7%) patients in the All Patients population, comprising 8 (1.5%) patients from the All UC population and 34 (3.3%) patients from the All NSCLC population. The 42 Grade 5 AEs were reported in a variety of SOC and the PTs reported for more than 1 patient were pneumonia (5 patients), cardiac arrest (3 patients), sudden death (3 patients), respiratory failure (2 patients), and cardiac tamponade (2 patients). Of the 42 Grade 5 AEs, 5 were considered by the investigator to be treatment-related, including cardio-respiratory arrest (1 patient in PCD4989g, NSCLC cohort), constrictive pericarditis (1 patient in FIR, NSCLC), cardiac failure (1 patient in BIRCH, NSCLC), pneumonia (1 patient in BIRCH, NSCLC), and sepsis (1 patient in IMvigor 201, UC).

Grade 5 AEs occurring > 30 days after the last dose of atezolizumab or after initiation of non-protocol anti-cancer therapy were reported in 12 (0.8%) patients in the All Patients population, comprising 3 (0.8%) patients in the All UC population (1 each upper gastrointestinal haemorrhage, respiratory distress and death), and 9 patients in the All NSCLC population (3 x pneumonia, 1 each gastric perforation, large intestine perforation, respiratory failure, cardiac arrest, jugular vein thrombosis, and death). Of the 12 Grade 5 AEs, 1 was considered to be treatment-related (respiratory failure in 1 patient in the All NSCLC population with onset 52 days after last dose of atezolizumab).

Other serious adverse events

In the All Patients population (n = 1547), 39.2% (n = 606) of patients reported at least one SAE. SAEs in the All Patients population reported in \geq 1% of patients in decreasing order of frequency were pneumonia and dyspnoea (3.0% each), pyrexia (2.3%), urinary tract infection (1.8%), pneumonitis (1.4%), back pain and pulmonary embolism (1.2% each), and acute kidney injury, abdominal pain and dehydration (1% each). Treatment-related SAEs were reported in 9.4% (n = 146) of patients in the All Patients population, and the only treatment-related SAE reported in \geq 1% of patients was pneumonitis (1.0%).

Other significant adverse events

In the All Patients population (n = 1547), 5.4% (n = 85) of patients experienced an AE resulting in withdrawal of study treatment. AEs resulting in withdrawal reported in \geq 3 patients (\geq 0.2%) were pneumonia, pneumonitis, and dyspnoea (0.3% each), and sudden death and pneumonia aspiration (0.2% each).

In the All Patients population (n = 1547), 25.6% (n = 396) of patients experienced an AE resulting in dose interruption. AEs resulting in dose interruption reported in \geq 1% of patients were dyspnoea (2.0%), pneumonitis (1.7%), fatigue (1.6%), pneumonia (1.3%), and diarrhoea (1.0%).

Given that nearly all patients experienced at least one AE, the data indicate the majority of AEs were manageable by temporary dose interruption and/or symptomatic treatment rather than discontinuation from the study.

Adverse events of special interest (AESI)

AESIs included potential dermatologic, hepatic, endocrine, and respiratory events as well as events of elevated liver function tests and influenza-like illness. In the All Patients

population (n = 1547), AESIs were reported in 26.2% (n = 405) of patients. AESI (PTs) reported in $\geq 1\%$ of patients were rash (9.3%), AST increased (4.3%), ALT increase (4.0%), hypothyroidism (3.2%), pneumonitis (2.7%), peripheral neuropathy (2.4%), maculopapular rash (1.9%), blood bilirubin increased (1.1%), and pruritic rash (1.0%).

Adverse drug reactions (ADRs) associated with atezolizumab

After review of all AEs (including AESIs) in the atezolizumab clinical development program, the sponsor defined ADRs currently considered to be associated with atezolizumab using pre-specified medical review methodology based on the frequency of AEs, all grades and Grade 3 or 4. In the All Patients population (n = 1547), 82.2% (n = 1271) of patients were identified as having an ADR. ADRs identified in $\geq 10\%$ of patients were fatigue (35.9%), decreased appetite (24.2%), nausea (22.4%), dyspnoea (20.5%), diarrhoea (17.6%), pyrexia (17.1%), rash (16.4%), vomiting (14.3%), arthralgia (12.5%), pruritus (10.9%), asthenia (10.3%).

Important adverse drug reactions (ADRs) – immune-related ADRs

Of the summarised ADRs, the sponsor identified a subset of immune-related events of particular clinical relevance (termed important ADRs), which included pneumonitis, hepatitis, colitis, hypothyroidism, hyperthyroidism, adrenal insufficiency, meningitis (non-infectious), encephalitis (non-infectious), myasthenic syndrome, Guillain-Barré syndrome, diabetes mellitus and pancreatitis. The list of important ADRs were identified using Standard MedDRA Query (SMQs) High Level Terms (HLTs) and a sponsor-defined search basket, which were considered more inclusive and standardised than the AEGTs approach used for the AESI analysis.

In the All Patients population (n = 1547), 11.4% (n = 177) of patients experienced an important ADR, the majority (72.9% (129/177)) of which were Grade 1-2. The most commonly identified important ADRs ($\geq 1\%$ of patients) were hypothyroidism (3.6%), diabetes mellitus (3.2%), pneumonitis (3.0%), and colitis (1.0%). Other important ADRs reported in $< 1\%$ of patients were hyperthyroidism (0.8%), pancreatitis (0.5%), hepatitis and noninfectious meningoencephalitis (0.3% each), adrenal insufficiency (0.1%) and Guillain-Barre syndrome ($< 0.1\%$). There were no cases of myasthenic syndrome in the All Patients population. In the All Patients population (n = 1547), 2.5% (n = 38) received systemic corticosteroids to treat important ADRs, with the majority of treatments being for pneumonitis (24/38).

Clinical laboratory tests, vital signs and ECG results

There were no clinically significant changes in clinical laboratory tests or vital signs over the course of treatment with atezolizumab in any of the studies. ECG data from studies PCD4989g and FIR, demonstrated no clinically relevant changes from baseline in the median values of any ECG parameter (heart rate, PR duration, QRS duration, QRS axis, QT duration, QTcB, QTcF, and RR duration). In PCD4989g, a concentration-QTc analysis (n = 417) was conducted using triplicate ECGs collected from patients receiving atezolizumab doses of 10, 15, 20 mg/kg under controlled conditions in the dose expansion cohorts. It can be reasonably inferred from the results of this analysis that clinically meaningful changes in QTcF are unlikely to occur with the proposed atezolizumab 1200 mg fixed-dose q3w dosing regimen for the proposed indications.

Anti-therapeutic antibodies (ATAs)

The post-baseline incidence of treatment emergent ATAs (treatment induced and enhanced) was 42.5% (540/1272) in the All Patients population, with similar percentages being observed in the All UC population (41.9% (161/384)) and the All NSCLC population (42.7% (379/888)). The incidence of all grade AEs, Grade 5 AEs, AEs leading to treatment withdrawal, AEs leading to dose interruption, and AESIs was similar irrespective of post-baseline ATAs status (negative or positive). However, the incidence of Grade 3-4 AEs was

higher in the ATA-positive group compared to the ATA-negative group (44.3% versus 38.4%), as was the incidence of SAEs (40.2% versus 33.5%). The higher incidence Grade 3-4 AEs in the ATA-positive group compared to the ATA-negative group was mainly driven by AEs reported in the SOC of *gastrointestinal disorders* (8.5% versus 5.7%, respectively), but no individual preferred term could be identified to explain this difference. The higher incidence of SAEs in the ATA-positive group compared to the ATA-negative was not driven by any individual SOC or PT.

In the All Patients population, the incidence of hypersensitivity and infusion-related reactions was low and did not significantly differ between ATA-negative and ATA-positive patients. Hypersensitivity events were reported in 18 patients (1.4%) in the All Patients population: 8 in ATA-negative patients (1.1%) and 10 in ATA-positive patients (1.9%) patients. Infusion related reactions were reported in 20 patients (1.6%) in the All Patients population: 11 in ATA-negative patients (1.5%) and 9 in ATA-positive patients (1.7%).

Special populations

Safety in the All Patients population was assessed based on age (< 65 and ≥ 65 years) and gender. While there some differences in the safety profile between the two age groups and the two genders were observed, these differences are not considered to warrant variations to the dosing regimen based on age or gender. Due to the imbalance in racial groups in the All Patients population (84.4% Caucasian) no meaningful conclusions can be drawn about safety based on race. There were no safety data in patients with hepatic or renal impairment. There were no formal safety data relating to drug-drug interactions. There were no safety data relating to the effects of atezolizumab on the ability to drive or operate machinery. There were no clinical studies assessing the safety of atezolizumab in pregnancy. It is unknown whether atezolizumab is excreted in human milk.

First round benefit-risk assessment

First round assessment of benefits

Urothelial carcinoma

It is difficult to interpret the benefits of atezolizumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy due to the absence of controlled efficacy data. The supportive Phase II study (IMvigor 210 Cohort 2) and the exploratory Phase I study (PCD4989g UC cohort) were both open-label, uncontrolled studies.

The potential benefits of treatment with atezolizumab based on the analyses from IMvigor 210 Cohort 2 are summarised below. The description of the results provided below focuses on best objective response as determined by IRF-assessment per RECIST v1.1, as this is considered to be the most conservative assessment and is the standard approach used to evaluate tumour response in cancer clinical trials.

In IMvigor 210 Cohort 2, the ORRs (IRF-assessed; RECIST v1.1) in the primary analysis (data cut-off 5 May 2015) for the three pre-defined treatment groups were 27.0% (27/100) in the IC2/3 subgroup, 18.3% (38/208) in the IC1/2/3 subgroup, and 15.1% (47/311) in the all-comers group. The ORR in each of the three pre-defined treatment groups was statistically significantly greater than the historical control response rate of 10%. The ORR results in the three pre-defined treatment groups based on IRF-assessment per RECIST v1.1 were consistent with the ORR results based on INV-assessment per RECIST, which were 26.0%, 21.2%, and 18.3%, respectively for the IC2/3, IC1/2/3 and all-comers treatment groups.

In IMvigor 210 Cohort 2, the ORR (IRF-assessed; RECIST v1.1) in the primary analysis (data cut-off 5 May 2015) for the two exploratory treatment groups of IC0 and IC1 were 8.7% (9/103) and 10.2% (11/108), respectively. The ORRs in these two exploratory treatment groups were not notably different from the historical control response rate of 10%.

In IMvigor 210 Cohort 2, in the primary analysis (data cut-off data 5 May 2015), the median DOR (IRF-assessed per RECIST v1.1) had not been reached in the IC2/3, IC1/2/3 or all-comers group treatment groups. The median duration of PFS (IRF-assessed; RECIST v1.1) was similar in the three treatment groups, being 2.14, 2.10 and 2.10 months, respectively, in the IC2/3, IC1/2/3, and all-comers group treatment groups. The median OS had not been reached in the IC2/3 subgroup, and was 8.0 months in the IC1/2/3 subgroup and 7.89 in the all-comers group.

In IMvigor 210 Cohort 2, the efficacy results for atezolizumab for the primary analysis (data cut-off date 5 May 2015) with a median duration of follow-up of 7.1 months for all-enrolled patients were consistent with the updated efficacy results for atezolizumab (data cut-off 14 September 2015) with a median duration of follow-up of 11.7 months for all-enrolled patients.

In IMvigor 210 Cohort 2, the supplementary analysis at the latest cut-off date of 27 November 2015 provided efficacy data for at least 1 year of follow-up for the last enrolled patient and a median duration of follow-up of 14.4 months for all-enrolled patients. The ORR (IRF-assessed; RECIST v1.1) was 26.0% (26/100), 18.4% (38/207) and 14.8% (46/310) in the IC2/3, IC1/2/3 and all-comers treatment groups, respectively. The ORR (IRF-assessed; RECIST v1.1) was 7.8% (8/103) and 11.2% (12/107) in the IC0 and IC1 treatment groups, respectively. The results suggest that ORR increases with increasing PD-L1 expression on ICs.

In IMvigor 210 Cohort 2, in the supplementary analysis at the latest cut-off date of 27 November 2015 the median DOR (IRF-assessed; RECIST v1.1) had not yet been reached for the IC1, IC2/3, IC1/2/3 or all-comers treatment groups, and was 12.7 months in the IC0 treatment group. The proportion of patients who were on-going responders was 50.0% (4/8), 91.7% (11/12), 84.6% (22/26), 86.8% (33/38), and 80.4% (37/46) in the IC0, IC1, IC2/3, IC1/2/3 and all-comers treatment groups, respectively. The sponsor considers that atezolizumab provided sustained and durable responses over the course of treatment, which represented clinical benefit when compared to published data for vinflunine (median DOR 7.4 months (range 4.5, 17.0 months)), docetaxel (median DOR of 4 months (range: 3.0, 8.0 months) and pemetrexed (median DOR of 8 months (range: 6.0, 18.0 months)).

In IMvigor 210 Cohort 2, in the supplementary analysis at the latest cut-off date of 27 November 2015 the median OS in the ITT population was 6.5, 6.7, 11.9, 9.0 and 7.9 months in the IC0 (n = 103), IC1 (n = 107), IC2/3 (n = 100), IC1/2/3 (n = 207), and all-comers (n = 310) treatment groups, respectively. The estimated OS rates for the land-mark 1 year analysis were 30/0%, 31.2%, 49.9%, 40.2% and 36.9% in the IC0, IC1, IC2/3, IC1/2/3 and all-comers treatment groups, respectively. The sponsor commented that the survival outcomes observed with atezolizumab were clinically meaningful when compared to published data for vinflunine (median OS of 6.9 months), docetaxel (median OS of 7.0 months) and pemetrexed (median OS of 6.7 months).

Non-small cell lung cancer

In this submission, the benefits of atezolizumab for the proposed indication are derived from one pivotal Phase II, randomised, open-label, controlled study (POPLAR), and two supportive Phase II single-arm open-label studies (BIRCH and FIR). The data from PCD4989g NSCLC Cohort are considered to be exploratory.

There were no Phase III studies in patients with previously treated locally advanced or metastatic NSCLC confirming the modest OS benefit of 2.9 months in favour of atezolizumab (median OS = 12.6 months) compared to docetaxel (median OS = 9.7 months) observed in POPLAR. This is a significant deficiency in the submission, given that POPLAR is the only study which provides randomised controlled efficacy data for atezolizumab relevant to the proposed NSCLC indication.

PFS and ORR data from POPLAR demonstrated similar results for patients in the atezolizumab and docetaxel arms, while the median DOR was approximately 2-fold longer in the atezolizumab arm compared to the docetaxel arm (14.3 versus 7.2 months, respectively). In POPLAR, median PFS was 2.7 months in the atezolizumab arm and 3.0 months in the docetaxel arm and the ORR was 14.6% in the atezolizumab arm and 14.7% in the docetaxel arm.

In both BIRCH and FIR, the Phase II efficacy data in atezolizumab-treated patients were single-arm, with the primary efficacy endpoint (ORR) in BIRCH being compared to response in historical controls. In BIRCH and FIR, the ORR (which was the primary efficacy endpoint in both studies) was 17.3% and 16.1%, respectively, in atezolizumab treated patients. The ORRs in these two single-arm studies are similar to the ORR of 14.7% in the atezolizumab arm of POPLAR. The survival data in BIRCH were too immature to define the median OS and the survival data in FIR were too immature to adequately define the upper 95% CI of the median OS of 10.6 months. Median PFS was similar in atezolizumab-treated patients in BIRCH, FIR and POPLAR, being 2.8, 2.7 and 2.7 months, respectively. The median DOR in atezolizumab-treated patients in BIRCH was notably shorter than in the atezolizumab arm in POPLAR (8.4 versus 14.3 months) and similar in duration to the docetaxel arm in POPLAR (8.4 versus 7.2 months). The response data in BIRCH were too immature to determine the median DOR.

Overall, it is considered that the cross-study comparisons of key efficacy data in atezolizumab-treated patients from BIRCH and FIR provide support for the pivotal efficacy data observed in POPLAR. However, adequate interpretation of the single-arm efficacy data from BIRCH and FIR is limited due to the absence of comparative data from randomised control arms. Overall, it is considered that benefits of atezolizumab for the proposed indication in patients with NSCLC from POPLAR, BIRCH and FIR are promising, but should be confirmed with Phase III randomised, controlled data in the relevant patient population. The benefits of atezolizumab observed in the submitted studies relating to the key efficacy endpoints of OS, PFS, ORR and DOR in the patient population directly relevant to the proposed indication are discussed below.

Overall survival (OS)

The results for OS for the pivotal study (primary analyses) and the two supportive studies are summarised below. The median duration of survival follow-up was 15.7 months (95% CI: 14.6, 16.3) in the docetaxel arm and 14.8 months (95% CI: 14.0, 15.7) in the atezolizumab arm in POPLAR, 8.4 months (95% CI: 8.2, 8.7) in the atezolizumab arm in BIRCH and 9.7 months (95% CI: 8.1, 12.6) in the atezolizumab arm in FIR.

Table 5: OS (primary analysis) in the pivotal study (POPLAR) and the two supportive studies (BIRCH, FIR).

	POPLAR (all comers)		FIR Cohort 2 (2L+)	FIR Cohort 2 (2L+)
	Docetaxel	Atezolizumab	Atezolizumab, PD-L1 selected	Atezolizumab, PD-L1 selected
Patient number n	143	144	520	93

	POPLAR (all comers)		FIR Cohort 2 (2L+)	FIR Cohort 2 (2L+)
Patients with events	95 (66.4%)	78 (54.2%)	187 (36.0%)	43 (46.2%)
Median OS months (95% CI)	9.7 (8.6, 12.0)	12.6 (9.7, 16.4)	NE (11.2, NE)	10.6 (5.7, NE)
Estimated 6-month OS rate	69.1%	75.4%	73.4%	58.6%
Estimated 12-months OS rate	41.8%	51.6%	55.3%	48.3%

In POPLAR, OS in the ITT population (irrespective of PD-L1 status) was the primary efficacy endpoint. In the primary analysis, at the clinical cut-off date of 8 May 2015 when 173 deaths had occurred, there was a clinically meaningful and statistically significant improvement in OS of 2.9 months in patients randomised to atezolizumab 1200 mg q3w (n = 143) compared to patients randomised to docetaxel 75 mg/m² q3w (n = 144): median OS = 12.6 versus 9.7 months, respectively; stratified HR = 0.73 (95% CI: 0.53, 0.99), p = 0.0404. The number of deaths was 78 (54.2%) in the atezolizumab arm and 95 (66.4%) in the docetaxel arm, and the event/patient ratio was 60%.

In POPLAR, an updated post-hoc OS analysis in the ITT population (irrespective of PD-L1 status), at the clinical cut-off date of 1 December 2015 when 200 deaths had occurred, continued to show a clinically meaningful survival benefit of 2.9 months in favour of atezolizumab compared to docetaxel: median OS = 12.6 versus 9.7 months, respectively; stratified HR = 0.69 (95% CI: 0.52, 0.92), p = 0.0106 for descriptive purposes only. The event/patient ratio was 70%.

In POPLAR, increasing clinical benefit in OS was seen with increasing PD-L1 expression. There was an OS benefit in favour of atezolizumab compared to docetaxel in the TC3 or IC3 subgroup (HR = 0.49 (95% CI: 0.22, 1.07)), the TC2/3 or IC2/3 subgroup (HR=0.54 (95% CI: 0.33, 0.89)), and the TC1/2/3 or IC1/2/3 subgroup (HR = 0.59 (95% CI: 0.40, 0.85)). In the TC0 and IC0 subgroup, OS was similar in both treatment groups (HR = 1.04 (95% CI: 0.62, 1.75)). The results for OS by PD-L1 expression in the updated analysis were consistent with the results for the primary analysis.

In POPLAR, the results of the subgroup analysis of OS in the ITT population based on baseline demographics and other characteristics were consistent with the primary analysis of OS in the total ITT population. The median duration of OS was longer in the atezolizumab arm than in the docetaxel arm for both tumour subtypes (that is, non-squamous cell HR = 0.69 (95% CI: 0.47, 1.01); 15.5 versus 10.9 months) versus squamous cell HR = 0.80 (95% CI: 0.49, 1.30); 10.1 versus 8.6 months). These results were consistent with the results for the updated tumour subtype analysis. The median duration of OS based on the number of prior therapies (1 versus 2) was longer in the atezolizumab arm than in the docetaxel arm for patients receiving 1 prior therapy (HR = 0.62 (0.42, 0.91); 16.4 versus 9.5 months), and similar in the two treatment arms for patients receiving 2 prior therapies (HR = 0.98 (95% CI: 0.60, 1.61)); 9.8 versus 9.7 months).

In both supportive studies (BIRCH and FIR), OS was a secondary efficacy endpoint. In BIRCH, key efficacy data of regulatory interest were provided by Cohorts 2+3 (2L+). In the both the TC2/3 or IC2/3 and the TC3 or IC3 subgroups in Cohorts 2+3 (2L+), the survival data were immature with the median survival duration not being reached in either of the subgroups. At the time of analysis, 36.0% (187/520) of patients had died in the TC2/3 or

IC2/3 subgroup and 31.2% (74/237) of patients had died in the TC3 or IC3 subgroup. In FIR, key data of key efficacy data of regulatory interest were provided by Cohort 2 (2L+). In this cohort, the survival data were immature in the TC3 or IC3 subgroup with the median duration of OS not being reached, while in the TC2/3 or IC2/3 subgroup median OS was 10.6 months (95% CI: 5.7, NE). At the time of analysis, 46.2% (43/93) of patients had died in the TC2/3 or IC2/3 subgroup and 36.8% (14/338) of patients had died in the TC3 or IC3 subgroup.

ORR, DOR, and PFS; other key efficacy endpoints

The results for the analyses of ORR, DOR and PFS are summarised below.

Table 6: ORR, DOR, and PFS in the pivotal study (POPLAR) and the two supportive studies (BIRCH, FIR).

	POPLAR (all comers)		BIRCH Cohorts 2+3 (2L+)	FIR Cohort 2 (2L+)
	Docetaxel	Atezolizumab	Atezolizumab, PD-L1 selected	Atezolizumab, PD-L1 selected
ORR per RECIST v1.1 *	n = 143	n = 144	n = 520 (all patients in cohort)	n = 93 (all patients in cohort)
Responders (%)	21 (14.7%)	21 (14.6%)	90 (17.3%)	15 (16.1%)
(95% CI)	(9.33, 21.57)	(9.26, 21.42)	(14.2, 20.8)	(9.3, 24.2)
DOR per RECIST v1.1 *	n = 21	n = 21	n = 90	n = 15
Patients with events (PD/death)	16 (76.2%)	9 (42.9%)	33 (36.7%)	21 (13.3%)
Median DOR months (95% CI)	7.2 (5.6, 12.5)	14.3 (11.6, NE)	8.4 (6.9, NE)	NE (10.4, NE)
PFS per RECIST v1.1 *	n = 143	n = 144	n = 520 (all patients in cohort)	n = 93 (all patients in cohort)
Patients with events (PD/death)	121 (84.6%)	124 (86.1%)	401 (77.1%)	69 (74.2%)
Median PFS months (95% CI)	3.0 (2.8, 4.1)	2.7 (2.0, 4.1)	2.8 (2.7, 2.9)	2.7 (1.5, 3.5)
Estimated 6-month PFS rate	30.1%	33.0%	30.0%	32.3%
Estimated 12-months PFS rate	11.9%	16.4%	11.9%	21.5%

*ORR, DOR and PFS were IRF-assessed for BIRCH, and INV-assessed for POPLAR and FIR.

