EU RISK MANAGEMENT PLAN FOR TECENTRIQ®/ATEZOLIZUMAB

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Rationale for submitting an updated RMP:

This atezolizumab (Tecentriq®) E.U. Risk Management Plan (RMP) version 29.1 (currently ongoing procedure EMEA/H/C/004143/II/0082) was prepared to consolidate the E.U. RMP version 29.0 with the currently approved E.U. RMP version 30.1 (procedure EMEA/H/C/004143/II/0083G).

The E.U. RMP v29.0 was prepared to support the extension of indication for Tecentriq (atezolizumab). This submission is based on data from Study MO29872 (IPSOS). The pooled monotherapy population in the RMP was updated to include safety-evaluable patients from Study MO29872 (IPSOS).

The E.U. RMP v29.1 includes the following revised indication statement, updated in agreement with the Committee for Human Medicinal Products (CHMP), following the assessment of Responses to the second Request for Supplementary Information (RSI): ″Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with advanced NSCLC who are ineligible for platinum-based therapy″.

Summary of significant changes in this RMP (v29.0, v29.1 including consolidation with v30.1):

Part	Summary of significant changes	Rationale
Part I	**Product Overview:** Information was included on the proposed extension of indication for Tecentriq. The proposed indication statement was revised. The brief product description, indication, pharmaceutical forms(s) and strengths, and dosage sections were updated to include subcutaneous formulation and dosages and align with the Summary of Product Characteristics.	Updated with IPSOS (Study MO29872) study data. Revision based on Committee for Human Medicinal Products (CHMP) request. Updated to align with the currently approved European Union (E.U.) Risk Management Plan (RMP) v30.1.
Part II, SI.2	The epidemiology section for non-small cell lung cancer (NSCLC) was updated.	New epidemiology data was available for NSCLC.
Part II, SIII.1	Clinical trial exposure in monotherapy was updated to include IPSOS (Study MO29872) study data in the existing pooled patient population. Study-specific data are presented separately as well. Clinical trial exposure in monotherapy was also updated to include data from Study BP40657 (IMscin001).	Updated with IPSOS (Study MO29872) study data. Updated to align with the currently approved E.U. RMP v30.1.
Part II, SIV.2	Updated to include development program for atezolizumab subcutaneous (SC) formulation.	Updated to align with the currently approved E.U. RMP v30.1.
Part II, SIV.3	Exposure of special populations included or not in clinical trial development program was updated.	Updated to align with the currently approved E.U. RMP v30.1 and to include IPSOS (Study MO29872) study data.
Part II, SV.1	Post-authorisation exposure was updated from the latest Period Benefit Risk Evaluation Report (PBRER) with data lock point (DLP) 17 May 2023. The table for Cumulative Exposure from Marketing Experience has been moved to Annex 7 and a reference to Annex 7 has been added in its place.	This section was updated to align with the atezolizumab PBRER 1122480 with DLP 17 May 2023. Updated to align with the currently approved E.U. RMP v30.1.