ORR and DOR

In POPLAR, the ORR (INV-assessed; RECIST v1.1) and the DOR (INV-assessed; RECIST v1.1) were secondary efficacy endpoints. The ORR in the ITT population (clinical cut-off date 8 May 2015) was modest and numerically similar in both treatment arms (14.6% (21/144), atezolizumab arm versus 14.7% (21/143), docetaxel arm). However, the median DOR was notably longer in the atezolizumab arm than in the docetaxel arm (14.3 versus 7.2 months, respectively; stratified HR = 0.41 (95% CI: 0.18, 0.96)). The median DOR (INV-assessed; RECIST v1.1) in the updated analysis (1 December 2015) continued to favour atezolizumab compared to docetaxel (18.6 versus 7.2 months, respectively).

In POPLAR, the ORR (INV-assessed; RECIST v1.1) was higher in the atezolizumab arm than in the docetaxel arm in the TC3 or IC3 subgroup (37.5% versus 13.0%), the TC2/3 or IC2/3 subgroup (22.0% versus 14.5%), and the TC1/2/3 or IC1/2/3 subgroup (18.3% versus 16.7%). However, the median DOR (INV-assessed; RECIST v1.1) was longer in the atezolizumab arm compared to the docetaxel arm only in the TC1/2/3 subgroup. In the TC0 and IC0 group, the ORR (INV-assessed; RECIST v1.1) was higher in the docetaxel arm than in the atezolizumab arm (9.8% versus 7.8%), with the median DOR (INV-assessed; RECIST v1.1) being 7.9 months in the docetaxel arm and not yet reached in the atezolizumab arm.

In BIRCH, the ORR (IRF-assessed; RECIST v1.1) was the primary efficacy endpoint. In Cohorts 2+3 (2+L), higher PD-L1 expression in the TC3 or IC3 subgroup was associated with higher ORR assessed by IRF per RECIST v1.1 compared to lower PD-L1 expression in the TC2/3 or IC2/3 subgroup (25.3% (60/237) versus 17.3% (90/520), respectively). In the TC2/3 or IC2/3 subgroup, the median DOR was 8.4 months (95% CI: 6.9, NE), with 36.7% of responders (33/90) experiencing an event (PD or death). In the TC3 or IC3 subgroup, the median DOR was 7.2 months (95% CI: 5.7, NE), with 38.3% of responders (23/60) experiencing an event (PD or death).

In FIR, the ORR (INV-assessed; RECIST v1.1) was the primary efficacy endpoint. In Cohort 2 (2L+), higher PD-L1 expression in TC3 or IC3 subgroup was associated with higher ORR assessed by INV per RECIST v1.1 compared to lower PD-L1 expression in the TC2/3 or IC2/3 subgroup (23.7% (9/38) versus 16.1% (15/93), respectively). The DOR (INV-assessed; RECIST v1.1) data were immature at the clinical cut-off date, with the median DOR not being reached in either the TC2/3 or IC2/3 subgroup or the TC3 or IC3 subgroup.

PFS

In POPLAR, the median PFS (INV-assessed; RECIST v1.1) in the ITT population was similar in the atezolizumab and docetaxel arms (2.7 versus 3.0 months, respectively; stratified HR = 0.94 (95% CI: 0.72, 1.23]). The proportion of patients with an event (death or PD) was 86.1% (124/144) in the atezolizumab arm and 84.6% (121/143) in the docetaxel arm. Median PFS was numerically greater in the atezolizumab arm compared to the docetaxel arm in the TC3 or IC3 subgroup (7.8 versus 3.9 months, respectively) and the TC2/3 or IC2/3 subgroup (7.8 versus 3.9 months, respectively), but not in the TC1/2/3 or IC1/2/3 subgroup (2.8 versus 3.0 months, respectively).

In BIRCH, in Cohorts 2+3 (2L+) the median PFS (IRF-assessed; RECIST v1.1) was 2.8 months in the TC2/3 or IC2/3 subgroup, with 77.1% (401/520) of patients experiencing an event (PD or death). In the TC3 or IC3 subgroup (n = 237), the median PFS (IRF-assessed; RECIST v1.1) was 4.1 months in the TC2/3 or IC2/3 subgroup, with 70.5% (167/237) of patients experiencing an event (PD or death). The data showed that the median duration of PFS increased with higher PD-L1 expression.

In FIR, in Cohort 2 (2L+), the median PFS (IRF-assessed; RECIST v1.1) was 2.7 months in the TC2/3 or IC2/3 subgroup, with 74.2% (69/93) of patients experiencing an event (PD or death). In the TC3 or IC3 subgroup, the median PFS (IRF-assessed; RECIST v1.1) was 4.1

months, with 65.8% (25/38) of patients experiencing and event (PD or death). The data showed that the median duration of PFS increased with higher PD-L1 expression.

Patient reported outcomes (PRO)

Patient reported outcome data, including EORTC QLQ-C30 and QLQ-LC13, were collected in BIRCH, FIR, and POPLAR. In patients in the atezolizumab arm in the three studies, no clinically meaningful change (improvement or decline) from baseline during the study period was observed in mean or median values in global health status, functioning (physical, role, emotional, cognitive, and social) or any of the symptom subscales. The results from the three studies indicate that atezolizumab does not have a detrimental impact on HRQoL.

In POPLAR, patients in the docetaxel arm also showed no clinically meaningful change (improvement or decline) from baseline during the study period in global health status, functioning (physical, role, emotional, cognitive, and social) or the lung cancer symptom subscales, but reported a clinically meaningful increase in alopecia.

In POPLAR, there was no difference in time to deterioration (defined as a 10 point increase above baseline) between the atezolizumab and docetaxel arms for lung cancer symptoms (cough, dyspnea, chest pain, or arm/shoulder pain).

PD-L1 unselected and selected patients

The sponsor is proposing that atezolizumab be approved in patients with NSCLC irrespective of PD-L1 expression on TCs or ICs. The main evidence for this proposal comes from the controlled efficacy data from POPLAR. In this study, the median duration of OS was statistically significantly longer in the atezolizumab arm compared to the docetaxel arm in the ITT population (all comers irrespective of PD-L1 expression), and the modest difference of 2.9 months between the two treatment arms is considered to be clinically meaningful (12.6 versus 9.7 months, respectively). The ORR (INV-assessed; RECIST v1.1) was modest in both treatment groups but numerically similar (14.6%, atezolizumab; 14.7%, docetaxel), while the median DOR (INV-assessed; RECIST v1.1) was approximately 2-fold longer in the atezolizumab arm than in the docetaxel arm (14.3 versus 7.2 months, respectively). Median PFS in the two treatment arms was similar (2.7 months, atezolizumab; 3.0 months, docetaxel), as was the percentage of patients experiencing PD or death (86.1% versus 84.6%). Overall, it is considered that the data from POPLAR provides promising support for the benefits of atezolizumab in patients with NSCLC irrespective of PD-L1 expression.

PD-L1 expression

The data from POPLAR indicate that OS improvement with atezolizumab is associated with increasing PD-L1 expression, with the greatest improvement seen in patients with the highest PD-L1 expression (TC3 or IC3 group). However, mutually exclusive subgroup analyses showed that all individual PD-L1 expression levels $\geq 1\%$ on TCs or ICs were independent contributors to the OS improvement seen with atezolizumab compared to docetaxel. The results indicate that the improvements in OS seen with atezolizumab in the TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3 subgroups are not being driven solely by patients with the highest PD-L1 expression levels (TC3 or IC3). Patients in the TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3 subgroups treated with atezolizumab also experienced a PFS benefit compared to patients treated with docetaxel. However, median OS and PFS results for patients in the TC0 or IC0 subgroup (that is, $< 1\%$ PD-L1 expression levels on TC0 or IC0) were similar in the atezolizumab and docetaxel arms.

In BIRCH, higher PD-L1 expression (TC3 or IC3) was associated with higher ORR and longer median PFS than lower PD-L1 expression (TC2/3 or IC2/3). In FIR, higher PD-L1 expression (TC3 or IC3) was associated with higher ORR than lower PD-L1 expression (TC2/3 or IC2/3).

In view of the association between higher PD-L1 expression and increased efficacy in patients with NSCLC treated with atezolizumab, it is recommended that all NSCLC patients to be treated with the drug have their PD-L1 expression levels determined. It is considered that this information will provide important prognostic information.

First round assessment of risks

Urothelial carcinoma

The IMvigor 201, Cohort 2 (n = 311, all-comers (irrespective of IC status)) population is considered to be the key patient group in the submission for assessing the risks of atezolizumab as second line or beyond treatment for locally advanced or metastatic UC in previously treated patients. The cohort consisted of 311 patients who had failed a prior platinum-containing chemotherapy regimen or progressed within 12 months of a platinum-based treatment administered in the adjuvant/neo-adjuvant setting and were treated with atezolizumab in the 2L+ setting. Interpretation of the safety is limited due to the absence of a controlled arm.

Patients in Cohort 2 (n = 311, all-comers) received atezolizumab 1200 mg q3w over a median period of 12.3 weeks (range: 0, 46 weeks). Treatment duration was ≤ 13 weeks for 51.8% of patients, > 13 to 26 weeks for 16.7% of patients, > 26 to 39 weeks for 26.0% of patients, and > 39 to 52 weeks for 5.5% of patients. The duration of exposure in Cohort 2 (all-comers) was short, with no patients in the cohort being exposed to atezolizumab for longer than 12 months. The absence of pivotal safety data beyond 12 months treatment with atezolizumab is a significant limitation of the safety data for this cohort.

Risk of experiencing an AE (irrespective of relationship to treatment)

AEs were reported in most patients in Cohort 2 (all-comers), with 95.8% (298/311) of patients experiencing at least one AE. The most commonly reported AEs (³ 10% of patients), in decreasing order of frequency, were fatigue (46.3%), decreased appetite (25.4%), nausea (23.8%), pyrexia and constipation (20.3% each), urinary tract infection (19.0%), diarrhoea (18.0%), vomiting (16.4%), dyspnoea (14.8%), back pain (14.5%), arthralgia (14.1%), anaemia (13.8%), haematuria (13.5%), pruritus (12.5%), abdominal pain and cough (12.2% each), and peripheral oedema (11.9%).

Risk of experiencing an AE related to treatment with atezolizumab

AEs considered by investigators to be related to treatment with atezolizumab were reported in the majority of patients in Cohort 2 (all-comers), with 65.3% (203/311) of patients experiencing at least one AE. The most commonly reported treatment-related AEs (≥ 5% of patients), in decreasing order of frequency, were fatigue (28.3%), nausea (12.9%), decreased appetite (10.9%), pruritus (10.0%), pyrexia (8.7%), diarrhoea (7.7%), rash (6.8%), arthralgia and vomiting (5.8% each), and chills (5.1%).

Risk of death

In Cohort 2 (all-comers), the risk of death occurring within 30 days of the last dose of atezolizumab due to an AE was small (1.3%, (4/311)). In Cohort 2 (all-comers), a total of 141 (45.3%, (141/311)) deaths were reported as of the clinical cut-off date of 5 May 2015. Of the 141 deaths, 34 (10.9%) occurred within 30 days of the last dose of atezolizumab and 107 (34.4%) deaths occurred beyond 30 days after the last dose of atezolizumab. The most common reason for death within 30 days of the last dose of atezolizumab was disease progression (44.1%, (137/311)). The other deaths in the 4 remaining patients due to Grade 5 AEs were reported in 1 patient each and included pulmonary sepsis, subileus, intracranial bleed (related to a previous cerebrovascular accident), and unknown cause. None of the Grade 5 AEs were considered to be treatment related.

Risk of experiencing SAEs other than death

In Cohort 2 (all-comers), the risk of experiencing at least one SAE was high (45.3%, (141/311)). SAEs reported in ≥ 3 patients ($\geq 1.0\%$), in decreasing order of frequency, were urinary tract infection (n = 19, 6.1%), haematuria (n = 10, 3.2%), pyrexia (n = 8, 2.6%), dyspnoea and acute kidney injury (2.3% each), dehydration, abdominal pain, pulmonary embolism, back pain and sepsis (n = 6, 1.9% each), small intestinal obstruction and pneumonia (n = 5, 1.6% each), hypercalcaemia, nausea and hydronephrosis (n = 4, 1.3% each), and hyponatraemia, pain, fatigue, pneumonitis, urosepsis, deep vein thrombosis, confusional state and pyelonephritis (n = 3, 1.0% each).

In Cohort 2 (all comers), 10.6% (33/311) of patients experienced at least one SAE considered to be related to treatment with atezolizumab. Treatment-related SAEs reported in more than 1 patient were pneumonitis (n = 3, 1.0%) and pyrexia (n = 2, 0.6%).

Risk of experiencing AEs leading to withdrawal

In Cohort 2 (all-comers), the risk of experiencing an AE leading to withdrawal from the study was small (3.2%, (10/311)). The data suggest that the majority of AEs reported in the cohort were manageable by temporary dose interruptions and/or symptomatic treatment. The AEs leading to withdrawal from the study were one each for retroperitoneal haemorrhage, subileus, pulmonary sepsis, sepsis, toxicity to various agents, posterior reversible encephalopathy syndrome (PRES), acute kidney injury, pneumonitis, pruritus, and no coding. Three of the AEs leading to withdrawal were considered by the investigator to be related to treatment (sepsis (resolved), acute kidney injury (resolved) and pneumonitis (death)). The case of PRES was not considered by the investigator to be related to treatment, but is of concern given that atezolizumab is associated with a risk of immune-mediated AEs.

Risk or experiencing AEs resulting in temporary interruption of dosing

In Cohort 2 (all-comers), the risk of experiencing at least one AE resulting in temporary interruption of the dosing regimen was commonly reported (26.7%, (83/311)). AEs leading to dose interruption and reported in ≥ 3 patients ($\geq 1.0\%$) were urinary tract infection (n = 8, 2.6%), diarrhoea (n = 6, 1.9%), fatigue and confusional state (n = 5, 1.6% each), pyrexia, dyspnoea, pneumonitis and blood bilirubin increased (n = 4, 1.3% each), and AST increased (n = 3, 1.0% each).

Risk of experiencing AESIs

There is a risk of experiencing AESI associated with treatment with atezolizumab, including dermatological reactions, hepatic events, gastrointestinal events, neurological events, endocrine events, pulmonary events, and systemic immune events. In Cohort 2 (all-comers), 25.4% (79/311) of patients reported at least one AESI during the study and most patients with an AESI had a Grade 1 or 2 event (83.5%, (66/79)). AESIs in Cohort 2 (all-comers) reported in ≥ 3 patients ($\geq 1\%$) by PT in decreasing order of frequency were rash (n = 31, 10%), increased AST (n = 13, 4.2%), increased ALT (n = 12, 3.9%), peripheral neuropathy (n = 8, 2.6%), increased bilirubin (n = 7, 2.3%), maculopapular rash (n = 7, 2.3%), pneumonitis and hypothyroidism (n = 6, 1.9% each), pruritic rash (n = 4, 1.3%), and transaminases increased (n = 3, 1.0%).

The most commonly reported AESIs were dermatological reactions, which were reported in 14.5% (n = 45) of patients. The most commonly reported dermatological reactions by PT ($\geq 1\%$ of patients) were rash in 31 (10.0%) patients, maculopapular rash in 7 (2.3%) patients, and pruritic rash in 4 (1.3%) patients. No cases of SJS or TEN were reported in the cohort.

Hepatic events reported as AESI were increased AST in 13 (4.2%) patients, increased ALT in 12 (3.9%) patients, increased blood bilirubin in 7 (2.3%) patient, increased transaminases in 3 (1.0%) patients, and autoimmune hepatitis and hepatitis in 1 (0.3%)

patient each. Endocrine events reported as AESI were hypothyroidism in 6 (1.9%) patients and TSH increased in 2 (0.6%) patients. Neurological events reported as AESIs were peripheral neuropathy in 8 (2.6%) patients. Gastrointestinal events reported as AESI were colitis in 1 (0.3%) patient. Pulmonary events reported as AESI were pneumonitis in 6 (1.9%) patients. Systemic immune events reported as AESI were cytokine release syndrome in 1 (0.3%) patient.

Risk of immune-mediated AEs (imAEs)

There is a risk of experiencing imAEs associated with atezolizumab treatment. In Cohort 2 (all-comers), the risk of experiencing an imAE was 6.4% (20/311). In these 20 patients, imAEs of Grade 3 or 4 severity were reported in 13 patients (4.2%, (13/311)) and imAEs of Grade 1 or 2 severity were reported in 7 patients (2.3%, (7/311)). There was an overlap between AESI and imAEs for some events.

The most commonly reported imAEs were pulmonary events, which were reported in 4 patients (1.3%, (4/311)). These events included dyspnoea in 2 patients (Grade 3 in each patient) and pneumonitis in 2 patients (Grade 3 and 4, one each). Hepatic imAEs were reported in 3 patients (1.0%, (3/311)), including 1 patient with Grade 3 increases in ALT, AST, and blood bilirubin, 1 patient with Grade 4 hepatitis, and 1 patient with Grade 3 autoimmune hepatitis. Gastrointestinal imAEs were reported in 2 patients, including 1 patient with Grade 3 diarrhoea and 1 patient with Grade 3 colitis. Dermatological imAEs were reported in 1 patient (Grade 3 rash). Neurological imAEs were reported in 1 patient (Grade 3 paraplegia). Other imAEs were reported in 2 patients (Grade 4 cytokine release in 1 patient; Grade 3 pericardial effusion in 1 patient).

Risk or ATAs

In IMvigor 210, 41.9% (161/384) of all patients treated with atezolizumab (Cohorts 1 and 2) had treatment-emergent ATAs. In Cohort 2 (all-comers), the percentage of patients experiencing AESIs was similar in ATA-positive and ATA-negative patients (30.7%, (35/114) versus 26.1%, (42/161), respectively). The only AESI reported in at least 10 patients in either of the ATA groups in Cohort 2 (all-comers) was rash: 20 (12.4%) ATA-negative patients and 11 (9.6%) ATA-positive patients. In Cohort 1 (all-comers), the percentage of patients experiencing AESIs was similar in ATA-positive and ATA-negative patients (25.5%, (12/47) versus 21.0%, (13/62), respectively). Overall, the risk of developing ATAs is high, but the presence of ATAs does not appear to significantly worsen the safety profile of atezolizumab.

Other risks

No clinically meaningful increased risks of laboratory abnormalities (haematological or clinical chemistry), or abnormal vital signs were identified. There were no data on ECG changes in IMvigor 201, but the totality of the ECG data presented in the submission does not give rise to concern. In particular, there is no evidence in the submitted data that atezolizumab is associated with QTc interval prolongation.

Risks in special groups

The pooled safety data from the All UC group indicate that no dose adjustments based on age or gender are required. There are no adequate safety data based on race, due to the imbalance in patient numbers across the different racial groups. Nearly all patients in the submission with UC were Caucasian. There were no data on the effect of hepatic impairment or renal impairment on the safety of atezolizumab.

Non-small cell lung cancer

General comments

The key study for the assessment of the risks of atezolizumab for the proposed usage in patients with NSCLC is POPLAR. This was Phase II, open-label, active-controlled study

which included 271 safety-evaluable patients, comprising 135 patients in the docetaxel arm and 142 patients in the atezolizumab arm. In the docetaxel arm, the median duration of treatment was 2.1 months (range: 0, 17 months) and the median number of treatment cycles was 4.0 (range: 1, 26). In the atezolizumab arm, the median duration of treatment was 3.7 months (range: 0, 19 months) and the median number of treatment cycles was 6.0 (range: 1, 28). The median dose intensity was 97.7% in both studies. Notably more patients in the atezolizumab arm received at least 6 months of treatment compared to patients in the docetaxel arm (40.1%, n = 57 versus 15.6%, n = 21), and 21.1% (n = 30) of patients in the atezolizumab arm received treatment for ≥ 12 months compared to 3.7% (n = 5) of patients in the docetaxel arm.

The safety profile of atezolizumab was qualitatively different from that of docetaxel, with lower risks for AEs in the atezolizumab arm known to be associated with docetaxel such as alopecia, nausea, diarrhoea, neutropaenia, febrile neutropaenia, and peripheral neuropathy. On the other hand, musculoskeletal pain and pneumonia were associated with a greater risk in patients treated with atezolizumab compared to patients treated with docetaxel.

In general, atezolizumab appeared to be better tolerated than docetaxel with notably lower patient incidences in the atezolizumab arm of AEs leading to withdrawal of treatment, AEs leading to dose modification/interruption, treatment-related AEs, treatment-related AEs leading to withdrawal of treatment, and treatment-related AEs leading to dose modification/interruption.

The major limitation relating to the assessment of the risks of treatment with atezolizumab based on the POPLAR data relates to the relatively small number of patients in the two treatment arms, and in particular the small number of patients treated for ≥ 12 months. It is noted that the primary analysis of OAK (Phase III), presented at the recent 2016 ESMO, includes safety data on 609 patients treated with atezolizumab and 578 patients treated with docetaxel. The reported safety dataset for the confirmatory Phase III study (OAK) provides a substantially larger number of patients on which to base firm conclusion relating to the comparative safety of atezolizumab and docetaxel than that provided by the Phase II study (POPLAR).

However, reassurance relating to the safety of atezolizumab for the proposed usage in NSCLC patients is provided by the All NSCLC data in a total of 1026 atezolizumab-treated patients from POPLAR, BIRCH, FIR, and PCD4989g, including 840 2L+NSCLC patients. In the 938 safety-evaluable patients in the All NSCLC population who were treated with atezolizumab 1200 mg q3w, the median duration of follow-up was 5.1 months (range: 0.5, 32.9 months), the median duration of exposure was 4.1 months (range: 0, 19.4 months), the median number of cycles was 6.5 (range: 1.0, 28.0), and the median dose intensity was 100% (range: 33, 147). Of the 938 safety-evaluable patients in the All NSCLC population treated with atezolizumab 1200 mg q3w, 59.6% (n = 559) were treated for 6 months and 6.9% (n = 65) were treated for > 12 months. The high-level safety profile of atezolizumab-treated patients in the All NSCLC group and the atezolizumab arm in POPLAR were similar (see below).

Table 7: High-level safety profiles of atezolizumab-treated patients from the All NSCLC group and POPLAR, and of docetaxel-treated patients from POPLAR

Patient n (%)	Atezolizumab treated patients		Docetaxel treated patients
	All NSCLC (n = 1026)	POPLAR (n = 142)	POPLAR (n = 135)

	Atezolizumab treated patients		Docetaxel treated patients
At least 1 AEs	976 (95.1%)	136 (95.8%)	130 (96.3%)
At least 1 treatment-related AE	675 (65.8%)	95 (66.9%)	119 (88.1%)
Grade 3-4 AEs	405 (39.5%)	57 (40.1%)	71 (52.6%)
Treatment-related Grade 3-4 AEs	120 (11.7%)	16 (11.3%)	52 (38.5%)
Grade 5 AEs	34 (3.3%)	6 (4.2%)	5 (3.7%)
Treatment-related Grade 5	4 (0.4%)	1 (0.7%)	3 (2.2%)
SAE	384 (37.4%)	50 (35.2%)	46 (34.1%)
Treatment-related SAE	99 (9.6%)	12 (8.5%)	23 (17.0%)
AE leading to withdrawal	64 (6.2%)	11 (7.7%)	30 (22.2%)
AE leading to dose interruption	261 (25.4%)	34 (23.9%)	44 (32.6%)
AESI of any grade	271 (26.4%)	42 (28.9%)	40 (29.6%)
AESI of Grade 3-4	48 (4.8%)	8 (5.6%)	4 (3.0%)
AESI of Grade 5	1 (<0.1%)	1 (0.7%)	0

Risks of adverse events irrespective of study drug treatment

In *POPLAR*, nearly all patients in both the docetaxel and atezolizumab arms experienced at least one AE (96.3% (130/135), 1325 events versus 95.8% (136/142), 1354 events, respectively). The most commonly reported AEs occurring in $\geq 20\%$ of patients in either the docetaxel arm or the atezolizumab arm (respectively), in decreasing order of frequency in the docetaxel arm, were fatigue (40.0% versus 38.7%), alopecia (38.5% versus 2.1%), nausea (33.3% versus 21.8%), diarrhoea (28.1% versus 16.9%), cough (24.4% versus 26.8%), constipation (23.7% versus 20.4%), decreased appetite (20.7% versus 34.5%), and dyspnoea (20.0% versus 26.8%).

AEs with a higher incidence (³ 5% more patients) in the atezolizumab arm than in the docetaxel arm were decreased appetite (34.5% versus 20.7%), dyspnoea (26.8% versus 20.0%), pyrexia (16.9% versus 11.9%), arthralgia (15.5% versus 8.9%), insomnia (13.4% versus 8.1%), musculoskeletal pain (13.4% versus 5.2%), and pneumonia (10.6% versus 3.0%).

AEs with a higher incidence ($\geq 5\%$ more patients) in the docetaxel arm than in the atezolizumab arm were alopecia (38.5% versus 2.1%), nausea (33.3% versus 21.8%), diarrhoea (28.1% versus 16.9%), asthenia (16.3% versus 9.9%), myalgia (13.3% versus 5.6%), neutropaenia (12.6% versus 1.4%), peripheral neuropathy (11.9% versus 1.4%), peripheral sensory neuropathy (8.9% versus 1.4%), febrile neutropaenia (8.1% versus 0.0%), dry skin (7.4% versus 2.1%), and nail disorder (6.7% versus 0.7%).

The duration of treatment was longer in patients treated with atezolizumab compared to patients treated with docetaxel (median of 3.7 months versus median of 2.1 months). Therefore, in order to explore whether the AEs reported in a higher proportion of patients ($\geq 5\%$ more patients) in the atezolizumab arm than in the docetaxel arm were associated with longer duration of exposure, analyses adjusted for the patient-years at risk were performed for decreased appetite, dyspnoea, pyrexia, arthralgia, insomnia, musculoskeletal pain, and pneumonia. The results showed that the AE rate per 100 patient years was higher in the atezolizumab arm than in the docetaxel arm for musculoskeletal pain and pneumonia, but not for arthralgia, decreased appetite, dyspnoea, insomnia or pyrexia. The results suggest that the increased risk of at least some of the AEs observed with atezolizumab compared to docetaxel might be due to the longer duration of exposure in patients treated with atezolizumab compared to patients treated with docetaxel.

Risks of treatment-related adverse events

In POPLAR, the risk of experiencing at least one treatment-related AE was notably greater in patients in the docetaxel arm than in the atezolizumab arm (88.1% (119/135) versus 66.9% (95/142)). Treatment-related AEs reported in $\geq 10\%$ of patients in either the docetaxel arm or the atezolizumab (respectively), with decreasing order of frequency in the docetaxel arm, were alopecia (37.8% versus 1.4%), fatigue (34.8% versus 20.4%), nausea (27.4% versus 12.0%), diarrhoea (22.2% versus 7.0%), anaemia (16.3% versus 5.6%), decreased appetite (15.6% versus 17.6%), asthenia (13.3% versus 6.3%), vomiting (11.9% versus 5.6%), constipation (11.9% versus 4.9%), peripheral neuropathy (11.1% versus 0.7%), and neutropaenia (11.1% versus 0.7%).

Risks of Grade 3-4 adverse events

In POPLAR, the risk of experiencing at least one Grade 3-4 AE was notably greater in the docetaxel arm than in the atezolizumab arm (52.6%, (71/135) versus 40.1%, (57/142)). Of note, Grade 3-4 neutropaenia, febrile neutropaenia, and fatigue all occurred notably more commonly in the docetaxel arm than in the placebo arm, while dyspnoea and pneumonia occurred notably more frequently in the atezolizumab arm. Grade 3-4 AEs reported in $\geq 5\%$ of patients in either the docetaxel arm or the atezolizumab arm (respectively) were neutropaenia (11.1% versus 0%), febrile neutropaenia (8.1% versus 0%), fatigue (7.4% versus 2.1%), dyspnoea (1.5% versus 7.0%), and pneumonia (1.5% versus 5.6%).

Risk of death

In POPLAR, AEs leading to death occurring ≤ 30 days of the last dose or prior to initiation of non-protocol anti-cancer therapy were reported in 11 patients, including 6 (4.2%) in the atezolizumab arm and 5 (3.7%) in the docetaxel arm. In the atezolizumab arm, the six Grade 5 AEs were cardiac failure (treatment-related), pulmonary embolism, pneumonia, embolism, ulcer haemorrhage, and pneumothorax. In the docetaxel arm, the five Grade 5 AEs were acute respiratory syndrome (treatment-related), sepsis (treatment-related), death (treatment-related), death and sepsis.

AEs leading to deaths occurring > 30 days after the last dose of study treatment or prior to initiation of non-protocol anti-cancer therapy were reported in 6 patients, including 4 (2.8%) in the atezolizumab arm and 2 (1.5%) in the docetaxel arm. In the atezolizumab arm, the four Grade 5 AEs were death, cardiac arrest, pneumonia and large intestine

perforation, all of which were considered to be unrelated to treatment. In the docetaxel arm, the two Grade 5 AEs were sepsis and death, both of which were considered to be unrelated to treatment.

Risk of SAEs

In POPLAR, the risk of experiencing a SAE was similar in the docetaxel and atezolizumab arms (34.1% versus 35.2%, respectively). SAEs reported in $\geq 2\%$ of patients in either the docetaxel arm or the atezolizumab arm (respectively), in decreasing order of frequency in the docetaxel arm, were febrile neutropaenia (5.2% versus 0%), pulmonary embolism (4.4% versus 1.4%), haemoptysis (2.2% versus 0.7%), pneumonia (2.2% versus 5.6%), sepsis (2.2% versus 0%), dyspnoea (0.7% versus 4.9%), pyrexia (0.7% versus 2.1%), and pleural effusion (0% versus 2.8%).

SAEs reported in $\geq 2\%$ more patients in the atezolizumab arm than in the docetaxel arm were pneumonia (5.6% versus 2.2%), dyspnoea (4.9% versus 0.7%) and pleural effusion (2.8% versus 0%). SAEs reported in $\geq 2\%$ more patients in the docetaxel arm than in the atezolizumab arm were febrile neutropaenia (5.2% versus 0%), pulmonary embolism (4.4% versus 1.4%), and sepsis (2.2% versus 0%).

In POPLAR, the risk of experiencing a treatment-related SAE was notably greater in the docetaxel arm than in the atezolizumab arm (17.0% versus 8.5%). Treatment related SAEs reported in ≥ 2 patients in either the docetaxel arm or the atezolizumab arm (respectively) were febrile neutropaenia (5.2% versus 0%), neutropaenia (1.5% versus 0%), pyrexia (0.7% versus 2.1%), pneumonia (1.5% versus 2.1%), sepsis (1.5% versus 0%), AST increased (0% versus 1.4%), and rash (0.0% versus 1.4%).

Risk of experiencing AEs leading to discontinuation of the study drug

In POPLAR, the risk of experiencing an AE leading to discontinuation of the study drug was significantly greater in the docetaxel arm than in the atezolizumab arm (22.2% versus 7.7%). AEs leading to study drug discontinuations reported in $\geq 1.0\%$ patients in either the docetaxel arm or the atezolizumab arm (respectively), in decreasing order of frequency in the docetaxel arm, were fatigue (3.0% versus 0%), peripheral sensory neuropathy (3.0% versus 0%), sepsis (2.2% versus 0%), death (1.5% versus 0%), peripheral neuropathy (1.5% versus 0%), and dyspnoea (0% versus 1.4%).

Risk of experiencing an AE leading to dose modification

In POPLAR, the risk of experiencing an AE leading to dose modification was greater in the docetaxel arm than in the atezolizumab arm (32.6% versus 23.9%). Dose modifications reported in $\geq 2\%$ of patients in either the docetaxel arm or the atezolizumab arm, in decreasing order of frequency in the docetaxel arm, were fatigue (6.7% versus 0.7%), febrile neutropaenia (3.7% versus 0%), peripheral sensory neuropathy (3.0% versus 0%), and pneumonia (0% versus 2.1%).

Overall, the POPLAR AE data suggest that the majority of AEs observed in the atezolizumab arm were manageable by dose interruption and/or symptomatic treatment rather than discontinuation of the study drug.

Risk of experiencing an AESI

In POPLAR, the risk of experience an AESI was similar in the docetaxel and atezolizumab arms (29.6% versus 28.9%, respectively). In both treatment arms, dermatological reactions were the most commonly reported AESIs and were observed in a similar percentage of patients in the docetaxel and atezolizumab arms (14.8% versus 16.2%, respectively). The most commonly reported dermatological AESI was rash, which was reported in 11.9% of patients in the docetaxel arm and 10.6% of patients in the atezolizumab arm. Grade 3 dermatological AESIs were reported in 1 patient in the

docetaxel arm (rash) and 2 patients in the atezolizumab arm (both rash). There were no cases of SJS or TENs observed in either of the two treatment arms.

The risk of experiencing a neurological AESI was notably greater in the docetaxel arm than in the atezolizumab arm (13.3% versus 2.1%), with peripheral neuropathy being the most commonly reported neurological AESI in both treatment arms (11.9% versus 1.4%, respectively). Grade 3 neurological AESIs were reported in 2 patients in the docetaxel arm (neuropathy peripheral x 1, polyneuropathy x 1).

The risk of experiencing a hepatic AESI was greater in the atezolizumab arm than in the docetaxel arm (5.6% versus 1.5%). The most commonly reported hepatic AESIs in the atezolizumab arm (vs the docetaxel arm) were AST increased (4.2% versus 0.7%) and ALT increased (4.2% versus 0%). Grade 3 or 4 hepatic AESIs were reported in 5 patients in the atezolizumab arm (2 patients with Grade 3 increased AST; 2 patients with Grade 3 increased AST and ALT).

The risk of experiencing an endocrine AESI was notably greater in the atezolizumab arm than in the docetaxel arm (6.3% versus 0.7%). The endocrine AESIs in the atezolizumab arm were hypothyroidism (x 8) and hyperthyroidism (x 1), and in the docetaxel arm the one event was hyperthyroidism (x1). There was one Grade 3 event of hypothyroidism in the atezolizumab arm, with all other endocrine AESIs in both treatment arms being Grade 1 or 2.

Gastrointestinal AESIs were reported in 0.7% of patients in the docetaxel arm (colitis x 1) and 1.4% of patients in the atezolizumab arm (colitis x 2, including 1 Grade 3 event). One patient in the atezolizumab arm experienced a musculoskeletal AESI (Grade 2 autoimmune arthritis). Pulmonary AESIs were reported in 0.7% of patients in the docetaxel arm and 2.8% of patients in the atezolizumab arm. All pulmonary AESIs were categorised as pneumonitis, with Grade 3 events being reported by 1 patient in each of the two treatment arms.

No cardiac, haematological, ocular, renal or non-specific immune AESIs were reported during the study.

Risk of experiencing and immune-mediated adverse event (imAE)

In POPLAR, the risk of experiencing an imAE was similar in the docetaxel and atezolizumab arms (7.4% versus 7.7%, respectively). Immune-mediated AEs reported in ≥ 1% of patients in either the docetaxel arm or the atezolizumab arm (respectively) were peripheral neuropathy (2.2% versus 0.7%), diarrhoea (1.5% versus 0.7%), rash (1.2% versus 2.1%), pneumonitis (0.7% versus 1.4%), colitis (0% versus 1.4%), and hypoxia (0% versus 1.4%).

Risk of developing anti-therapeutic antibodies (ATAs)

In POPLAR, 54.5% (73/134) of patients in the atezolizumab arm developed protocol-defined ATAs, including 70 patients with 'treatment-induced' ATA responses and 3 patients with 'treatment-enhanced' ATA responses. Overall, the risks of atezolizumab treatment in ATA-positive and ATA-negative patients did not markedly differ between the two patient groups. The incidence of AESIs was similar in ATA-positive and ATA-negative patients (30.1% versus 30.6%, respectively). The development of ATAs did not appear to be associated with hypersensitivity or infusion related reactions. Of the ATA-negative patients, one experienced a hypersensitivity AE and one experience an infusion-related reaction. No ATA-positive patients experienced a hypersensitivity AE or an infusion-related reaction.

Risk of developing clinical chemistry abnormalities

No clinically relevant changes in median values for haematology and clinical chemistry laboratory parameters occurred during the study. The majority of patients did not

experience a clinically relevant increase in AE Grade in any haematological or clinical chemistry laboratory parameters during the study. However, the proportion of patients with Grade 3 decreases in the absolute lymphocyte count at any time during the study was notably greater in the docetaxel arm than in the atezolizumab arm (21.9% versus 6.9%), as was the proportion of patients with Grade 4 decreases in the absolute neutrophil count (17.2% versus 0.8%), Grade 3 decreases in the absolute white blood cell count (7.8% versus 0.8%) and Grade 4 decreases in the absolute white blood cell count (7.8% versus 0.8%). There were no marked differences between the two treatment arms in the proportion of patients with Grade 3 or 4 changes in clinical chemistry parameters, with nearly all changes being reported in $\leq 5\%$ of patients in both treatment arms.

Haematology laboratory abnormalities reported as AEs during the study occurring in $\geq 2\%$ of patients in either treatment arm (docetaxel versus atezolizumab) were anaemia (19.3% versus 16.2%), neutropaenia (12.6% versus 1.4%), thrombocytopaenia (0.7% versus 4.2%), lymphopaenia (2.2% versus 0.7%), and INR increased (2.2% versus 0%).

Clinical chemistry laboratory abnormalities reported as AEs during the study occurring in $\geq 2\%$ of patients in either treatment arm (docetaxel versus atezolizumab) were hypokalaemia (3.0% versus 6.3%), hyponatraemia (2.2% versus 5.6%), hypomagnesaemia (3.7% versus 4.9%), AST increased (0.7% versus 4.2%), ALT increased (0.0% versus 4.2%), and hypoalbuminaemia (3.0% versus 2.8%), alkaline phosphatase increased (0% versus 2.8%), and creatinine increased (0% versus 2.1%).

Risks of developing clinically significant changes in vital signs or ECG findings

In POPLAR, the risks of developing clinically significant changes in vital signs or clinically abnormal ECG findings during the study in either of the two treatment arms were negligible.

Risk of experiencing AEs in special populations

Overall, the safety profile of atezolizumab in POPLAR was comparable across the PD-L1 expression subgroups (TC3 or IC3 subgroup, TC2/3 or IC2/3 subgroup, and TC1/2/3 or IC1/2/3 subgroup).

In POPLAR, there were no formal safety data assessing differences between the docetaxel and the atezolizumab arms based on age, gender, race, hepatic impairment, or renal impairment.

In the All NSCLC population, the high-level AE profile in atezolizumab-treated patients was similar in the patients aged < 65 years ($n = 532$) and patients aged ≥ 65 years ($n = 494$). In the All NSCLC population, the high-level AE profile in atezolizumab-treated patients was similar in males ($n = 610$) and females ($n = 416$). In the All NSCLC population, no meaningful interpretation of safety data in atezolizumab-treated patients based on race can be made due to the imbalance in patient numbers across the groups ($n = 849$, 82.8%, Caucasian; $n = 108$, 10.5%, Asian; $n = 24$, 2.3%, black; and $n = 43$, 4.2%, other).

First round assessment of benefit-risk balance

Urothelial carcinoma

The submitted efficacy data are considered to be too limited to allow adequate characterisation of the benefits of atezolizumab for the proposed indication (UC). Based on the totality of the safety data (UC plus NSCL) it is considered that the risks of atezolizumab for the proposed indication (UC) are acceptable. However, treatment with atezolizumab is not without risks. Therefore, in the absence of adequate data satisfactorily establishing the benefits of treatment with atezolizumab for the proposed usage in patients with UC it is considered that the benefit-risk balance for this usage is unfavourable.

Non-small cell lung cancer

The benefits of atezolizumab for the proposed usage in patients with NSCLC are considered to be promising, but require confirmation with efficacy data from a Phase III study. Based on both the totality the safety data (NSCLC plus UC) and the safety data relating specifically to NSCLC it is considered that the identified risks of atezolizumab for the proposed indication (NSCLC) are acceptable. However, treatment with atezolizumab is not without risks. Therefore, in the absence of confirmatory data satisfactorily establishing the benefits of treatment with atezolizumab for the proposed usage in patients with NSCLC it is considered that the benefit-risk balance for this usage is unfavourable. However, the benefit-risk balance for the proposed usage in patients with NSCLC might become favourable if the promising benefits of atezolizumab observed in the pivotal Phase II study (POPLAR) and the two supportive Phase II studies (BIRCH and FIR) are confirmed by the Phase III study (OAK).

First round recommendation regarding authorisation

Urothelial carcinoma

It is recommended that the application to register atezolizumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy be *rejected* on the grounds of inadequate demonstration of efficacy for the proposed indication. The reasons for rejection are summarised below.

The submission included no confirmatory Phase III studies establishing the efficacy or safety of atezolizumab for the proposed indication compared to control treatment. In particular, there were no confirmatory data establishing that atezolizumab provides an OS or PFS benefit compared to control treatment with vinflunine, a chemotherapeutic agent approved in Australia for a similar indication to that proposed for atezolizumab. The TGA adopted EMA guideline relating to the evaluation of cancer medicines indicates that in determining the efficacy of single-agent experimental medicines *in Phase III confirmatory studies* the agent should be compared to the 'best available' comparator (CHMP/EWP/205/95/Rev.4/Corr).²⁷ It is considered that there is no reason to deviate from the TGA adopted guideline in the current submission, given that there is an appropriate registered comparator (vinflunine) for the indication of interest. In addition, based on the sponsor's covering letter it appears that the sponsor considers that vinflunine, docetaxel and pemetrexed all are appropriate comparators for the treatment of UC.

Neither the Phase II pivotal study nor the Phase I supportive study pre-specified either OS or PFS as a primary efficacy endpoint. The relevant TGA adopted EMA guideline for the evaluation of cancer medicines state that OS or PFS/DFS should be a primary efficacy endpoint for *confirmatory Phase III oncology trials* (CHMP/EWP/205/95/Rev.4/Corr).²⁸ It is considered that there is no reason to deviate from adopted guideline in the current submission, given that there is an appropriate registered comparator (vinflunine) for the indication of interest. In addition, based on the sponsor's covering letter it appears that the sponsor considers that vinflunine, docetaxel and pemetrexed are appropriate comparators for the treatment of UC.

IMvigor 210, the supportive Phase II study was open-label and single-arm. The ORRs observed for atezolizumab in the IC2/3, IC12/3 and all-comers treatment groups at the data cut-off of 5 May 2015 were formally compared to a historical control response rate of

²⁷ Guideline on the evaluation of anticancer medicinal products in man.

²⁸ Guideline on the evaluation of anticancer medicinal products in man.

10% determined from the published literature. The results showed that the co-primary ORR efficacy endpoints, IRF-assessed by RECIST v1.1 and INV-assessed per mRECIST, were statistically significantly higher than the historical control response rate. However, for regulatory purposes, the comparisons are considered to be supportive rather than confirmatory due to the biases associated with cross-study comparisons (for example, different study designs, different patient characteristics, and different lengths of exposure).

The DOR and OS for atezolizumab appeared to be longer when compared to published data for vinflunine, docetaxel and pemetrexed. However, for regulatory purposes, the cross-study comparisons are considered to be supportive rather than confirmatory. The interpretation of DOR, PFS, and OS data are problematic without data from a formal comparative treatment arm from a randomised controlled study.

It is noted that the sponsor's developmental plan includes a Phase III study (IMvigor 211) aimed at evaluating the efficacy of atezolizumab compared to chemotherapy with respect to OS in patients with locally advanced or metastatic urothelial bladder cancer after failure with platinum containing chemotherapy. It is recommended that the application to register atezolizumab for the treatment of UC be re-submitted when the results of this study become available.

Non-small cell cancer

It is recommended that the application to register atezolizumab for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy be **rejected** on the grounds of inadequate demonstration of efficacy for the proposed indication. The reasons for rejection are summarised below.

The submission included no confirmatory Phase III study establishing the efficacy of atezolizumab compared to relevant control treatment (for example, docetaxel) for the proposed indication. The pivotal Phase II study (POPLAR) demonstrated a modest statistically significant and clinically meaningful survival benefit of 2.9 months in patients treated with atezolizumab (n = 144) compared to patients treated with docetaxel (n = 143) in the primary analysis; median OS = 12.6 versus 9.7, respectively; stratified HR = 0.73 (95% CI: 0.53, 0.99), p = 0.0404. The updated OS analysis continued to show a 2.9 month survival benefit in favour of atezolizumab compared to docetaxel. The survival benefit for atezolizumab from POPLAR is promising, but is modest and the patient numbers in both treatment arms are relatively small. Furthermore, there were no other randomised, controlled studies in the submission comparing OS in atezolizumab-treated patients with a control treatment (for example, docetaxel). Survival data for atezolizumab from the supportive, single-arm, Phase II study (BIRCH) are too immature to define the median OS. In addition, the survival data for atezolizumab, from the supportive, single-arm, Phase II study (BIRCH) are too immature to fully characterise OS, with the upper 95% CI for OS being not estimable.

The PFS data (median duration) from POPLAR are similar in the atezolizumab and docetaxel arms (2.7 versus 3.0 months, respectively) as are the ORR data (14.6% versus 14.7%, respectively), while the median DOR is approximately 2-fold longer in the atezolizumab arm compared to the docetaxel arm (14.3 versus 7.2 months). The ORR in BIRCH (17.3%) and FIR (16.1%) in atezolizumab-treated patients was similar to the ORR in the atezolizumab arm in POPLAR (14.6%). The median duration of PFS was similar in atezolizumab-treated patients in BIRCH, FIR, and POPLAR (that is, 2.8, 2.7 and 2.7 months, respectively). The median DOR was notably longer in atezolizumab-treated patients in POPLAR compared to BIRCH (that is, 14.3 versus 8.4 months), and was not estimable in the atezolizumab arm in FIR due to immaturity of the data. Overall, the single-arm efficacy data from BIRCH and FIR in atezolizumab-treated patients are considered to provide

support for the efficacy data for atezolizumab observed in POPLAR. However, interpretation of the single-arm data from BIRCH and FIR in atezolizumab-treated patients is limited due to the lack of a control arm in both studies. In particular, it is difficult to make clinically meaningful conclusions relating to DOR, PFS and OS from BIRCH and FIR in the absence of controlled data.

Additional comment

It is noted that efficacy and safety data from the primary analysis of the Phase III study (OAK) comparing atezolizumab (1200 mg q3w) to docetaxel (75 mg/m² q3w) in previously treated patients with locally advanced or metastatic NSCLC have been recently reported;²⁹ and that the OS data from this analysis have been included in the currently approved US label for atezolizumab. The design of this Phase III study (OAK) appears to be similar to that of the submitted Phase II study (POPLAR), but includes a substantially larger number of enrolled patients (n = 1,225). The efficacy data provided in the US label report that the median OS in the atezolizumab arm (n = 425) was 13.8 months compared to 9.6 months in the docetaxel arm (n = 425): stratified HR = 0.74 (0.63, 0.87), p = 0.0004 (stratified log-rank test). Data in the public domain summarising the results of the study presented at the ESMO conference in October 2016 report that an OS benefit in favour of atezolizumab was seen regardless of PD-L1 expression levels, with an unstratified HR of 0.75 (0.59, 0.96) in the TC0 and IC0 subgroup and an unstratified HR of 0.41 (95% CI: 0.27, 0.64) in the TC3 or IC3 subgroup. As part of its post-first round response to the first round clinical evaluation report, the sponsor is requested to provide the efficacy and safety data from the primary analysis.

Second round evaluation

For details of the second round evaluation including the issues raised by the evaluator (Clinical questions), the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

Urothelial carcinoma

After consideration of the sponsor's responses to the clinical questions the conclusions relating to the benefits of atezolizumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy remain unchanged from those provided earlier. The benefits of atezolizumab for the treatment of UC are promising but are considered to require confirmation by data from a randomised, controlled Phase III study (for example, IMvigor 211).

The sponsor's post-first round response included updated efficacy data (ORR and DOR) for the supportive Phase II study (IMvigor 210 Cohort 2) and the exploratory Phase I study (Study PCD4989g UC cohort). In IMvigor Cohort 2, the updated ORR at the 4 July 2016 cut-off (median duration of follow-up 21.1 months) and the primary analysis of the ORR at the 5 May 2015 cut-off (median duration of follow-up 7.1 months) were consistent in the all-comers, IC2/3, IC1 and IC0 treatment groups. The ORR at both time-points was IRF-assessed per RECIST v1.1. The results from IMvigor Cohort 2 indicate that the ORR is

²⁹ Barlesi et al. Primary Analysis from OAK, a randomised Phase III study comparing atezolizumab with docetaxel in advanced NSCLC. Presidential Symposium 2, Main Auditorium, Sunday 9 October 2016. Accessed from the Roche.com website on 21 October 2016.

durable over time. In IMvigor 210 Cohort 2, at the time of the primary analysis the median DOR had not been reached in the all-comers, IC2/3, IC1 and IC0 treatment groups, while in the updated analysis a median DOR of 13.3 months was observed in the IC0 group. At the time of the updated analysis, the median DOR had still not been reached in the all-comers, IC2/3 and IC1 treatment groups.

In IMvigor Cohort 2, the updated ORR results (4 July 2016 cut-off) continued to demonstrate a response relationship between PD-L1 status (as determined by the SP-142 IHC assay) and the ORR. The updated ORRs were 28.0% (28/100) (95% CI: 19.5, 37.9), 11.2% (12/107) (95% CI: 5.9%, 18.8%) and 8.7% (9/103) (95% CI: 4.1, 15.9) in the IC2/3, IC1 and IC0 treatment groups, respectively. The results showed that increased PD-L1 expression on tumour-infiltrating immune cells resulted in higher ORRs. The updated ORR in the all-comers treatment group was 15.8% (49/310) (95% CI: 11.9, 20.4).

In IMvigor Cohort 2, the updated ORR results (4 July 2016 cut-off) showed that the lower 95% CI for the response excluded 10% (historical control response rate) for the all-comers and IC2/3 treatment groups, but not for the IC1 and IC0 treatment groups. The results for the updated ORR analysis (4 July 2016 cut-off) were consistent with the results for the primary analysis of the ORR (5 May 2015 cut-off). The results raise doubts about the benefits of atezolizumab treatment in patients with UC who do not express PD-L1 on tumour-infiltrating immune cells (that is, IC0) or with low levels of PD-L1 expression (that is, IC1). While the all-comers treatment group (that is, patients included irrespective of PD-L1 expression) demonstrated an ORR benefit compared to historical control the results appear to be driven primarily by patients with IC2/3 expression.

The updated efficacy data (ORR and DOR) from the exploratory study PCD4989 (UC cohort) at the 31 March 2016 cut-off date (n = 94) were consistent with the data from the primary analysis at the 2 December 2014 data cut-off with a minimum follow-up of 12 weeks (n = 87, OR-evaluable population).

Non-small cell lung cancer

After consideration of the responses to the clinical questions it is considered that the benefits of atezolizumab for the proposed usage in patients with NSCLC are favourable.

The data from the pivotal Phase III study (OAK) submitted with the sponsor's post-first round report confirmed the promising benefits associated with atezolizumab observed in the supportive Phase II studies POPLAR, BIRCH and FIR. The data from OAK support the benefits of atezolizumab for the treatment of patients with 2L+ NSCLC regardless of PD-L1 expression on immune-infiltrating cells or tumour-cells. The benefits of treatment with atezolizumab compared to docetaxel observed in OAK are summarised below.

Overall survival (OS); primary efficacy endpoint

The two co-primary endpoints of OS in the primary population and the TC1/2/3 or IC1/2/3 subgroup both showed statistically significant and clinically meaningful improvements in survival in the atezolizumab arm compared to the docetaxel arm.

In the primary population (ITT), median OS was 4.2 months longer in the atezolizumab arm than in the docetaxel arm, and the difference between the two treatment arms was both statistically significant and clinically meaningful. The median OS was 13.8 months (95% CI: 11.8, 15.7) in the atezolizumab arm and 9.6 months (95% CI: 8.6, 11.2) in the docetaxel arm, with death being reported in 63.8% (271/425) and 70.1% (298/425) of patients in the two treatment arms, respectively. The stratified HR was 0.73 (95% CI: 0.62, 0.87; p = 0.0003, log-rank), which represents a 27% relative reduction in the risk of death in the atezolizumab arm compared to the docetaxel arm. The 12-month OS rate was 54.7% in the atezolizumab arm and 41.1% in the docetaxel arm, and the 24-month OS rates were 29.2% and 20.6% in the two treatment arms, respectively. The Kaplan-Meier plot showed

clear separation of the survival curves from approximately 3 months onwards in favour of atezolizumab compared to docetaxel.

In the TC1/2/3 or IC1/2/3 subgroup, median OS was 5.4 months longer in the atezolizumab arm than in the docetaxel arm, and the difference between the two treatment arms was both statistically significant and clinically meaningful. The median OS was 15.7 months (95% CI: 12.6, 18.0) in the atezolizumab arm and 10.3 months (95% CI: 8.8, 12.0) in the docetaxel arm, with death being reported in 62.7% (151/241) and 67.1% (149/222) of patients in the two treatment arms, respectively. The stratified HR was 0.74 (95% CI: 0.58, 0.93; $p = 0.0102$, log-rank), which represents a 26% relative reduction in the risk of death in the atezolizumab arm compared to the docetaxel arm. The 12-month OS rate was 58.0% in the atezolizumab arm and 42.8% in the docetaxel arm, and the 24-month OS rates were 29.8% and 24.8% in the two treatment arms, respectively. The Kaplan-Meier plot showed clear separation of the survival curves from approximately 3 months onwards in favour of atezolizumab compared to docetaxel.

The median OS was longer in the atezolizumab arm than in the docetaxel arm in the PD-L1 expression subgroups TC3 or IC3, TC2/3 or IC2/3 and TC0 and IC0, and the differences between the two treatment arms were considered to be clinically meaningful in each of these subgroups. The OS benefit associated with atezolizumab was positively related to PD-L1 expression, with the greatest survival benefit being observed in patients with the highest PD-L1 expression (TC3 or IC3 subgroup).

Of particular note, in patients with no or low PD-L1 expression (TC0 and IC0 subgroup) the median OS was 3.7 months longer in the atezolizumab arm than in the docetaxel arm. The median OS was 12.6 months (95% CI: 9.6, 15.2) in the atezolizumab arm and 8.9 months (95% CI: 7.7, 11.5) in the docetaxel arm, with death being reported in 64.4% (116/180) and 73.4% (146/199) of patients in the two treatment arms, respectively. The unstratified HR was 0.75 (95% CI: 0.59, 0.96; $p = 0.0215$, log-rank), which represents a 25% relative reduction in the risk of death in the atezolizumab arm compared to the docetaxel arm. The 12-month OS rate was 51.0% in the atezolizumab arm and 40.1% in the docetaxel arm, and the 24-month OS rates were 29.8% and 17.2% in the two treatment arms, respectively.

The OS results for the TC0 and IC0 subgroup support approval of atezolizumab for the proposed usage irrespective of PD-L1 expression status, although a greater survival benefit can be anticipated in patients expressing higher PD-L1 expression.

The OS benefit was greater in the atezolizumab arm than in the docetaxel arm for both non-squamous and squamous cell NSCL. The unstratified HR was similar for the two histological subgroups, but the numerical difference in median OS between the two treatment arms was greater for patients with non-squamous histology compared to patient with squamous histology. In patients with non-squamous NSLC, the median OS was 11.2 months (95% CI: 9.3, 12.6) in the docetaxel arm and 15.6 months (95% CI: 13.3, 17.6) in the atezolizumab arm (unstratified HR = 0.73 (95% CI: 0.60, 0.89)). In patients with squamous NSLC, the median OS was 7.7 months (95% CI: 6.3, 8.9) in the docetaxel arm and 8.9 months (95% CI: 7.4, 12.8) in the atezolizumab arm (unstratified HR = 0.73 (95% CI: 0.54, 0.98)).

In addition to the histology subgroups, an OS survival benefit for atezolizumab relative to docetaxel was seen in the majority of other clinically relevant subgroups, including age, sex, race, ECOG status, number of prior therapies, brain metastases, and tobacco use history. However, patients with EGFR mutation-positive disease or KRAS mutation-positive disease treated with atezolizumab did not experience improvement in OS compared to docetaxel.

While an OS benefit was observed with atezolizumab in the majority of subgroups the results in some of the subgroups should be interpreted cautiously due to small patient numbers and/or wide 95% CIs for the hazard ratios.

Progression free survival (PFS); secondary efficacy endpoint

In contrast to OS, the median duration of PFS was shorter in the atezolizumab arm than in the docetaxel arm for both the primary population (ITT) and the TC1/2/3 or IC1/2/3 subgroup. However, the differences in PFS between the two treatment arms in both patient populations were not statistically significant or clinically meaningful. The reason for the OS benefit in the atezolizumab arm compared to docetaxel not translating into a similar PFS benefit is unknown, but appears to be related to a higher incidence of disease progression in the atezolizumab arm than in the docetaxel arm.

In the primary population (ITT), the median duration of PFS (investigator-assessed; RECIST v1.1) was 1.2 months longer in the docetaxel arm than in the atezolizumab arm (4.0 months (95% CI: 3.3, 4.2) versus 2.8 months (95% CI: 2.6, 3.0)). However, the difference between the two treatment arms was not statistically significant (stratified HR = 0.95 (95% CI: 0.82, 1.10)); $p = 0.4928$, log-rank), and is considered not to be clinically meaningful. The percentage of patients with a PFS event was 89.4% (380/425) in the atezolizumab arm ($n = 48$ death; $n = 332$ disease progression) and 88.2% (375/425) in the docetaxel arm ($n = 85$ death; $n = 290$ disease progression). The PFS event free rate at 12 months was 18.2% in the atezolizumab arm and 10.7% in the docetaxel arm, and the 24-month PFS event free rates were 8.5% and 1.9% in the two treatment arms, respectively.

In the TC1/2/3 or IC1/2/3 subgroup, the median duration of PFS (investigator-assessed; RECIST v1.1) was 1.3 months longer in the docetaxel arm than in the atezolizumab arm (4.1 months (95% CI: 2.9, 4.3) versus 2.8 months (95% CI: 2.6, 4.0)). However, the difference between the two treatment arms was not statistically significant (stratified HR = 0.91 (95% CI: 0.74, 1.12)); $p = 0.3806$, log-rank), and is considered not to be clinically meaningful. The percentage of patients with a PFS event was 89.6% (216/241) in the atezolizumab arm ($n = 27$ death; $n = 189$ disease progression) and 86.9% (193/222) in the docetaxel arm ($n = 44$ death; $n = 149$ disease progression). The PFS event free rate at 12 months was 19.0% in the atezolizumab arm and 12.4% in the docetaxel arm, and the 24-month PFS event free rates were 8.2% and 2.3% in the two treatment arms, respectively.

Objective response rate (ORR); secondary efficacy endpoints

In contrast to OS, the ORR did not significantly differ between the atezolizumab and the docetaxel treatment arms in either the primary population (ITT) or the TC1/2/3 or IC1/2/3 subgroup.

In the primary population (ITT), the ORR (investigator-assessed; RECIST v1.1) was similar in the atezolizumab and docetaxel arms (13.6% (58/425) versus 13.4% (57/425), respectively, $p = 0.9209$, CMH). Of the 58 responders in the atezolizumab arm, 6 were complete responders and 52 were partial responders and of the 57 responders in the docetaxel arm, 1 was a complete responder and 56 were partial responders. The number of patients with missing values was notably higher in the docetaxel arm than in the atezolizumab arm ($n = 74$ (17.4%) versus $n = 30$ (7.1%)), respectively).

In the TC1/2/3 or IC1/2/3 subgroup, the ORR (investigator-assessed; RECIST v1.1) was similar in the atezolizumab and docetaxel arms (17.8% (43/241) versus 16.2% (36/222), respectively, $p = 0.6425$, CMH). Of the 43 responders in the atezolizumab arm, 5 were complete responders and 38 were partial responders and of the 36 responders in the docetaxel arm, 1 was a complete responder and 35 were partial responders. The number of patients with missing values was notably higher in the docetaxel arm than in the atezolizumab arm ($n = 42$ (18.9%) versus $n = 17$ (7.1%)), respectively).

Duration of response (DOR); secondary efficacy endpoint

Although the ORR did not significantly differ between the atezolizumab and docetaxel treatment arms in either the primary population (ITT) or the TC1/2/3 or IC1/2/3 subgroup, the median DOR was notably longer in the atezolizumab arm than in the docetaxel arm in both patient populations.

In the primary population (ITT), the median DOR (investigator-assessed; RECIST v1.1) was 10.1 months longer in the atezolizumab arm than in the docetaxel arm. The median DOR was 16.3 months (95% CI: 10.1, NE) in the atezolizumab arm and 6.2 months (95% CI: 4.9, 7.6) in the docetaxel arm (stratified HR = 0.31 (95% CI: 0.18, 0.55); $p < 0.0001$, log-rank). At the time of the clinical cut-off date, 51.7% of atezolizumab responders were ongoing compared to 17.5% of docetaxel responders. Examination of the Kaplan-Meier plot showed clear separation of the curves in favour of atezolizumab compared to docetaxel from approximately 3 months onwards.

In the TC1/2/3 or IC1/2/3 subgroup the median DOR (investigator-assessed; RECIST v1.1) was 9.8 months longer in the atezolizumab arm than in the docetaxel arm. The median DOR was 16.0 months (95% CI: 9.7, NE) in the atezolizumab arm and 6.2 months (95% CI: 4.9, 9.2) in the docetaxel arm (stratified HR = 0.31 (95% CI: 0.15, 0.62); $p = 0.0006$, log-rank). At the time of the clinical cut-off date, 46.5% of atezolizumab responders were ongoing compared to 11.1% of docetaxel responders. Examination of the Kaplan-Meier plot showed clear separation of the curves in favour of atezolizumab compared to docetaxel from approximately 4 months onwards.

Patient reported outcomes (PROs); secondary objectives

Completion rates for PRO assessment instruments in both arms were consistently high over the course of treatment. The average global health status and functioning scores (that is, physical, role, social, emotional, and cognitive) as measured by the EORTC QLQ-C30 did not show clinically meaningful deterioration over time in either of the two treatment arms, suggesting maintained HRQoL and patient-reported functioning for patients remaining on treatment.

Patients in both the atezolizumab and docetaxel arms did not show clinically meaningful worsening in commonly reported cancer treatment-related symptoms of fatigue, nausea/vomiting, diarrhoea, constipation and sore mouth. However, patients in the docetaxel arm demonstrated clinically meaningful worsening in alopecia and peripheral neuropathy throughout treatment, while no clinically worsening of these two outcomes were observed in patients in the atezolizumab arm.

Patients in the atezolizumab arm demonstrated prolonged time until the deterioration of patient-reported chest pain compared to patients in the docetaxel arm (stratified HR = 0.72 (95% CI: 0.55, 0.93)). The median time to clinically meaningful deterioration in chest pain severity was 8.3 months in the docetaxel arm compared to 18.0 months in the atezolizumab arm. These findings are consistent with the supportive analyses relating to chest pain which suggest that patients in the atezolizumab arm were experiencing less chest pain severity at the time of radiographic disease progression per RECIST v1.1 compared to patients in the docetaxel arm.

Second round assessment of risks***Urothelial carcinoma***

After consideration of the additional safety data in the post-first round response, the risks of atezolizumab for the proposed usage in patients with UC are unchanged from those identified in this CER. It is considered that the risks of atezolizumab for the proposed usage in patients with UC are satisfactory.

Non-small cell lung cancer

After consideration of the responses to the clinical questions it is considered that the risks of atezolizumab for the proposed usage in patients with NSCLC are satisfactory and are consistent with the risks described in the first round assessment.

The risks of treatment with atezolizumab in patients with NSCLC have been updated by the safety data from OAK in 1187 patients, including 609 patients in the atezolizumab arm and 578 patients in the docetaxel arm. In addition, a total of 1636 patients have been exposed to at least one dose of atezolizumab in the NSCLC clinical trial program, based on the safety data in atezolizumab-treated patients from the Phase III study OAK (n = 609), the Phase II studies BIRCH (n = 659), POPLAR (n = 142) and FIR (n = 137) and the NSCLC cohort of the Phase I study PCD4989g (n = 89). Overall, it is considered that the risks of treatment with atezolizumab for the proposed usage in patients with NSCLC are acceptable, and that the safety profile of the atezolizumab for the proposed usage is favourable compared to docetaxel.

In OAK, the median short duration of exposure in both treatment arms is a limitation of the safety data and precludes assessment of the long-term risks associated with atezolizumab (3.4 months, atezolizumab versus 2.1 months, docetaxel). The median number of treatment doses administered in the study was smaller in the docetaxel arm than in the atezolizumab arm (4.0 versus 6.0, respectively), as was the number of patients treated for at least 6 months (n = 65, 11.2% versus n = 202, 33.2%) and for at least 12 months (n = 14, 2.4% versus n = 125, 20.5%). Overall, the short duration of exposure to treatment, the relatively small number of doses administered, and the small number of patients exposed for at least 6 and 12 months is not unexpected in patients with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen.

OAK – risk assessment

The comparative risks of treatment with docetaxel or atezolizumab for the proposed usage in patients with NSCLC based on the safety data from OAK are outlined below. The comparative risks of the two treatments should be interpreted with regard to the longer median duration of exposure in the atezolizumab arm compared to the docetaxel arm (3.4 versus 2.1 months, respectively).

Adverse events irrespective of relationship to treatment

Nearly all patients in both the docetaxel arm and the atezolizumab arm experienced at least one AE (96.0% (555/578), 5905 events versus 94.1% (573/609), 5225 events, respectively). The most commonly reported AEs reported in $\geq 5\%$ of patients in either treatment arm (docetaxel versus atezolizumab), in descending order of frequency in the docetaxel arm, were: fatigue (35.5% versus 26.8%); alopecia (34.9% versus 0.5%); diarrhoea (24.4% versus 15.4%); anaemia (23.5% versus 11.5%); decreased appetite (23.5% versus 23.5%); nausea (22.7% versus 17.7%), and cough (18.2% versus 23.2%).

AEs reported in $\geq 5\%$ more patients in the docetaxel arm than in the atezolizumab arm were: fatigue (35.5% versus 26.8%); alopecia (34.9% versus 0.5%); diarrhoea (24.4% versus 15.4%); anaemia (23.5% versus 11.5%); nausea (22.7% versus 17.7%); myalgia (15.7% vs. 6.4%); neutropaenia (15.6% versus 1.6%); oedema peripheral (14.2% versus 8.9%); neuropathy peripheral (11.2% versus 3.9%); stomatitis (10.9% versus 3.1%); febrile neutropaenia (10.7% versus 0.2%); dysgeusia (10.0% versus 3.0%); neutrophil count decreased (9.5% versus 0.3%); peripheral sensory neuropathy (7.4% versus 1.0%); mucosal inflammation (7.1% versus 1.5%); and nail disorder (5.2% versus 0%).

AEs reported in $\geq 5\%$ more patients in the atezolizumab arm than in the docetaxel arm were cough (23.2% versus 18.2%) musculoskeletal pain (10.5% versus 4.3%) and pruritus (8.2% versus 3.1%). The adjusted rates for patient-years at risk in the docetaxel

arm and the atezolizumab arm for musculoskeletal pain were 14.12 and 20.75 events per 100 patient-years at risk, respectively, and for pruritus were 15.17 and 21.03 events per 100 patient-years, respectively.

Treatment-related adverse events

The risk of experiencing at least one treatment-related AEs was notably greater in the docetaxel arm than in the atezolizumab arm (85.8% (496/578) versus 64.0% (390/609)). The most commonly reported treatment-related AEs reported in $\geq 10\%$ of patients in either of the two treatment arms (docetaxel versus atezolizumab), in descending order of frequency in the docetaxel arm, were: alopecia (34.3% versus 0.5%); fatigue (30.6% versus 14.3%); decreased appetite (20.1% versus 8.5%); anaemia (19.7% versus 3.9%); nausea (19.4% versus 8.7%); diarrhoea (18.9% versus 7.7%); asthenia (16.6% versus 8.4%); neutropaenia (14.7% versus 1.1%); myalgia (14.0% versus 3.4%); febrile neutropaenia (10.6% versus 0%); stomatitis (10.2% versus 2.1%); and neuropathy peripheral (10.0% versus 1.0%). Each of the 12 treatment-related AEs reported in $\geq 10\%$ of patients in either of two treatment arms were reported more frequently in the docetaxel arm than in the atezolizumab arm.

Risk of Grade ≥ 3 adverse events

The risk of experiencing at least one Grade ≥ 3 AEs, irrespective of relationship to treatment, was greater in the docetaxel arm than in the atezolizumab arm (56.1% (324/578) versus 38.9% (237/609), respectively). The difference was primarily due to the higher incidence of Grade 3 or 4 AEs in the docetaxel arm than in the atezolizumab arm (53.6% (310/578) versus 37.3% (227/609), respectively). Grade 5 AEs were reported in a comparable proportion of patients in both treatment arms (2.4% (14/578) docetaxel versus 1.6% (10/609) atezolizumab).

Grade ≥ 3 AEs, irrespective of relationship to treatment reported in $\geq 5\%$ of patients in either treatment arm (docetaxel versus atezolizumab), in descending order of frequency in the docetaxel arm, were: neutropaenia (13.0% versus 0.5%); febrile neutropaenia (10.7% versus 0.2%); neutrophil count decreased (9.0% versus 0.2%); anaemia (5.7% versus 3.4%); and pneumonia (5.4% versus 3.4%). Each of the 5 Grade ≥ 3 AEs reported in $\geq 5\%$ of patients in each treatment arm were reported more frequently in the docetaxel arm than in the atezolizumab arm.

Risk of death

The risk of death due to an AE within 30 days of the last dose of the study drug was comparable in the two treatment arms (2.4% (14/578) docetaxel versus 1.6% (10/609) atezolizumab). Grade 5 AEs reported in at least 2 patients in either treatment arm (docetaxel versus atezolizumab) were pneumonia (2 versus 1), sepsis (1 versus 2), respiratory tract infection (2 versus 0), and sudden death (2 versus 1). No Grade 5 AE was reported in 3 or more patients in either treatment arm. One patient in the docetaxel arm experienced a Grade 5 respiratory tract infection, which was considered by the investigator to be treatment-related.

The risk of death due to an AE occurring more than 30 days after the last dose of the study drug was comparable in the two treatment arms (1.7% (10/578) docetaxel versus 2.5% (15/609) atezolizumab). Grade 5 AEs reported in at least 2 patients in either treatment arm (docetaxel versus atezolizumab) were death (3 versus 5) and sepsis (1 versus 2). No patient in either treatment arm experienced a fatal AE that was considered by the investigator to be related to treatment.

Risk of SAEs

The risk of experiencing at least one SAE, within the 30-day treatment window and irrespective of relationship to treatment, was similar in the two treatment arms (31.3% (181/378) docetaxel versus 31.9% (194/609) atezolizumab). SAEs reported in $\geq 2\%$ of

patients in either treatment arm (docetaxel versus atezolizumab), in descending order of frequency in the docetaxel arm, were: febrile neutropaenia (6.4% versus 0%); pneumonia (5.4% versus 3.3%); dyspnoea (1.4% versus 2.0%); and pleural effusion (1.0% versus 0%).

The risk of experiencing at least one treatment-related SAE up to the data cut-off date was greater in the docetaxel arm than in the atezolizumab arm (17.6% (102/578) versus 10.3% (63/609), respectively). Treatment-related SAEs reported in $\geq 1\%$ of patients in either treatment arm (docetaxel versus atezolizumab) were: febrile pneumonia (6.2% versus 0%); pneumonia (1.9% versus 0.3%); diarrhoea (1.0% versus 0%); and pneumonitis (0% versus 1.0%).

Risk of experiencing an AE leading to withdrawal of study treatment

The risk of withdrawing from study treatment due to AEs was notably greater in the docetaxel arm than in the atezolizumab arm (18.7% (108/578) versus 7.6% (46/609), respectively). AEs resulting in withdrawal from treatment reported in $\geq 1\%$ of patients in either treatment arm (docetaxel versus atezolizumab), in descending order of frequency in the docetaxel arm, were: fatigue (2.6% versus 0.2%); paraesthesia (1.9% versus 0%); neuropathy peripheral (1.7% versus 0%); asthenia (1.7% versus 0%); pneumonia (1.2% versus 0.5%); dyspnoea (1.0% versus 0.2%); and oedema peripheral (1.0% versus 0%). Each of the 7 most commonly reported AEs leading to treatment withdrawal occurred more frequently in patients in the docetaxel arm than in the atezolizumab arm.

Risk of AEs leading to dose modification

In both treatment arms, the risk of AEs leading to dose modification was notably higher than the risk of AEs resulting in withdrawal from treatment. This finding suggests that AEs were generally manageable by dose modification rather than treatment discontinuation. In OAK, dose reductions for management of AEs were allowed for docetaxel but not for atezolizumab, while dose delays, skipped cycles and infusion interruptions for AEs were allowed in both treatment arms.

The risk of AEs leading to dose modification was notably greater in patients in the docetaxel arm than in the atezolizumab arm (36.3% (210/578) versus 25.0% (152/609), respectively). AEs resulting in dose modification reported in $\geq 1\%$ of patients in either treatment arm (docetaxel versus atezolizumab), in descending order of frequency in the docetaxel arm, were: febrile neutropaenia (6.2% versus 0%), neutropaenia (4.2% versus 0.2%); fatigue (3.1% versus 1.1%); neutrophil count decreased (2.9% versus 0.2%); asthenia (2.1% versus 0.8%); diarrhoea (1.9% versus 0.8%); pneumonia (1.7% versus 2.1%); anaemia (1.6% versus 0.3%); respiratory tract infection (1.4% versus 1.0%); leukopaenia (1.2% versus 0%); neuropathy peripheral (1.2% versus 0.2%); peripheral sensory neuropathy (1.2% versus 0%); pyrexia (1.0% versus 1.0%); oedema peripheral (1.0% versus 0.2%); dyspnoea (1.0% versus 1.6%); decreased appetite (1.0% versus 0.2%); and back pain (0% versus 1.3%).

Risk of experiencing AESIs

The risk of experiencing an AESI up to the data cut-off date was greater in the atezolizumab arm than in the docetaxel arm (30.2% (184/609) versus 22.8% (132/578), respectively). AESIs reported in $\geq 1\%$ of patients in either treatment arm (docetaxel versus atezolizumab) and in descending order of frequency in the docetaxel arm were: neurologic reactions (11.8% versus 4.6%); dermatologic reactions (10.4% versus 14.4%); hepatic reactions (2.6% versus 8.2%); pulmonary reactions (0.7% versus 1.8%); and endocrine reactions (0.3% versus 5.6%). Of note, neurologic reactions were reported more frequently in the docetaxel arm than in the atezolizumab arm, while dermatologic, hepatic, endocrine, and pulmonary reactions were all reported more frequently in the atezolizumab arm than in the docetaxel arm. Ocular, musculoskeletal and joint,

gastrointestinal, cardiac, renal, haematologic and other non-specific immune reactions categorised as AESIs were reported in $\leq 1\%$ of patients in either of the two treatment arms and in a similar proportion of patients in the two arms. The risk of experiencing dermatologic, hepatic, endocrine, pulmonary and neurologic reactions of special interest are reviewed in more detail below.

Dermatologic reactions were reported less frequently in patients in the docetaxel arm than in the atezolizumab arm (10.4% versus 14.4%). The majority of dermatologic reactions were Grade 1 or 2 in severity, with no patients in the docetaxel arm experiencing a Grade 3 event and 4 (0.7%) patients in the atezolizumab arm experiencing a Grade 3 event (rash x 2, maculopapular rash x 1, and pemphigoid x 1). Dermatologic reactions (MedDRA PT, any Grade) reported in $\geq 1\%$ of patients in either treatment arm (docetaxel versus atezolizumab) were: rash (8.5% versus 9.7%); rash maculopapular (0.9% versus 1.0%); and eczema (0.5% versus 1.1%).

Hepatic reactions were reported less frequently in patients in the docetaxel arm than in the atezolizumab arm (2.6% versus 8.2%). The majority of hepatic reactions were Grade 1 or 2 in severity, and Grade ≥ 3 AEs were reported in 3 (0.5%) patients in the docetaxel arm and 13 (2.1%) patients in the atezolizumab arm. The Grade ≥ 3 AEs reported in the docetaxel arm were AST increased (2x Grade 3), ALT increased (2x Grade 3) and bilirubin increased (2x Grade 3). The Grade ≥ 3 AEs reported in the atezolizumab arm were AST increased (5x Grade 3), ALT increase (6x Grade 3), bilirubin increased (1x Grade 4), and hepatitis (1x Grade 4). Hepatic reactions (MedDRA PT AEs (any grade)) reported in $\geq 1\%$ of patients in either treatment arm (docetaxel versus atezolizumab) were AST increased (2.1% versus 6.2%), ALT increased (2.4% versus 5.7%), and bilirubin increased (0.3% versus 1.1%).

Endocrine reactions were reported less frequently in the docetaxel arm than in the atezolizumab arm (0.3% versus 5.6%). All endocrine reactions except one were Grade 1 or 2 in severity, with the exception being pancreatitis (Grade 3) in one patient in the atezolizumab arm. Endocrine reactions (MedDRA PT AEs (any grade)) reported in $\geq 1\%$ of patients in either treatment arm (docetaxel versus atezolizumab) were hypothyroidism (0.2% versus 3.0%), TSH increased (0.2% versus 1.0%), and hyperthyroidism (0% versus 1.1%).

Pulmonary reactions were reported less frequently in the docetaxel arm than in the atezolizumab arm (0.7% versus 1.8%). In both treatment arms, pulmonary reactions were mainly Grade 1 or 2 in severity, with Grade 3 AEs being reported in 2 (0.3%) patients in the docetaxel arm (2x pneumonitis) and 5 (0.8%) patients in the atezolizumab arm (4 x pneumonitis, and 1x organising pneumonia). The only pulmonary reaction (MedDRA PT AEs (any grade)) reported in $\geq 1\%$ of patients in either treatment arm (docetaxel versus atezolizumab) was pneumonitis (0.7% versus 1.0%).

Neurologic reactions were reported more frequently in the docetaxel arm than in the atezolizumab arm (11.8% versus 4.6%). The majority of neurologic reactions in both treatment arms were Grade 1 or 2 in severity, with Grade 3 AEs being reported in 7 (1.2%) patients in the docetaxel arm (7x peripheral neuropathy) and 3 (0.5%) patients in the atezolizumab arm (3x Guillain-Barre syndrome). The only neurologic reaction (MedDRA PT AEs (any grade)) reported in $\geq 1\%$ of patients in either treatment arm (docetaxel versus atezolizumab) was neuropathy peripheral (11.2% versus 3.9%).

Risk of experiencing imAEs

The risk of experiencing an immune-mediated AE requiring the use of systemic corticosteroids (imAE) up to the data cut-off date was greater in the atezolizumab arm than in the docetaxel arm (12.6% [77/609] versus 9.5% [77/609], respectively). ImAEs reported in $\geq 1\%$ of patients in either treatment arm (docetaxel versus atezolizumab), in descending order of frequency in the docetaxel arm, were: neuropathy peripheral (4.3%

versus 0%); rash (3.6% versus 1.3%); ALT increased (0.9%, versus 1.0%); pneumonitis (0.7% versus 1.0%); and dyspnoea (0.2% versus 1.1%). In the docetaxel arm, imAEs Grade 3-4 in severity were reported in 6 (1.1%) patients and in the atezolizumab arm imAEs Grade 3-4 in severity were reported in 38 (6.2%) of patients.

Approximately three-quarters of patients with imAEs were captured in the AESI analysis, with 101 of the 132 patients with imAEs (76.5%) being described as having AESIs. Of the 101 patients captured in both AE categories (55 docetaxel-treated patients and 46 atezolizumab-treated patients), 79.2% experienced Grade 1 or 2 events and 20.8% experienced Grade 3 or 4 events.

Among all safety evaluable patients, 5 (0.9%) patients in the docetaxel arm and 16 (2.6%) patients in the atezolizumab arm experienced Grade 3 or 4 events that were reported in both the AESIs and imAEs analyses. The following Grade 3 or 4 events were reported in no docetaxel-treated patients and 1-2 (0.2%-0.3%) atezolizumab-treated patients: rash, pemphigoid, Guillain-Barre syndrome, optic neuritis, transaminases increased, hepatitis, systemic inflammatory response syndrome, and Henoch-Schonlein purpura nephritis. In addition, Grade 3 or 4 pneumonitis was reported in 2 (0.3%) patients in the docetaxel arm and 4 (0.7%) patients in the atezolizumab arm. Grade 3 or 4 events reported in more docetaxel-treated patients than atezolizumab-treated patients (greater by 1 patient) were peripheral neuropathy, ALT increased, AST increased, and blood bilirubin increased.

Among the Grade 3 or 4 imAEs that were not captured in the AESI analysis, the following events were reported in no docetaxel-treated patients and 1-2 (0.2%-0.3%) atezolizumab-treated patients: hypoxia, acute respiratory failure, pruritus, dermatitis bullous, drug eruption, erythema multiforme, meningitis, encephalitis, pneumonia, diarrhoea, drug-induced liver injury, hepatic function abnormal, hepatitis acute, hypersensitivity, myalgia, neuralgia, retinopathy, and hyperglycaemia. In addition, Grade 3 or 4 dyspnoea was reported in 1 patient (0.2%) in the docetaxel arm and 2 patients (0.3%) in the atezolizumab arm. Only the event of respiratory failure was reported in more docetaxel-treated patients than atezolizumab-treated patients (1 patient and 0 patients, respectively).

Risk of developing immune disorder (MedDRA, SOC)

The risk of developing an immune disorder (MedDRA, SOC), irrespective of relationship to the study drug, was 2.8% (16/578) in the docetaxel arm and 1.6% (10/609) in the atezolizumab arm. The AEs (MedDRA PT) of clinical interest in the treatment arms (docetaxel versus atezolizumab) were: hypersensitivity (1.9% versus 1.0%); drug hypersensitivity (0.5% versus 0.5%); and anaphylactic reaction (0.3% versus 0%).

Risk of developing laboratory test abnormalities

There were no clinically relevant changes in mean and median values for haematology and blood chemistry laboratory safety parameters during the study. Clinically relevant shifts in laboratory parameters were defined as shifts from Grade 0, 1, or 2 at baseline to Grade 3 or 4 post baseline. Clinically relevant shifts in haematology parameters to low absolute total neutrophil count, low white blood cell count and low absolute lymphocyte count occurred notably more frequently in the docetaxel arm than in the atezolizumab arm. No notable differences between the two treatment arms were reported for clinical chemistry shifts.

Risk of developing ATAs

The baseline prevalence of ATAs was 3.5% (21/593) in all atezolizumab-treated patients. Post-baseline, 30.4% (172/565) of atezolizumab-treated patients had treatment-emergent ATAs (that is, ATA positive, the sum of treatment-induced ATA and treatment-enhanced ATA). Of these 172 ATA-positive patients, 171 (99.4%) had 'treatment-induced' ATA responses and 1 (0.6%) had a 'treatment-enhanced' ATA response. Of the 171 patients

with 'treatment-induced' ATA responses, 98 (57.3%) had transient ATA responses and 73 (42.7%) had a persistent response. There were no clinically meaningful differences in efficacy or safety outcomes between ATA-positive and ATA-negative patients.

Risk of developing clinically significant changes in vital signs or ECG findings

In Oak, ECG recordings were obtained during screening and when clinically indicated. No systematic assessment of ECG changes were undertaken during the course of the study. At screening, 1 patient in the docetaxel arm and 3 patients in the atezolizumab arm were reported to have a clinically significant ECG abnormality. Post-baseline, one patient in the atezolizumab arm had a clinically significant ECG abnormality on Day 128 after 6 doses of atezolizumab (Grade 2 non-serious AE 'electrocardiogram QT prolonged'). The patient had a non-clinically significant ECG abnormality at baseline, together with atrial fibrillation and hypertension as part of her past medical history. The investigator considered the AE to be unrelated to study treatment and related to concurrent illness. Study treatment was interrupted and the event resolved after 2 days. The patient had a non-clinically significant abnormal ECG on Day 387, but did not experience any other ECG-related AEs.

Vital signs included heart rate, respiratory rate, blood pressure, and temperature. At all infusions, vital signs (heart rate, respiratory rate, blood pressures, and temperature) were determined within 60 minutes before and 30 ± 10 minutes after the infusion. Vital signs were also collected during the first infusion (every 15 ± 5 minutes). During subsequent infusions, vital signs were collected if clinically indicated. Overall, atezolizumab treatment had no clinically meaningful effect on vital signs. Both systolic and diastolic blood pressure showed small median decreases or increases in comparison with baseline for patients receiving atezolizumab.

Risks in special populations

Overall, the safety profiles of the docetaxel and atezolizumab arms were similar across the PD-L1 expression subgroups and between histology subgroups (squamous and non-squamous).

There were no comparative subgroup safety data based on age, gender or race.

Second round assessment of benefit-risk balance

Urothelial carcinoma

After consideration of the additional efficacy data for atezolizumab for the proposed usage in patients with UC and the totality of the safety data for atezolizumab in patients with UC and NSCLC, the benefit-risk balance for atezolizumab for the proposed usage in patients with UC remains unfavourable. The promising benefits of atezolizumab for the proposed usage in patients with UC demonstrated in the single-arm Phase II study IMvigor (Cohort 2) require confirmation in a pivotal Phase III study comparing the efficacy and safety of atezolizumab with an appropriately justified control in the target UC population.

Non-small cell lung carcinoma

After consideration of the additional efficacy and safety data from the pivotal, confirmatory Phase III study (OAK) for atezolizumab for the proposed usage in patients with NSCLC and the totality of the safety data for atezolizumab in patients with UC and NSCLC, the benefit-risk balance for atezolizumab for the proposed usage in patients with UC is favourable.

Second round recommendation regarding authorisation

Urothelial carcinoma

Approval of atezolizumab is *not recommended* for the treatment of patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy. The reasons for this recommendation are provided the first round assessment.

Non-small cell lung cancer

Approval of atezolizumab *is recommended* for the treatment of patients with locally advanced or metastatic NSCLC with progression on or after prior chemotherapy.

The proposed wording of the indication differs from that being proposed by the sponsor, but is considered to more closely reflect the relevant NSCLC population in the relevant Phase III and Phase II studies supporting approval in this patient population.

Population pharmacokinetics

Scope of the dossier

The data provided for evaluation included one validation study (Study PopPK-1067735), the original population pharmacokinetic data files used in the study and descriptive files. In addition there were two exposure response studies for evaluation (Study Exp-1068603 and Study Exp-1068447). The following study reports were also provided for background information: Study PopPK-1066935, Study PopPK-1067394, Study Exp-1067242 and Study Exp-1068446.

Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetic data supplied to the evaluator support the dosing regimen proposed by the sponsor and the pharmacokinetic information in the PI document. The sponsor has conducted extensive modelling and simulation in support of the dosing regimen. The population pharmacokinetic model developed in Study PopPK-1067735 was successfully validated in Study PopPK-1067735. The exposure response Studies Exp-1068603 and Exp-1068447, supported the dosing regimen proposed by the sponsor.

Evaluator's overall conclusions on pharmacodynamics

The dose response studies evaluated in this report support the dosing strategy proposed by the sponsor and the pharmacodynamic information presented in the PI.

Dosage selection for the pivotal studies

Not applicable to the population pharmacokinetic evaluation.

Clinical efficacy

Not applicable to the population pharmacokinetic evaluation.

Clinical safety

Not applicable to the population pharmacokinetic evaluation.

First round benefit-risk assessment

First round assessment of benefits

See Table 8.

Table 8: First round assessment of benefits

Indication	
Benefits	Strengths and Uncertainties
Atezolizumab has a demonstrable exposure response relationship between AUC _{SS} and objective response rate	The evidence supporting this is strong.

First round assessment of risks

See Table 9.

Table 9: First round assessment of risks

Risks	Strengths and Uncertainties
Atezolizumab has a demonstrable exposure response relationship between AUC _{SS} and adverse events of special interest	The evidence supporting this is strong.

First round assessment of benefit-risk balance

The data presented for population pharmacokinetic evaluation support a favourable benefit risk balance.

First round recommendation regarding authorisation

The population pharmacokinetic evaluator has no objection to authorisation arising from the population pharmacokinetic data.

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation³⁰

- The sponsor has submitted EU-RMP version 1.0 (dated 24 March 2016; data lock point (DLP) 25 February 2016) and Australian-Specific Annex (ASA) version 1.0 (dated May 2016) in support of this application. In its post-first round response, the

³⁰ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

sponsor did not submit updated versions of the EU-RMP or ASA but has committed to making changes to the summary of safety concerns as recommended by the RMP Evaluator in the next version of the EU RMP and ASA.

- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below. Changes agreed to by the sponsor in its post-first round response are highlighted.

Table 10: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Immune-related hepatitis	Ü	-	Ü	Ü*
	Immune-related pneumonitis	Ü	-	Ü	Ü*
	Immune-related colitis	Ü	-	Ü	Ü*
	Immune-related pancreatitis	Ü	-	Ü	Ü*
	Immune-related endocrinopathies: <ul style="list-style-type: none"> • Diabetes mellitus • Hypothyroidism • Hyperthyroidism • Adrenal insufficiency 	Ü	-	Ü	Ü*
	Immune-related neuropathies: <ul style="list-style-type: none"> • Guillain-Barré syndrome • Myasthenic syndrome / myasthenia gravis 	Ü	-	Ü	Ü*
	Immune related meningoencephalitis	Ü	-	Ü	Ü*
Important potential risks	Infusion-related reactions	Ü	-	Ü	Ü*
	Embryofetal toxicity	Ü	-	Ü	-
	Anti-therapeutic antibodies	Ü	Ü	Ü	-
	Immune-related vasculitis [^]	Ü	-	-**	-
	Immune-related myositis [^]	Ü	-	-**	-
	Immune related nephritis [^]	Ü	-	-**	-
	Immune-related ocular inflammatory toxicities [^]	Ü	-	-**	-
Severe cutaneous adverse reactions [^]	Ü	-	-**	-	

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
Missing information	Use in patients with history of active autoimmune disease	Ü	-	Ü	-
	Use in patients with history of severe reactions to immune check point inhibitors	Ü	-	Ü	-
	Concomitant use with other immuno-modulatory drugs	Ü	Ü	Ü	-
	Potential pharmacodynamic interaction with systemic immunosuppressants including corticosteroids	Ü	-	Ü	-
	Concomitant administration of live attenuated vaccine	Ü	Ü	Ü	-
	Use in patients with severe organ impairment	Ü	-	Ü	-
	Use in paediatric patients	Ü	Ü	Ü	-
	Use in pregnancy and lactation	Ü	-	Ü	-
	Long term use	Ü	-	Ü	-

*Additional risk minimisation activities recommended by the RMP Evaluator and accepted by the sponsor. ^ Safety concerns and additional risk minimisation activities agreed to by sponsor. ** Routine risk minimisation not specified in the sponsor's Section 31 response.

- Additional pharmacovigilance activities are planned for the following Important Identified Safety Concerns:
 - Anti-therapeutic antibodies.
 - Concomitant use with other immunomodulatory drugs.
 - Concomitant administration of live attenuated vaccine.
 - Use in paediatric patients.
- No additional risk minimisation activities were proposed by the sponsor in the initial RMP documents. The RMP evaluator recommended the following additional risk minimisation activities for all the immune-related adverse events, severe infection and infusion reactions:
 - Health Care Professional Education – Management guide for immune-related adverse events.
 - Wallet sized Patient Alert Card.
- In its post-first round response, the sponsor has agreed to implement additional risk minimisation activities as recommended.

New and outstanding recommendations from second round evaluation

- Following consideration of the sponsor's response, the following outstanding and new recommendations should be addressed:

- (outstanding) The revised ASA should include a table that compares the final wording of the routine risk minimisation measures for each safety concern in the EU SmPC and Australian PI.
- (new) The sponsor should submit the revised EU-RMP and ASA as soon as available and assign pharmacovigilance and risk minimisation activities for all the new Important Potential Risks.
- (new) The sponsor should consider whether ongoing trials will collect additional data on the newly added safety concerns. If so, they should be assigned as additional pharmacovigilance activities in the revised EU-RMP and/or ASA.
- (new) The revised ASA should include the routine risk minimisation measures proposed for the newly added safety concerns.
- (new) The HCP brochure and a Patient Alert Card should be provided to the TGA for review prior to implementation of these activities at the commercial launch of atezolizumab in Australia.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

The EU-RMP (version 1.0, dated 24 March 2016, data lock point 25 February 2016), with Australian Specific Annex (version 1.0, dated May 2016), to be revised to the satisfaction of the TGA, must be implemented (see outstanding issues above).

Other advice to the Delegate

The Delegate may wish to consider if the PI should include information regarding the additional Important Potential Risks proposed for inclusion by the sponsor as follows:

- immune-related: vasculitis, myositis, nephritis and ocular inflammatory toxicities;
- severe cutaneous adverse reaction.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no objections on quality grounds to approval of Tecentriq. Batch release testing and compliance with CPD are recommended as conditions of registration.

Nonclinical

There was no objection to registration on nonclinical grounds. Arteritis was seen in toxicity studies.

Proposed Pregnancy Category is D; see comments about binding of atezolizumab to syncytiotrophoblasts.

Clinical

The following table is to orient readers to key studies provided in the dossier.

Table 11: Key clinical studies

UC	NSCLC
Controlled	Controlled
Nil	OAK (evaluated in second round) (Rittmeyer et al, Lancet, 2016) atezolizumab versus docetaxel (n = 425 per arm for main analysis); 2L
	POPLAR (G028753) atezolizumab (n = 144) versus docetaxel (n = 143); 2L (8.5.2015 DBL for primary analysis; 1.12.2015 DBL for update)
Uncontrolled	Uncontrolled
IMvigor210 (Rosenberg et al 2016) Cohort 1 (1L cisplatin ineligible): n = 122 Cohort 2 (2L+): n = 316 (initial CSR with DBL 5.5.15; multiple subsequent updates)	BIRCH (PD-L1 enriched) (G028754) 1L: n = 139 2L: n = 267 3L: n = 253 FIR (PD-L1 enriched) (G028625) 1L: n = 31 2L: n = 93 2L: (brain mets) n = 13
PCD4989g (UC cohort) (first in human) 2L+: n = 93 with follow-up	PCD4989g (NSCLC) (first in human) N = 88

Pharmacology

Overall, the evaluator concluded that PK are adequately characterised.

There were no dedicated pharmacology studies, so there was emphasis on PK and PD data from studies that also informed about efficacy and also more emphasis on population PK and exposure-response analyses.

It should be noted regarding dose proportionality that the highest mg/kg dose group was 20 mg/kg, which does not encompass patients given a flat 1200 mg dose who weigh less than 60 kg.

According to the final PopPK report (106693), body weight, gender, albumin, tumour burden and ATA influenced clearance and / or volume of distribution.

Although atezolizumab is described as Fc-engineered, the clinical report states that 'the metabolism of atezolizumab is unlikely to differ from that of endogenous IgG proteins'.

- *Questions for sponsor:*
 - *What are the implications, if any, of Fc-engineering of atezolizumab in terms of metabolism or recycling, for example, via FcRn or other endocytic proteins?*
 - *It is stated that ‘in general, molecules with a molecular weight above 50 kDa do not undergo renal elimination due to their inability to cross the renal glomerular membrane due to size’. Is there any experience with atezolizumab in patients with, for example, nephrotic syndrome or other significant proteinuria (where it is plausible that clearance may differ)? Is there any view about whether the PI should offer advice about use, or modified use, of atezolizumab in such circumstances? It is noted that patients with low albumin tended towards higher clearance – was this driven by patients whose low albumin was due to significant proteinuria?*

OAK was a confirmatory Phase III study in NSCLC, evaluated in Round 2. It accrued PK data, and many patients contributed data. The evaluator considered that PK results in OAK were consistent with known PK of atezolizumab.

The absence of dedicated PK studies extended to the absence of dedicated studies in patients with impaired hepatic or renal function. PopPK approaches did not include data from patients with moderate or severe hepatic impairment, and the number of patients with severe renal impairment who contributed data to PopPK analyses was small (n = 8). While the PopPK approach did not suggest an impact on atezolizumab PK of renal dysfunction, it should be noted that the analysis does not excluded altered clearance in patients with significant proteinuria (see above).

Population PK

TGA commissioned a PopPK Evaluation Report for atezolizumab.

Population PK analyses were also considered by the clinical evaluator. Of note, ‘no covariate induced more than 27% change from typical values when evaluated at extreme values (that is, 10th and 90th percentile)’.

Analysis of the effects of baseline covariates on systemic exposure revealed that, for example, body weight influences CL and V1, and that these effects together contribute to potentially clinically relevant increases in exposure, in the range 32 to 40%, for a 54 kg patient relative to a 77 kg patient.

Efficacy (urothelial carcinoma)

IMvigor210 was a Phase II, single-arm, open-label study in patients with locally advanced or metastatic urothelial cancer.

Patients in Cohort 1 (1L cisplatin ineligible; n = 122) were:

- treatment naive for inoperable locally advanced or metastatic or recurrent UC (for patients who had received prior adjuvant/neoadjuvant chemotherapy for UC, a treatment-free interval of greater than 12 months between the last treatment administration and the date of recurrence was required in order to be considered treatment-naïve in the metastatic setting)
- cisplatin ineligible (one or more of the following: (a) impaired renal function (GFR > 30 but < 60 mL/min); (b) a hearing loss (measured by audiometry) of 25 dB at two contiguous frequencies; (c) Grade ≥ 2 peripheral neuropathy (that is, sensory alteration or paraesthesias; including tingling); and (d) ECOG performance score of 2).

It is noted by the evaluator that patients in cohort 1 do not fall within the proposed UC indication. The focus below is on Cohort 2.

Patients in Cohort 2 (2L; n = 316) had metastatic disease and (a) disease progression during or following treatment with 1+ platinum-containing regimens in the metastatic setting; (b) disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant regimen; or (c) intolerance to a platinum-containing chemotherapy regimen (that is, discontinuation due to Grade 4 haematological or Grade 3-4 other toxicity).

Only patients with sufficient tumour tissue for PD-L1 testing were enrolled. In UC, primary assessment focused on PD-L1 expression on tumour immune-infiltrating cells (ICs), not tumour cells. Median age was 66 years; 78% were male; 74% had bladder cancer (13.5% had renal pelvis cancer, 7.4% had ureteric cancer, 1.6% had urethral cancer); PD-L1 expression is: about a third had IC2/3, a third had IC1 and a third had IC0. 61% had received ≥ 2 systemic regimens in any setting.

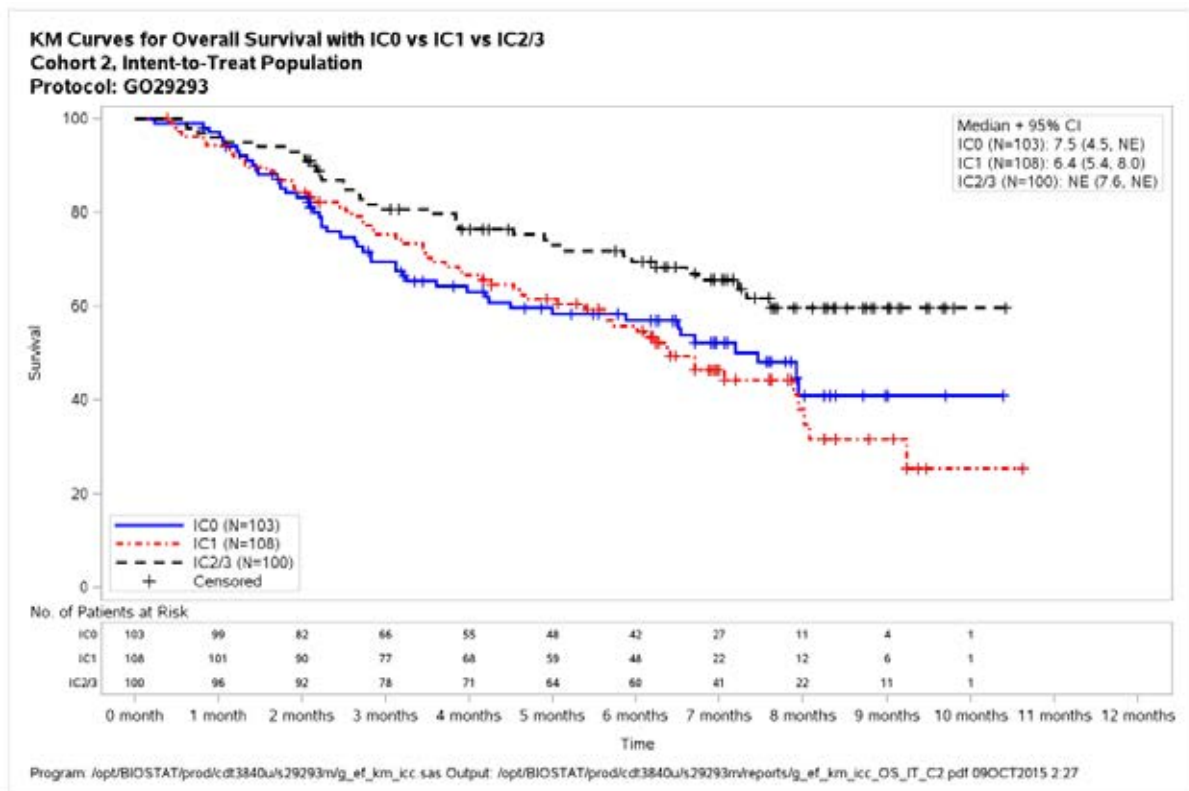
The primary efficacy endpoint was ORR, using an independent review facility and RECIST 1.1 (Cohort 1), or that and investigator assessment and a modified RECIST (Cohort 2). Comparisons were planned to be made with historical outcomes, but the benchmark of 10% ORR is 'the lower boundary of the modest 10-20% response range suggested by the literature'.

In Cohort 1, IRF-assessed ORR was 19.3%, which included 5% CR (DBL 14/9/2015).

In Cohort 2, investigator-assessed ORR using mRECIST (DBL 5.5.2015) was 18.3%; using IRF / RECIST 1.1, the ORR was 15.1%. There was a trend towards higher ORRs with higher PD-L1 expression (ORR for IC0: 8.7%; for IC1: 10.2%; for IC2/3: 27%); thus, results across 'all comers' were driven by relatively good results in those with higher IC PD-L1 expression. Median duration of response was not reached (the database lock of 5.5.2015 allowed at least 24 weeks of follow-up for the last enrolled patient, and a median length of follow-up of 7.1 months).

ORR in subgroups is analysed and beyond IC status, disparities were noted for sex (males, ORR = 16.9%; females, 8.7%), ECOG performance status (0, ORR = 23.9%; 1 = 9.8%), site of primary tumour (bladder, ORR = 17.3%; others, <10%), liver metastases (yes, ORR = 6.3%; no, 19.1%), Hb < 10 g/dL (yes, ORR = 8.7%; no, 16.9%), histology (transitional cell, 15.8%; mixed, 7.4%) and prior use of BCG (yes, 9.6%; no, 16.8%). Modelling indicates PD-L1 status remains influential after adjusting for ECOG PS, liver mets and low Hb. Data do not exclude that tumour burden (for example, presence of liver metastases) influences efficacy.

Median PFS was 2.1 months, consistent with best objective response of progressive disease in about half of subjects. Median OS was 7.9 months across all comers; a median had not been reached in those with IC2/3.

Figure 2: KM curves for OS with IC0 versus IC1 versus IC2/3

There was a series of efficacy updates based on updated database locks (DBLs):

- Results based on the 14 September 2015 DBL (median follow-up 11.7 months) were similar; responses remained durable. Median OS in the IC2/3 group was now 11.4 months (versus 8.8 months in all comers).
- Results based on the 27 November 2015 DBL (median follow-up 14.4 months) were similar, although a few patients had shifted from partial to complete responses.
- In the second round, a further update was provided within a Clinical Overview, this time with a DBL of 4.7.2016 (median duration of follow-up, 21 months). For ORR and DoR, little has changed except the upper limit of durable response times; 32 of 49 (65.3%) were still responding. Furthermore, in the all-comers cohort, median OS was now 7.9 months (1 yr OS rate, 36.9%).

Quality of life outcomes were not evaluated.

An exposure-efficacy analysis was conducted for IMvigor 2010; no relationship between ORR and exposure was found.

Study PCD4989g (UC component) is described; its outcomes support the view that patients with higher IC scores were more likely to achieve an OR. Updated analysis (DBL 31.3.2016) is discussed by the sponsor as quoted in the CER:

...in the updated analysis of Study PCD4989g with a clinical cutoff date of 31 March 2016 and an overall median follow-up of 29.2 months, the ORR was 31.8% (95% CI: 13.9%, 54.9%) for IC2/3 patients and 18.8% (95% CI: 9.0%, 32.6%) for the IC0/1 subgroup. In the IC0 subgroup, the updated ORR was 11.1% (95% CI: 1.38%, 34.71%). Similarly, the median IRF-assessed DOR per RECIST v1.1 was not reached overall or in the IC2/3 or IC0 subgroups and was 27.6 months (range, 2.9–32.7 months; 32.7 is a censored value) in the IC1 subgroup. The majority of responders (16 of 24 patients [66.7%]) still had an ongoing response at the updated data cutoff. The

Sponsor has updated the Product Information with this data because it represents the longest follow-up.

The evaluator notes that with this updated analysis, median OS was 10.1 months in all comers (with a 1 year OS rate of 45.6% and a 2 year OS rate of 30.3%).

Efficacy (non-small cell lung cancer)

Emphasis is placed on review of the confirmatory study OAK.

OAK was a randomised, open-label study against docetaxel, in patients with locally advanced or metastatic NSCLC who had progressed during or after platinum-based chemotherapy for advanced disease. From the CER:

Patients were required to have received 1-2 previous cytotoxic chemotherapy regimens (≥ 1 platinum based combination therapy) for stage IIIB or IV NSCLC. Patients with EGFR mutations or an ALK fusion oncogene were also required to have received previous tyrosine kinase inhibitor therapy.

With reference to PD-L1 status, all comers were enrolled, if tumour tissue was available for PD-L1 expression testing – however standard exclusions applied, for example, a common reason for screening failure was presence of known active or untreated CNS lesions.

Randomisation was stratified by IC status, by number of prior chemotherapy regimens and by NSQ versus SQ histology. 612 patients received docetaxel, and n = 613 atezolizumab.

While 1225 patients were enrolled, primary analysis was in the 850 subjects first randomised (n = 425 per arm). This was a consequence of the study being re-sized to power for testing OS benefit in the TC3 or IC3 subgroup. Data were presented for the first 850 subjects.

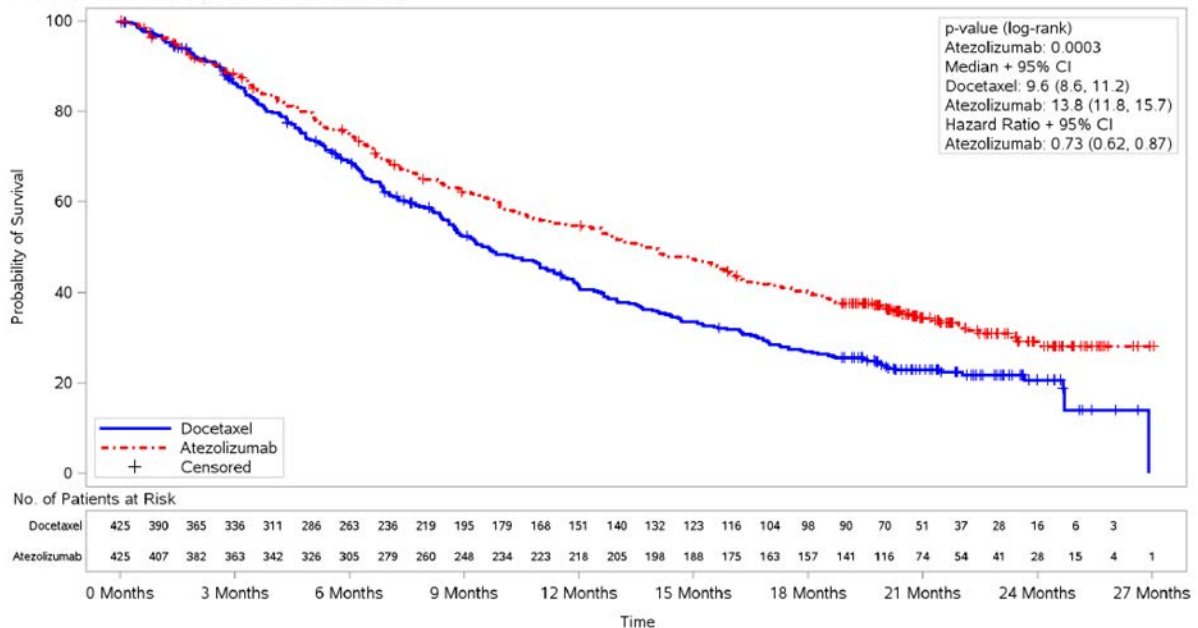
Of n = 425 per arm, 5.4% in the docetaxel arm versus 0.9% in the atezolizumab arm did not receive treatment, mainly due to withdrawn consent in the docetaxel arm.

Baseline characteristics: median age was 64 yrs; 61% were male, 70% were White and 21% Asian. 75% in each arm had received 1 prior line of therapy for advanced disease; 74% had NSQ NSCLC; median time from diagnosis was 13-14 months; 93.2-95.5% of patients had metastatic disease; 10% had EGFR mutation and 6-8% had KRAS mutation (overall; but 12% and 22.5% respectively in those with known mutation status). Prevalence of 'TC3 or IC3' was 16%, 'TC2/3 or IC2/3' 31%, and 'TC1/2/3 or IC1/2/3' 54%, that is, TC0 & IC0 presumably 46%.

The primary efficacy endpoint was overall survival. In the primary population of 850 subjects, the stratified OS HR was 0.73 (95% CI 0.62-0.87), and median OS was 9.6 versus 13.8 months. The OS KM curve follows.

Figure 3: KM plot of OS with stratified analysis.

Kaplan-Meier Plot of Overall Survival with Stratified Analysis
First 850 Randomized Intent-to-Treat Patients
Protocol: GO28915 (Data Cut: 7JUL2016)



The 12-month OS rate was 54.7% in the atezolizumab arm and 41.1% in the docetaxel arm, and the 24-month OS rates were 29.2% and 20.6% in the two treatment arms, respectively.

In the TC1/2/3 or IC1/2/3 subgroup, the OS HR was 0.74 (95% CI 0.58-0.93), and median OS was 10.3 versus 15.7 months.

Further analysis suggested good atezolizumab outcomes were driven by IC and by TC expression of PD-L1.

For OS outcomes for other subgroups according to PD-L1 expression status, high expression was associated with a dramatic OS benefit (HR 0.41), but no expression (TC0 & IC0) still retained a HR of 0.75 (95% CI 0.59-0.96) (and a difference in median OS of 3.7 months favouring atezolizumab).

OS HR outcomes were consistent across SQ and NSQ histologies; across arms, patients with NSQ NSCLC lived longer than patients with SQ NSCLC.

PFS was not improved with atezolizumab (HR 0.95; median 4 months for docetaxel versus 2.8 months for atezolizumab), although there was variation by PD-L1 expression status.

ORR was based on investigator assessment using RECIST 1.1. ORR was not improved with atezolizumab (13.4-13.6% across arms) although there was marked variation by PD-L1 expression status (for example, TC3 or IC3: 10.8% versus 30.6% favouring atezolizumab; TC0 & IC0, 10.6% versus 7.8% respectively). Also, for all comers, there were more CRs for atezolizumab than for docetaxel (1.4% versus 0.2%), and more progressive disease for atezolizumab (44% versus 27.5%). For responders, duration of response was clearly greater on atezolizumab (for all comers, median 16.3 versus 6.2 months; HR 0.34).

- *Question for sponsor (regarding OAK outcomes and NSCLC / UC more broadly):*
 - *Has any attempt been made to model which patients are more likely to have a best objective response of progressive disease, when treated with atezolizumab, for example, based on baseline characteristics, early outcomes (AEs or imaging) or predicted PK? Is there any indication that patients with a best objective response of*

progressive disease might have an accelerated tempo of disease on atezolizumab compared to docetaxel?

Treatment with atezolizumab (vs no such treatment) beyond progression was also analysed, although outcomes are difficult to interpret because of lack of randomisation.

The evaluator noted that, regarding patient-reported outcomes, completion rates were high. No differences across arms in standard PROs were seen, except that in patients on docetaxel, alopecia and peripheral neuropathy impacted on quality of life. Also, there was a longer time to deterioration in chest pain for atezolizumab arm patients (median TTD, 8.3 versus 18 months; HR 0.72 (95% Ci 0.55-0.93)).

POPLAR was a randomised, open label study versus docetaxel, in patients with locally advanced, unresectable/inoperable or metastatic NSCLC who had progressed during or after platinum-based treatment for advanced disease (or who had recurrence within 6 months of treatment with a platinum-based adjuvant/neoadjuvant regimen).

With reference to PD-L1 status, all comers were enrolled, if tumour tissue was available for PD-L1 expression testing – however standard exclusions applied, for example, a common reason for screening failure was presence of known active or untreated CNS lesions.

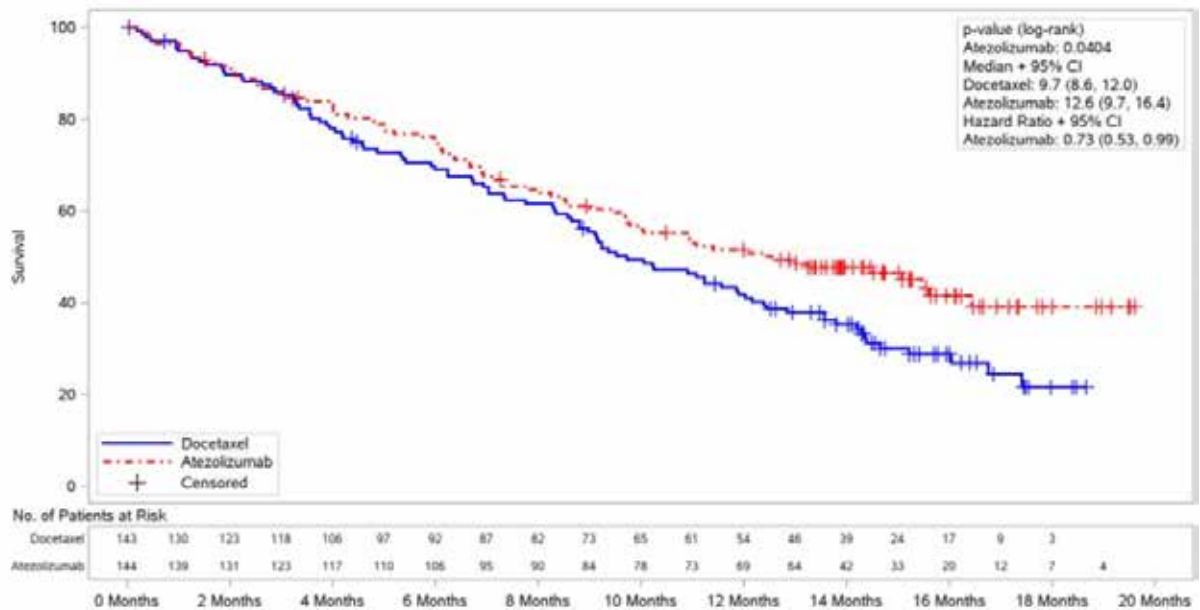
Randomisation was stratified by IC status, by number of prior chemotherapy regimens and by NSQ versus SQ histology. 143 patients received docetaxel, and n = 144 atezolizumab.

Mean baseline age was 62 years; 66% had NSQ NSCLC; 66% had received 1 prior therapy (and 34% 2 prior lines); 95.5% had metastatic as opposed to locally advanced disease. Baseline testing for driver mutations was not required, but few of those tested had EGFR, ALK or KRAS mutations. A higher proportion of patients in the docetaxel arm had brain metastases (10.5% versus 5.6%). A summary of baseline PD-L1 expression is shown below.

Table 12: Baseline PD-L1 expression

Subgroup	Docetaxel (n = 144)	Atezolizumab (n = 144)	All Patients (n = 287)
TC3 or IC3	16.1% (n = 23)	16.7% (n = 24)	16.4% (n = 47)
TC2/3 or IC2/3	38.5% (n = 55)	34.7% (n = 50)	36.6% (n = 105)
TC1/2/3 or IC1/2/3	71.3% (n = 102)	64.6% (n = 93)	67.9% (n = 195)
TC0 and IC0	28.7% (n = 41)	35.4% (n = 51)	32.1% (n = 92)

The primary efficacy endpoint was overall survival. At the primary analysis (DBL 8 May 2015), median OS in the docetaxel arm was 9.7 months, and for atezolizumab, 12.6 months; the HR was 0.72 (95% CI 0.54-0.98). The KM curve follows.

Figure 4: KM plot of OS at primary analysis

OS HR was 0.49 for those with TC3 or IC3. Only at TC0 and IC0 was the OS HR 1.04, suggesting overall outcomes were driven by good results in patients with high PD-L1 IC expression (without strong evidence of bad outcomes versus docetaxel in non-expressers). Analysis suggested good atezolizumab outcomes were driven by TC expression of PD-L1 more than IC expression, though this analysis was not definitive.

An updated analysis (DBL 1 December 2015) produced similar outcomes, and also showed no difference in OS HRs in SQ and NSQ subsets.

There was no difference in PFS outcomes across arms (TC3/IC3 patients trended towards PFS benefit, HR 0.60 (95% CI 0.31-1.16) but TC0&IC0 patients had a HR of 1.12 (95% CI 0.72-1.77)).

There was no difference in ORR outcomes across arms. There was a better ORR with high PD-L1 expression. Duration of response was longer in atezolizumab responders than in docetaxel responders, especially based on the 1 December 2015 DBL.

Patient-reported outcomes were assessed. In patients on atezolizumab, there was no improvement or decline from baseline; this was also the case for patients on docetaxel, except that alopecia was reported.

Other studies were uncontrolled and are supportive, although BIRCH in particular studied a fairly large number of patients (around 660). Where comparison was possible, their efficacy outcomes were not divergent from those of OAK and POPLAR.

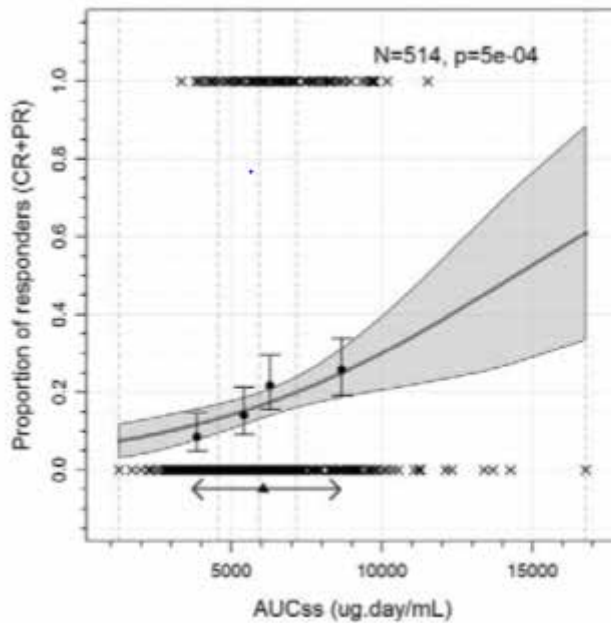
BIRCH enrolled patients with higher PD-L1 TC or IC expression (a large fraction of patients were screening failures due to PD-L1 status), and its primary endpoint was ORR. It included 1L, 2L and 3L patients.

FIR enrolled patients with higher PD-L1 TC or IC expression; its primary endpoint was ORR. Outcomes were broadly consistent with those in other NSCLC studies.

Study PCD4989g (NSCLC cohort) is exploratory.

Other analyses

Exposure-efficacy analyses were conducted with data from BIRCH and POPLAR. In BIRCH, a link between AUCs and ORR was found.

Figure 5: AUCss versus proportion of responders

Based on simulation, 'the estimated expected ORR ranged from 11% to 25% for the AUCss at the 10th and 90th percentiles, with an ORR of 16% at the median AUCss' (CER). Patients at the 90th percentile of weight have been estimated to have a 21% decrease in AUCss, and this is within the 10th to 90th percentiles (translating to an estimated 13% ORR, comparable to 16% ORR at the median AUCss).

In the analysis of POPLAR, no relationship between ORR and AUCss was found, and a weak paradoxical correlation between Cmax and ORR was uncovered. A correlation between overall survival and AUCss and other measures of exposure was seen. The correlation between high exposure and lower hazard ratio for OS was maintained after correcting for number of metastatic sites and albumin level.

Table 13: AUCss versus HR.

AUCss (µg.day/mL)	HR	95% PI	HR Plot
3393.1 [1974, 4143]	0.86	(0.82,0.91)	
4749.7 [4143, 5548]	0.77	(0.72,0.82)	
6902.9 [5548, 10766]	0.61	(0.56,0.68)	

Overall, there is a suggestion that in the range of exposures encountered in key studies, there is a correlation between higher exposure and better outcomes.

Safety

Exposure

Prior to submission of OAK in NSCLC in second round, the submission included safety data on n = 1547 subjects (a third with UC, two-thirds with NSCLC); some other safety data from PCD4989g were in patients with other tumour types. Median duration of exposure to atezolizumab 1200 mg q3wk was 3.5 months (range, 0-19.4 months; corresponding to a median of 6 cycles, range 1-28), with 35.7% receiving 6+ months of treatment and only 4.7% (all NSCLC) receiving 12+ months of treatment. Median duration of safety follow-up was 4.5 months (range, 0.5-32.9 months).

The clinical evaluator writes:

The main limitation of the exposure data related to the small number of patients exposed to atezolizumab for > 12 months. The absence of long-term safety data is a deficiency in the submitted clinical dossier, given that the sponsor proposes that atezolizumab be administered for as long as it continues to demonstrate clinical benefit or until toxicity occurs...

In the second round evaluation, the evaluator notes provision of an updated safety analysis based on n = 2160 patients, which appears to reflect the addition of OAK patients who received atezolizumab. Median duration of safety follow-up remained at 4.5 months (range changed to 0.5-53 months). The evaluator notes that no new safety signals emerged from the updated safety analysis; the proposed PI does however reflect the updated safety analysis.

General indices

When considering the frequency of key AE categories for the 'all patients' group, treatment-related Grade 3-4 AEs were seen in 12%; treatment-related fatal AEs in 0.3%; treatment-related serious AEs in 9.4%; and AEs leading to treatment withdrawal in 5.4% (3.8% for UC, 6.2% for NSCLC). The clinical evaluator writes:

Given that nearly all patients experienced at least one AE, the data indicate the majority of AEs were manageable by temporary dose interruption and/or symptomatic treatment rather than discontinuation from the study.

Adverse event profile

As shown by the difference across UC and NSCLC cohorts in AEs such as cough, dyspnoea, UTI and haematuria, many of these AEs relate to the underlying disease process. Common treatment-related AEs (as per investigator opinion) were fatigue (21.4%), nausea (11.2%) and decreased appetite (10.5%). Separately, the sponsor 'called' adverse drug reactions; the commoner ADRs were:

...fatigue (35.9%), decreased appetite (24.2%), nausea (22.4%), dyspnoea (20.5%), diarrhoea (17.6%), pyrexia (17.1%), rash (16.4%), vomiting (14.3%), arthralgia (12.5%), pruritus (10.9%), asthenia (10.3%), abdominal pain (8.0%), musculoskeletal pain (6.3%), chills (6.1%), influenza-like illness (5.3%), hyponatraemia and hypokalaemia (4.6% each), AST increased (4.2%), ALT increased (3.9%), hypothyroidism and hypotension (3.5% each), pneumonitis (3.0%), diabetes (3.1%), dysphagia (2.7%), nasal congestion and hypoxia (2.5% each), and thrombocytopenia (2.4%).

Grade 3-4 AEs seen in >2% of patients were dyspnoea, anaemia, fatigue, hyponatraemia and pneumonia. Six treatment-related deaths were reported: cardiorespiratory arrest; constrictive pericarditis; cardiac failure; pneumonia; sepsis; and respiratory failure (the latter, occurring >30 days after last dose). Many SAEs appear related to underlying disease; commoner treatment-related serious AEs were pneumonitis (1.0%), pyrexia (0.8%), diarrhoea (0.6%), colitis, nausea, AST increased (0.4% each), ALT increased, hypothyroidism and muscle weakness (0.3% each).

Adverse events of special interest were seen in around a quarter of all patients, and were commonly rash (12.4% altogether), AST increased (4.3%), ALT increased (4.0%), hypothyroidism (3.2%), pneumonitis (2.7%), peripheral neuropathy (2.4%) and blood bilirubin increased (1.1%). In a separate approach, the sponsor listed 'important ADRs'. 11.7% of patients had an important ADR; around 3% of all patients had an 'important ADR' of Grade 3-4. The evaluator writes:

The most commonly identified important ADRs ($\geq 1\%$ of patients) were immune-related hypothyroidism (3.6%), immune related diabetes mellitus (3.2%), immune-related pneumonitis (3.0%), and immune-related colitis (1.0%).

The FDA Medical Review for the UC application noted that thyroid function testing was not performed frequently and that thyroid AEs may be underreported in IMvigor 210.

- *Question for sponsor:*
 - *Have other studies of atezolizumab used more intensive TFT monitoring? Is there any suggestion of higher rates of thyroid AEs where more intensive monitoring is used?*

Regarding important ADRs, thrombocytopenia was not included in the basket of possible important ADRs. Also, most patients with the important ADR of diabetes reported 'hyperglycaemia' – it is not clear whether this reflects new onset diabetes mellitus.

- *Question for sponsor:*
 - *Did reports of hyperglycaemia reflect new-onset DM? How many patients became insulin dependent or could otherwise be considered to have new-onset DM? Did any of these patients also report pancreatitis?*

Despite the frequency of diarrhoea (for example, 17.6% with an ADR), immune-related colitis was called in only 1.0%. It is also notable that across 1547 subjects, there were no AEs of myasthenic syndrome.

- *Question for sponsor:*
 - Please comment on efficacy and safety outcomes for patients with 'treatment-enhanced' ATAs (across all key studies – IMvigor210, POPLAR, OAK).

The evaluator focuses on the safety profile seen in POPLAR. OAK is considered a more robust study (it is much larger) so emphasis is given to OAK (later); notable outcomes from consideration of POPLAR were:

- the longer median duration of treatment for atezolizumab (2.1 versus 3.7 months) and higher proportion of subjects with 6+ months of treatment (15.6% for docetaxel versus 40.1% for atezolizumab)
- the much higher rate of treatment withdrawal due to related AEs in the docetaxel arm (17.8%) than the atezolizumab arm (1.4%)
- the different AE profile across arms, including a large difference in rates of pneumonia (3.0% for docetaxel, 10.6% for atezolizumab) and other more predictable differences (alopecia, peripheral neuropathy, and so on)
- an AE rate per 100 PY higher for atezolizumab than for docetaxel for only two AEs, namely, musculoskeletal pain and pneumonia. Although there was an imbalance for pneumonia, there was an imbalance in the other direction for both febrile neutropenia and sepsis, for serious AEs.
- The proportion of patients with grade 4 low platelets was 1.5% for docetaxel, and 2.9% for atezolizumab.

The evaluator considers safety data from OAK, where 1187 patients were included in the 'safety evaluable' population (n = 578 docetaxel, 609 atezolizumab). Median duration of treatment was 2.1 versus 3.4 months respectively, and the proportion of patients receiving at least 6 months treatment was 11.2% versus 33.2%. Of note from consideration of OAK, the following points are made.

The clinical evaluator considers that results indicate atezolizumab was better tolerated than docetaxel, and also that no new safety signals were identified in OAK.

AEs seen in $\geq 10\%$ in either arm (docetaxel versus atezolizumab), in order of decreasing frequency in the docetaxel arm, were: fatigue (35.5% versus 26.8%); alopecia (34.9% versus 0.5%); diarrhoea (24.4% versus 15.4%); anaemia (23.5% versus 11.5%); decreased appetite (23.5% versus 23.5%); nausea (22.7% versus 17.7%); asthenia (19.7% versus 19.0%); dyspnoea (19.4% versus 19.4%); cough (18.2% versus 23.2%); myalgia (15.7% versus 6.4%); neutropaenia (15.6% versus 1.6%); constipation (14.2% versus 17.6%); pyrexia (13.1% versus 17.7%); peripheral oedema (14.2% versus 8.9%); peripheral neuropathy (11.2% versus 3.9%); stomatitis (10.9% versus 3.1%); vomiting (10.7% versus 12.2%); febrile neutropaenia (10.7% versus 0.2%); arthralgia (10.0% versus 12.0%); dysgeusia (10.0% versus 3.0%); back pain (7.3% versus 11.0%); and musculoskeletal pain (4.3% versus 10.5%).

For both musculoskeletal pain and pruritus, the increased rate for atezolizumab persisted when adjusted for exposure; for musculoskeletal pain, this was also seen in POPLAR.

- *Question for sponsor:*
 - *Please characterise the AE of musculoskeletal pain in more detail – can this be attributed to, for example, onset of RA-type symptoms, or arthritis / myalgia seen in SLE and other autoimmune conditions?*

There was no increased incidence of pneumonia in the atezolizumab arm, in OAK (for example, Grade 3+ pneumonia: 5.4% for docetaxel, 3.4% for atezolizumab).

Pneumonitis was reported as a serious AE in 1.0% of atezolizumab subjects (but a further 0.8% had eitherILD or organising pneumonia AESIs; and another 1.1% used steroids to treat the AE of dyspnoea).

- *Question for sponsor:*
 - *Please comment on whether patients who required steroids to treat dyspnoea (that is, 1.1% of patients in OAK) should be categorised as having pneumonitis. Unless there was a pre-existing history of asthma or COPD, and a presentation consistent with asthma or COPD, or a definitive diagnosis of some other cause of dyspnoea, it would be more conservative to assume a diagnosis of pneumonitis.*

Only one AE of T1DM was listed amongst endocrine AESIs, for atezolizumab. It is notable that there were three reports of Guillain-Barre syndrome in that arm. Also of note was a single case of Henoch-Schonlein purpura nephritis. One atezolizumab patient had hepatic AEs complying with Hy's Law (and two others did not comply apparently because their LFT abnormalities resolved on steroids). Furthermore, there were reports of pemphigoid, bullous dermatitis, drug eruption and erythema multiforme.

Overall, 12.6% of atezolizumab patients needed steroids to treat immune-mediated AEs (but 9.5% of docetaxel subjects also needed steroids to treat imAEs).

Exposure-response analyses

Exposure-safety analyses were conducted for urothelial carcinoma and NSCLC. The safety parameters investigated were 'grade ≥ 3 AEs' and 'AEs of special interest'. In IMvigor, no correlation was found. In the pooled NSCLC dataset, increasing exposure (AUC₀₋₂₄) was weakly correlated with a decrease in AEs of grade 3-5, but weakly correlated with an increase in AESIs. Overall, there is no strong evidence of a clinically important relationship between exposure and AEs.

There was no dedicated thorough QT study. In Study PCD4989g, a concentration-QTc analysis was conducted. No strong evidence of an impact on QTc interval was uncovered.

Immunogenicity was investigated across six Phase I/II studies (Studies PCD4989g; JO28944; IMvigor 2010, BIRCH, POPLAR, FIR). There was a quite high incidence of anti-drug antibodies across studies (16.7% to 54.5%), with baseline prevalence 0-7.9%. The

PopPK analysis estimated that patients who were ATA-positive had an atezolizumab clearance that was around 16% higher than ATA-negative patients. The evaluator writes that 'ATA status had no consistent effects on efficacy based on ORR assessment in patients with UC or NSCLC' and that there was no correlation with safety outcomes either. Of note from the CER:

In the All Patients population, the incidence of both hypersensitivity and infusion related reactions (MedDRA AE PTs) was low and similar for ATA-positive and ATA-negative patients. Hypersensitivity events were reported in 18 (1.4%) patients, comprising 8 (1.1%) ATA-negative patients and 10 (1.9%) ATA-positive patients. Infusion-related reactions occurred in 20 patients (1.6%), comprising 11 (1.5%) ATA-negative patients and 9 (1.7%) ATA-positive patients.

The evaluator states that due to the high number of neutralising antibody assay 'indeterminate' results, no conclusions can be drawn about the effect of neutralising antibodies. Given the high frequency of ATAs, this is considered a deficiency.

Risk management plan

The RMP was generally acceptable. Healthcare professional education and a patient alert card are planned to help minimise risk. A proposed condition of registration was:

The EU-RMP (version 1.0, dated 24 March 2016, data lock point 25 February 2016), with Australian Specific Annex (version 1.0, dated May 2016), to be revised to the satisfaction of the TGA, must be implemented (see outstanding issues above).

- Question for sponsor:
 - The safety specification does not include 'Infection' or a related term, for example, as an important identified or potential risk, despite the US PI including 'Infection' under its list of Warnings and Precautions. Can the sponsor provide an update about the FDA's view of atezolizumab's risk of causing infection after FDA's review of OAK?

Risk-benefit analysis

Delegate's considerations

Clinical (urothelial carcinoma)

In the main study, IMvigor210, Cohort 1 included first-line (1L) cisplatin-ineligible patients, and Cohort 2 included second line (2L+) patients. The sponsor proposes use in patients 'after prior chemotherapy' (in the advanced setting), so emphasis is on outcomes in Cohort 2.

The main study, IMvigor210, was uncontrolled. This contrasts with Study VFL 302, which was the pivotal study supporting TGA approval in 2011 of vinflunine (a randomised study of vinflunine + best supportive care (BSC) versus BSC alone).

In IMvigor210 Cohort 2, 91.3% of patients had transitional cell histology (that is, TCC) and others had mixed histology including a TCC component. This reflects the inclusion requirement of TCC (also termed UCC). The sponsor is applying for use in 'urothelial carcinoma' which is taken to equate with TCC of the urothelial tract.

In IMvigor210, the primary endpoint was objective response rate (ORR), seen in 15.8% at latest database lock (DBL), 4 July 2016. Median duration of response had not been reached. Overall survival (OS) was a secondary endpoint and OS data were fairly mature. Median OS was 7.9 months at the most recent DBL.

In gauging whether efficacy results from IMvigor210 are satisfactory, comparison with historical outcomes in the same population (second/subsequent line (2L+) that is, previously treated for metastatic UC) is needed. Cross-study comparison runs the risk of inaccuracy, so the absence of a controlled study is a major deficiency for the atezolizumab UC dataset.

Despite the problems associated with historical comparisons, it is relevant that in VFL 302, adding vinflunine resulted in a median OS of 6.9 months (versus 4.6 months for BSC, although the HR was 0.88 (95% CI 0.69-1.10)). In VFL 302, ORR was 8.6% - all responses were PRs - and median duration of response (DoR) was 7.4 months.

Complete response (CR) rates were notable in IMvigor210. At the 4 July 2016 DBL, in 'all comers' (regarding PD-L1 expression) as assessed by the independent review facility (IRF): 19/310 patients (6.1%) had a CR. The contribution of CRR to ORR is important (6.1% CR + 9.7% PR = 15.8% OR). Most CRs were in IC2/3 patients, but some were seen in IC0/1 patients. On the other hand, at the earlier DBL of 5th May 2015 (primary analysis) best objective response of progressive disease was seen in half of all subjects.

Efficacy outcomes are driven by patients whose tumour-infiltrating immune cells (ICs) (and / or tumour cells, TCs) have moderate to strong expression of PD-L1. Based on the latest DBL, ORR was 28% for IC2/3 (moderate to strong expression), 11.2% for IC1 and 8.7% for IC0. (Efficacy outcomes did not appear driven by high PD-L1 expressers in the 1L cisplatin ineligible cohort, to the same extent).

ORRs of 9-11% are close to the sponsor's historical benchmark, 10%. Conclusions about similarity of efficacy are best based on non-inferiority studies, where there should be enough statistical power to show with reasonable certainty that results in the experimental arm are not worse than control arm results by a pre-specified and clinically justifiable margin (delta). In IMvigor210, not only is there no formal non-inferiority approach, but also, the evaluator notes that historical studies often had ORRs >10%.

In atezolizumab responders, there was good durability (median DoR not reached in IC2/3 and IC1 patients; 13.3 months in IC0 patients).

Overall survival was better in the IC2/3 subgroup than IC1 or IC0 subgroups.

No information was gathered in IMvigor210 about quality of life outcomes.

Safety outcomes appeared to follow patterns established by PD-1 inhibitors, with no clear-cut new signals. The safety profile in UC patients can bridge to an extent from the larger NSCLC dataset. The immune-related toxicity of atezolizumab is in contrast to the toxicity profile of chemotherapy agents that might be used in 2L UC.

Clinical (non-small cell lung cancer)

With the provision of OAK (a large randomised study versus docetaxel) and POPLAR (a smaller randomised study versus docetaxel), and fairly mature OS data in both studies, there is very strong evidence to support approval of atezolizumab in the 2L NSCLC setting. Docetaxel is a reasonable choice of comparator.

In OAK, the stratified OS HR was 0.73 (95% CI 0.62-0.87), and median OS was 9.6 versus 13.8 months favouring atezolizumab over docetaxel. While neither PFS nor ORR outcomes showed a particular benefit of atezolizumab over docetaxel, it is relevant that duration of response was better with checkpoint inhibition. Also, there was modest evidence of improved quality of life (for example, median time to deterioration in chest pain was prolonged with atezolizumab; furthermore, alopecia and peripheral neuropathy did not impact on quality of life in the atezolizumab arm, but did in the docetaxel arm).

Regarding OS outcomes for subgroups by PD-L1 status, high expression was associated with major benefit (HR 0.41), but no expression (TC0 & IC0) retained a HR of 0.75 (95% CI 0.59-0.96) (and a difference in median OS of 3.7 months favouring atezolizumab).

One point of concern, outweighed by data noted above, is that in OAK there was a higher rate of progressive disease (as best objective response) in the atezolizumab arm than in the docetaxel arm.

In POPLAR, there was a modest increase in risk of infection (vs docetaxel, known to predispose to infection) in the atezolizumab arm. The US PI has a Precaution about infection. However, in the much larger OAK study, this signal did not persist.

The evaluator also expressed an opinion about diagnostic testing for PD-L1:

In view of the association between higher PD-L1 expression and increased efficacy in patients with NSCLC treated with atezolizumab, it is recommended that all NSCLC patients to be treated with the drug have their PD-L1 expression levels determined. It is considered that this information will provide important prognostic information.

The indication as proposed does not ask for prior use of agents targeting ALK and EGFR where actionable mutations exist. The indication should be updated in this regard. It is noted from OAK that patients with EGFR mutations did not have an OS benefit with atezolizumab (HR 1.24 versus docetaxel).

Clinical (pharmacology)

The impact of anti-atezolizumab antibodies has not been fully elucidated. Trough levels were lower in ATA positive subjects across multiple studies. PopPK analysis estimated that ATA-positive patients had clearance around 16% higher than ATA-negative patients. In NSCLC, a correlation between exposure and ORR was present. The assay to determine whether ATAs were neutralising is being refined.

Proposed action

The Delegate supports approval of the following indications:

Tecentriq is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, Tecentriq should be used after progression on or after targeted therapy.

Tecentriq is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma with progression on or after prior chemotherapy (see CLINICAL TRIALS for influence of PD-L1 expression on outcomes).

The Clinical Trials section would provide details about: PD-L1 assays used in trials; expression of PD-L1 in trial patients; and outcomes according to PD-L1 status. The Dosage and Administration section would recommend baseline testing for PD-L1.

At this stage, the Delegate is minded to approve the UC indication without restriction by PD-L1 status, but the Delegate is particularly interested in the ACM's view on this matter.

- The Delegate thinks there is sufficient evidence of good benefit in IC2/3 'moderate to high' PD-L1 expressers, relative to plausible alternative treatments (acknowledging the need for cross-study comparisons).
- In patients with no or weak PD-L1 expression, the Delegate also minded to approve use. The evidence does not formally rule out worse outcomes than might be expected with an approved agent (vinflunine) or with off-label use of various other agents. Also, the sponsor's choice of 10% ORR as the historical standard is open to debate. However, ORRs around that mark seem reasonably likely for atezolizumab in 2L UC 'IC0/1' patients; and beyond that, durable responses were attained, and CRs were (rarely) observed. These findings, in combination with the quite different and overall more tolerable AE profile of atezolizumab, suggest to me that approval in the UC0/1 cohort may be the preferable course of action.

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

- Taking into account the design and outcomes of IMvigor210, is benefit sufficiently well demonstrated for atezolizumab in 2L+ metastatic UC patients who have:
 - No tumour-infiltrating immune cell PD-L1 expression (IC0);
 - Weak tumour-infiltrating immune cell PD-L1 expression (IC1); and
 - Moderate to strong tumour-infiltrating immune cell PD-L1 expression (IC2/3).
- Should the PI recommend PD-L1 testing in NSCLC? Or, given apparent benefit in ‘PD-L1 negative’ patients, should this be left to clinician / patient choice?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The sponsor agrees with the Delegate that Tecentriq (atezolizumab) should be registered for secondline and beyond (2L +) locally advanced or metastatic non-small cell lung cancer (NSCLC) and 2L + locally advanced or metastatic urothelial carcinoma (UC) in ‘all-comer’ populations (without regard to programmed death-ligand 1 (PD-L1) expression levels).

The sponsor makes comment on the advice sought by the Delegate of the ACM in this document.

Introduction

In NSCLC, data from pivotal Phase III Study GO28915 (OAK), together with supporting data from the Phase II Study GO28753 (POPLAR), provide substantial clinical evidence to support a positive benefit-risk profile of atezolizumab compared with standard-of-care chemotherapy in 2L+ NSCLC patients, regardless of PD-L1 expression.

In UC, atezolizumab demonstrated clinically meaningful and durable responses in the pivotal Phase II Study GO29293 (IMvigor210). While numerical increases in ORR are observed with higher levels of PD-L1 expression, durable responses are observed across all tumour-infiltrating immune cell (IC) groups. The results of the Phase Ib Study PCD4989g are supportive of the results from the IMvigor210, demonstrating overall efficacy of atezolizumab in these patient populations and in a uniformly lethal disease for which limited therapeutic development has taken place in the past 30 years. Given the significant toxicity of chemotherapy, atezolizumab provides a more tolerable option with clinically meaningful efficacy. The recently reported Phase III study GO29294 (IMvigor 211) also support the clinically meaningful benefit demonstrated in IMvigor210.

Together, the safety analyses included in the submission dossier based on 2160 evaluable patients indicate that atezolizumab has an acceptable safety profile and was well tolerated in both NSCLC and UC patient populations which are characterised by advanced age with multiple comorbidities.

Thus, it is the sponsor’s position that the data support the proposed indications and support the use without regard to PD-L1 expression levels. In addition, although PD-L1 expression has been shown to correlate with outcome, a recommendation to test patients prior to accessing the treatment will not provide additional information to treating physicians regarding patients who may not benefit from atezolizumab therapy. The relationship between PD-L1 expression and outcome is comprehensively reported in the Clinical Trials section of the PI.

Atezolizumab has demonstrated clinical benefit in patients with 2L + UC

UC is one of the most common as well as challenging genitourinary malignancies to treat worldwide. UC 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 patients with UC remains a clinically challenging problem.³¹

Despite the efficacy of first-line regimens for patients treated with cisplatin-based therapies, responses show limited durability, with nearly all patients experiencing disease progression. With acknowledgment of the limitations of cross-trial comparisons, the IMvigor210 data for atezolizumab compares favourably with that of vinflunine, which is currently approved in Australia for 2L UC. The approval of vinflunine was based on data from a single randomised Phase III study that compared vinflunine plus best-supportive care (BSC) with BSC alone in 370 patients with advanced UC progressing after a platinum-containing therapy. In this study, patients were permitted only one prior therapy for metastatic disease (2L patients only). The benefit conferred with vinflunine was modest. The intent-to-treat (ITT) analysis showed an improvement in response rate (8.6% vs. 0%) with median duration of response (DOR) of 7.4 months (95% CI: 4.5, 17.0) for the vinflunine plus BSC arm but did not show a statistically significant overall survival (OS) benefit for vinflunine plus BSC compared with BSC alone (6.9 vs. 4.6 months; hazard ratio (HR) = 0.88; 95% CI: 0.69, 1.12). Vinflunine is TGA registered but is not Pharmaceutical Benefits Scheme listed, so it is not a well-established standard of care in Australia.

Although several chemotherapeutic agents have been studied in the 2L setting over the last three decades, the overall responses are not durable, and treatment is associated with considerable toxicity. Thus, effective and tolerable novel therapeutic options with durable responses are urgently needed for these patients. The approval of atezolizumab for 2L+ UC based on IMvigor210 in the US (approved May 2016), Canada (approved April 2017), and New Zealand (approved April 2017) provides a valuable treatment option where a high unmet need exists.

The sponsor believes that the totality of the data generated thus far in Studies IMvigor210 and PCD4989g demonstrate a positive benefit-risk profile of atezolizumab in all patients irrespective of the level of PD-L1 IC expression. The data along with the high unmet need in metastatic UC support the registration of atezolizumab as a clinically significant innovative therapeutic option for the treatment for patients.

Moreover, the most recent data analysis from Study IMvigor210 (July 2016 data cut) provides evidence that with further follow-up objective response rates (ORRs) translate into overall survival benefit and illustrate the utility of ORR as an acceptable demonstration of therapeutic efficacy. Finally, appended to this response, the sponsor has included topline results from the Phase III Study IMvigor211 that support consistency of the efficacy of atezolizumab in a Phase III trial.

IMvigor210 demonstrates robust and durable responses in patients with 2L UC

Study IMvigor210 was a two-cohort, single-arm study designed to evaluate the efficacy and safety of atezolizumab in patients with locally advanced or metastatic UC. Confirmed ORR based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) was selected as a primary endpoint for Study IMvigor210 based on the observation of durable responses with cancer immunotherapy, which are believed to represent direct benefit to patients.

In the primary analysis for Cohort 2 (2L+ metastatic UC), the study met its co-primary endpoints in all subgroups (IC2/3, IC1/2/3, and all comers), demonstrating clinically

³¹ Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64:9–29.

meaningful and statistically significant improvements of ORR per independent review facility (IRF)- assessed RECIST v1.1 and per investigator-modified RECIST compared with a historical chemotherapy control response rate of 10%. In the all-comers population, a statistically significant ORR of 15.1% was demonstrated (p-value = 0.0058). In the IC2/3 subgroup, a clinically meaningful, statistically significant ORR of 27.0% was demonstrated (p-value = 0.0001 compared with a historical control of 10%). In the IC0 and IC1 subgroups, the ORRs were similar to the historical control: the ORR was 8.7% and 10.2%, respectively.

An updated data analysis of IMvigor210 Cohort 2 (clinical cut-off date of 4 July 2016) was performed, with a median survival follow-up of 21.1 months (95% CI: 20.7, 21.5) in the all-comers population. At the time of the update, which provides an additional 15 months of follow-up from the time of the primary analysis, the efficacy of atezolizumab remained clinically meaningful. The more mature DOR and OS data clearly establish that the benefit observed is durable over time regardless of the level of PD-L1 expression.

The IRF-assessed confirmed ORR in Cohort 2 remained consistent with the ORR reported in the primary analysis in all IC subgroups and in the all-comers population, with additional responders being observed over time (49 in the updated all-comers analysis vs. 47 in the primary analysis). Responses, including complete responses (CRs), were detected in all PD-L1 subgroups, including in the IC0 and IC1 subgroups. The confirmed ORR was 16% in the all-comers population, 28% in the IC2/3 subgroup, 19% in the IC1/2/3 subgroup, 11% in the IC1 subgroup, and 9% in the IC0 subgroup.

Of note, complete responses accounted for 39% (19 of 49) of the observed responses in all-comers. Seven additional CRs were observed at the 21-month follow-up analysis (19 total CRs in updated all-comers analysis vs. 12 CRs in all-comers at primary analysis). In comparison with the 6% CR rate in the all-comers, the CR rate in the pivotal vinflunine study was 0%. CRs in the IMvigor210 study were also detected in patients with poor prognostic factors such as low Eastern Cooperative Oncology Group (ECOG) performance status, visceral and liver metastases, and Bellmunt scores of 1 or 2.

Responses were durable as of the 21-month follow-up analysis. Approximately 65% of patients (32 of 49) experienced ongoing responses, with a DOR range of 2.1 - 22.6 months. The median DOR was not reached in the IC1, IC1/2/3, and IC2/3 subgroups and in the all-comers population. The median DOR in the IC0 subgroup was 13.3 months. Within the IC0 subgroup, 5 of 9 responders progressed, but all 5 continued to show benefit with treatment beyond progression. The durable responses conferred by atezolizumab, which were observed across all IC subgroups, represent a meaningful clinical benefit when compared with such therapies as vinflunine with a median DOR of 7.4 months (range, 4.5 - 17.0 months), docetaxel with a reported median DOR of 4 months (range, 3.0 - 8.0 months), and pemetrexed with a median DOR of 8 months (range, 6.0 - 18.0 months).³²

In the 21-month follow-up analysis, the median OS was 7.9 months in the all-comers population, 11.9 months in IC2/3, 9 months in IC1/2/3, 6.7 months in IC1, and 6.5 months in IC0. Notably, in patients who had only one prior line of therapy for metastatic UC (2L-only patients), the population similar to the historical comparator studies, the median OS in the all-comers population was 9.0 months, NE (not reached) in the IC2/3 subgroup, and 10.9 months in the IC1/2/3 subgroup.

³² McCaffrey J, Hilton S, Mazumdar M, et al. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. *J Clin Oncol* 1997;15:1853-7; Bellmunt J, Theodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol* 2009;27:4454-61; Bambury RM, Benjamin DJ, Chaim JL, et al. The safety and efficacy of single-agent pemetrexed in platinum-resistant advanced urothelial carcinoma: a large single institution experience. *Oncologist* 2015;20:508-15.

The survival outcomes conferred by atezolizumab, irrespective of PD-L1 status, are clinically meaningful when compared with therapies such as vinflunine with a median OS of 6.9 months, docetaxel with a median OS of 7.0 months, and pemetrexed with a median OS of 6.7 months.³³ The 12-month landmark OS rates compared favourably with historic estimates of approximately 20%,³⁴ reaching 37% among all-comers, 50% in the IC2/3 subgroup, 40% in the IC1/2/3 subgroup, and 30% and 31% in the IC0 and IC1 subgroups, respectively, as well as 38% in the 2L-only patients.

The safety profile based on the updated analyses with a median follow-up of 21-months was consistent with results from the primary analysis, as well as with results from other single-agent atezolizumab trials. Moreover, the safety profile was consistent between the IC subgroups. No new safety concerns were identified. The majority of patients were able to tolerate atezolizumab, with a 3.9% rate of adverse events leading to treatment withdrawal. This compared favourably with the treatment discontinuation rate of 21% reported in the pivotal vinflunine study.³⁵ The preponderance of deaths (211 of 226, or 93%) in Cohort 2 were due to disease progression. Overall, atezolizumab treatment was well tolerated, with a manageable adverse event profile. Moreover, with an 18% Grade 3-4 adverse event rate, atezolizumab compares favourably with the significant toxicity experienced with standard chemotherapies such as vinflunine, which includes Grade 3 or 4 neutropaenia (50%), anaemia (19%), fatigue (19%), constipation (16%), nausea (2%), and vomiting (3%).

Data from the recently unblinded randomised Phase III Study IMvigor211 is provided as an appendix to this response. The topline results from IMvigor211 were announced on 10 May and the full data will be presented publically later this year. Therefore, in the interim, the sponsor requests the data reported in this response to be treated confidentially. IMvigor211 investigated the efficacy and safety of atezolizumab compared with an investigator's choice of vinflunine, docetaxel, or paclitaxel in patients with locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy. IMvigor211 enrolled a total of 931 patients between January 2015 and February 2016. The primary endpoint of OS was assessed in three pre-defined patient populations (PD-L1 IC2/3 and IC 1/2/3 subgroups and the ITT population) using a fixed-sequence, hierarchical testing procedure. The primary pre-specified endpoint of OS was not met; however, overall, atezolizumab provided a positive benefit-risk profile. The safety and efficacy results were consistent with those of previous studies. Efficacy measures such as 12-month OS and DOR afforded evidence of a clinically meaningful benefit with atezolizumab across all IC subgroups. The safety profile of atezolizumab, including low rates of adverse events leading to treatment withdrawal and treatment interruption, as well as a low frequency of treatment-related Grade 3/4 adverse events, were consistent across the IC subgroups and appeared qualitatively different from that of conventional cytotoxic chemotherapy, indicating that atezolizumab is a more tolerable alternative to chemotherapy.

In aggregate, the clinical benefit, in the context of a tolerable safety profile, observed in Study IMvigor210 (Cohort 2), Study IMvigor211 and supported by data from the 2L +

³³ McCaffrey J, Hilton S, Mazumdar M, et al. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. *J Clin Oncol* 1997;15:1853-7; Bellmunt J, Theodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol* 2009;27:4454-61; Bambury RM, Benjamin DJ, Chaim JL, et al. The safety and efficacy of single-agent pemetrexed in platinum-resistant advanced urothelial carcinoma: a large single institution experience. *Oncologist* 2015;20:508-15.

³⁴ Agarwal N, Bellmunt J, Maughan BL, et al. Six-month progression-free survival as the primary endpoint to evaluate the activity of new agents as second-line therapy for advanced urothelial carcinoma. *Clin Genitourin Cancer* 2014;12:130-7.

³⁵ Vinflunine Australian Public Assessment Report (AusPAR).

metastatic UC cohort from the Phase Ia Study PCD4989g demonstrates the consistent, clinically meaningful, and durable benefit of atezolizumab treatment irrespective of the level of PD-L1 expression.

The sponsor is continuing to investigate the safety and efficacy of atezolizumab in patients with urothelial carcinoma. Study MO29983 (SAUL) is an ongoing open-label, single arm, multicentre, safety study of atezolizumab in locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract. Study WO30070 (IMvigor130) is an ongoing Phase III multicentre, randomised, placebo-controlled study of atezolizumab as monotherapy and in combination with platinum-based chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma.

Baseline PD-L1 testing is not warranted for patient access to atezolizumab

Non-small cell lung cancer

The sponsor seeks to establish atezolizumab monotherapy as a new treatment option for patients with 2L + locally advanced or metastatic NSCLC. The totality of the data clearly demonstrates a consistent and meaningful clinical benefit in atezolizumab-treated patients with 2L + NSCLC, irrespective of PD-L1 expression, compared with standard-of-care chemotherapy.

The pivotal Phase III Study OAK was a large prospectively planned, randomised, open-label, active-controlled, multicentre Phase III study that allows a robust evaluation of efficacy and safety of atezolizumab for patients with 2L+ NSCLC. OAK enrolled an all-comer population of patients (regardless of PD-L1 expression) with locally advanced or metastatic NSCLC that had progressed during or after a platinum-containing regimen in the 2L/3L setting. At randomisation, patients were stratified by PD-L1 IC status, histology, and line of therapy. The primary objective of the study was to investigate the OS benefit of atezolizumab compared with docetaxel in patients with NSCLC after treatment failure with platinum-containing chemotherapy.

In OAK, the co-primary endpoints in ITT and TC1/2/3 and IC1/2/3 were met. A statistically significant and clinically meaningful improvement in OS was observed for patients assigned to atezolizumab in the all-comer (ITT) population compared with docetaxel.

Based on the efficacy data from OAK, it is clear that OS benefit with atezolizumab is seen across all PD-L1 expression cut-offs evaluated. While there is pronounced benefit in the TC3 or IC3 patients, it is important to note that the lowest PD-L1 expression subgroup (TC0 and IC0) had a similar OS benefit as the ITT population as well as the TC1/2/3 or IC1/2/3 subgroup. In light of these data, it is the sponsor's opinion that PD-L1 testing will not add additional information to treating physicians regarding patients who may not benefit from atezolizumab therapy; rather, it provides information on patients who may do better than most. As such the sponsor does not agree on the need to add a recommendation to the PI that patients should be PD-L1 tested at baseline prior to access to atezolizumab.

Opdivo (nivolumab), a PD-1 inhibitor currently TGA approved for an 'all-comer' indication in squamous and non-squamous NSCLC does not include a recommendation for PD-L1 testing prior to access to treatment. This is despite a positive relationship being observed between PD-L1 expression and outcome in the pivotal Study CA209057 in non-squamous NSCLC.³⁶ The EU SPC for Opdivo states:

Patients with tumour PD-L1 expression by all predefined expression levels in the nivolumab group demonstrated greater likelihood of improved survival compared to

³⁶ Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med*. 2015 Oct 22;373(17):1627-39.

docetaxel, whereas survival was similar to docetaxel in patients with low or no tumour PD-L1 expression.

Urothelial carcinoma

Based on the positive benefit-risk profile of atezolizumab observed in all patients with metastatic UC across all IC subgroups including IC2/3, IC1 and IC0, the sponsor is of the opinion that the decision to test should be left to the physician in discussion with the patient.

Conclusion

The sponsor agrees with the Delegate that Tecentriq (atezolizumab) should be registered for 2L+ locally advanced or metastatic NSCLC and 2L + locally advanced or metastatic UC in 'all-comer' populations. In addition, although PD-L1 expression has been shown to correlate with outcome, it is the sponsor's position that a recommendation to test patients prior to accessing the treatment will not provide additional information to treating physicians regarding patients who may not benefit from atezolizumab therapy. The sponsor believes the relationship between PD-L1 expression and outcome is comprehensively reported in the Clinical Trials section of the PI.

Advisory Committee Considerations³⁷

The ACM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Tecentriq single-use vial containing 1200 mg of atezolizumab in a 20 mL concentrated solution of atezolizumab to have an overall positive benefit-risk profile for the indication:

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

The ACM taking into account the submitted evidence of efficacy, safety and quality, and considered Tecentriq single-use vial containing 1200 mg of atezolizumab in a 20 mL concentrated solution of atezolizumab to have an overall negative benefit-risk profile for the indication:

Tecentriq is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy.

Specific advice

ACM advised the following in response to the Delegate's specific questions on the submission:

1. *Taking into account the design and outcomes of IMvigor210, is benefit sufficiently well demonstrated for atezolizumab in 2L+ metastatic UC patients who have: (a) No tumour-infiltrating immune cell PD-L1 expression (IC0); (b) Weak tumour-infiltrating immune cell PD-L1 expression (IC1); and (c) Moderate to strong tumour-infiltrating immune cell PD-L1 expression (IC2/3).*

³⁷ The ACM provides independent medical and scientific advice to the Minister for Health and TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the *Therapeutic Goods Regulations 1990*. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in 2010. ACM encompasses pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

2. The ACM agreed that based on IMvigor210, benefit was sufficiently demonstrated in all 3 subgroups. ACM noted that there is no tenable alternative to immunotherapy for this population of patients. A response rate of 15-19% suggests promising efficacy relative to a historical control ORR of 10%. ACM also noted that differences in ORR by PD-L1 status varied somewhat depending on how ORR was measured (standard RECIST versus other). *Should the PI recommend PD-L1 testing in NSCLC? Or, given apparent benefit in 'PD-L1 negative' patients, should this be left to clinician / patient choice?*

The ACM agreed that prognostic testing for PD-L1 expression in NSCLC is recommended but not mandatory. The ACM also agreed that it would be reasonable for PD-L1 testing in NSCLC be left to the discretion of treating clinicians in the absence of robust and consistent data.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of Tecentriq as indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.

The ACM, taking into account the submitted evidence of efficacy and safety, including top-level outcomes of IMvigor211 supplied at the pre-ACM response stage (that is, after the usual TGA evaluation phase) agreed that Tecentriq single-use vial containing 1200 mg of atezolizumab in a 20 mL concentrated solution of atezolizumab has an overall negative benefit-risk profile for the proposed indication of:

Tecentriq is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy.

In making this recommendation, the ACM:

- noted the lack of randomised data in IMvigor210;
- noted that IMvigor211 provides substantial data regarding efficacy and safety in the proposed urothelial carcinoma patient population, but only top-level data have been provided at the pre-ACM Response stage, and these top-level data do not sufficiently clearly show benefit in the proposed population, or allow assessment of benefit-risk in potentially relevant subgroups.

Post ACM period

Following the availability of the ACM resolution, the sponsor discussed with the Delegate the proposed UC indication. The Delegate communicated the need to review the full Clinical Study Report for Study IMvigor211. The sponsor communicated that only top-level results from Study IMvigor211 were currently available. A Clinical Study Report was expected to be available in Q4 2017.

The sponsor subsequently withdrew the proposed UC indication from the scope of this application in order to not delay availability of atezolizumab for NSCLC patients.

The sponsor communicated its position that the results of Study IMvigor211 showed a treatment effect of atezolizumab consistent with the submitted studies in the second-line mUC population (Studies PCD4989g and IMvigor210, Cohort 2). The study demonstrated that, at the time of the primary analysis, a numerically higher proportion of patients were alive and deriving benefit compared with chemotherapy. For patients who responded to atezolizumab, the duration of response was substantially longer compared with chemotherapy. The atezolizumab safety profile was consistent with previous data from UC as well as with data from previous single-agent studies in other indications. The safety

data showed no new safety signals and demonstrated a more favourable safety profile for atezolizumab compared to chemotherapy. Based on these data, it was the sponsor's position that the benefit-risk profile of atezolizumab treatment compared to chemotherapy was favourable for second-line mUC patients.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Tecentriq [atezolizumab (rch)] 1200 mg/20 mL injection concentrated vial, indicated for:

Tecentriq is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, Tecentriq should be used after progression on or after targeted therapy.

Specific conditions of registration applying to these goods

The Tecentriq atezolizumab (rch) EU RMP, version 1.0, dated 24 March 2016 (data lock point 25 February 2016), with ASA, version 1.0, dated May 2016, and any future updates, as agreed with the TGA, must be implemented in Australia.

Batch Release Testing & Compliance with Certified Product Details

All batches of Tecentriq imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

Each batch of Tecentriq imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

The sponsor must supply:

- Certificates of Analysis of all active ingredient (drug substance) and final product.
- Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
- Evidence of the maintenance of registered storage conditions during transport to Australia.
- Five vials of each batch for testing by the TGA Laboratories Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

Attachment 1. Product Information

The PI for Tecentriq approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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