Part	Summary of significant changes	Rationale
Part II, SVII.3.1	<u>Information on Important Identified Risks</u> The characterisation of the safety concerns was updated with the available safety data from the IPSOS study and from IMscin001 (BP40657) study. Preferred Terms were updated for Adrenal Insufficiency, Myocarditis, Hypophysitis, and Severe Cutaneous Adverse Reactions. Evidence source for Haemophagocytic Lymphohistiocytosis (HLH) has been updated. <u>Information on Important Potential Risks</u> Attenuated efficacy or reduced tolerability in patients with anti-drug antibodies (ADAs): The baseline prevalence has been removed and the post baseline incidence of treatment-emergent ADAs was summarised in a table. Data from the IMscin001 (BP40657) study was added. The incidence of ADAs against recombinant human hyaluronidase enzyme PH20 (rHuPH20) after administration of atezolizumab SC was added.	Updated with IPSOS (Study MO29872) study data and to align with the currently approved E.U. RMP v30.1. Preferred Terms were updated to align with the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1. Updated to align with the currently approved E.U. RMP v30.1. Updated to align with the currently approved E.U. RMP v30.1. Updated to align with the currently approved E.U. RMP v30.1.
Part II, SVII.3.2	Information on missing information i.e., 'Long term use' has been removed.	Updated to align with the currently approved E.U. RMP v30.1.
Part II, SVIII	'Long-term use' has been removed as a safety concern.	Updated to align with the currently approved E.U. RMP v30.1.
Part III, III.2 and III.3	Study MO29983 (SAUL) has been removed from Additional Pharmacovigilance Activities.	Updated to align with the currently approved E.U. RMP v30.1.
Part IV	Study GO29293 (IMvigor210) has been removed from the list of post authorisation efficacy studies.	Updated to align with the currently approved E.U. RMP v30.1.
Part V, V.1 and V.3	“Relevant information for patient in PIL” was added to the routine risk minimisation activities for the risk of embryo-fetal toxicity. The safety concern 'Long term use' has been removed from the tables related to risk minimisation measures.	Updated to align with the currently approved E.U. RMP v30.1.

Part	Summary of significant changes	Rationale
Part V, V.2 and V.3	The dissemination date for the Direct Healthcare Professional Communication (DHPC) for Severe Cutaneous Adverse Reactions (SCARs) was added to the relevant tables.	Updated to align with the currently approved E.U. RMP v30.1.
Part VI, I	Indication statement was updated with the proposed extension of indication for Tecentriq. The proposed indication statement was revised. Description of the medicine and dosage were updated to include Tecentriq SC.	Updated with IPSOS (Study MO29872) study data. Revision based on CHMP request. Updated to align with the currently approved E.U. RMP v30.1.
Part VI, II.A and II.B	Information on missing information i.e., 'Long term use' has been removed.	Updated to align with the currently approved E.U. RMP v30.1.
Part VI, II.B	The dissemination date for the DHPC for SCARs was added. The evidence source for HLH has been updated. “Relevant information for patient in PIL” was added to the routine risk minimisation activities for the risk of embryo-fetal toxicity. The risk of ADAs was updated in line with Part II, SVII.3.1.	Updated to align with the currently approved E.U. RMP v30.1.
Part VI, II.C.1	Study GO29293 (IMvigor210) is no longer listed under studies which are conditions of marketing authorisation.	Updated to align with the currently approved E.U. RMP v30.1.
Part VI, II.C.2	Study MO29983 (SAUL) is no longer listed under other studies in post-authorisation development plan.	Updated to align with the currently approved E.U. RMP v30.1.
Annex 2	Study MO29983 (SAUL) has been moved to completed studies.	Updated to align with the currently approved E.U. RMP v30.1.
Annex 3	Protocol for Study MO29983 (SAUL) has been removed.	Updated to align with the currently approved E.U. RMP v30.1.
Annex 5	Protocols for Study WO30070 (IMvigor130) and Study GO29293 (IMvigor210) have been removed.	Updated to align with the currently approved E.U. RMP v30.1.

Part	Summary of significant changes	Rationale
Annex 7	References to new literature and updated summary tabulations of prospective and retrospective Individual Case Safety Reports on pregnancy from the most recent PBRER were added. References to Study WO30070 (IMvigor130) Updated CSR, Study MO29983 (SAUL) Final CSR and Study GO29293 (IMvigor210) Final CSR were added. The table for Cumulative Exposure from Marketing Experience has been moved from the core report to Annex 7.	New key references were added in Part II, SI.2 (epidemiology) and more recent summary tabulations were available from PBRER 1122480 with DLP 17 May 2023. Updated to align with the currently approved E.U. RMP v30.1. Updated to align with the currently approved E.U. RMP v30.1.
Annex 8	Annex 8 was updated to reflect the changes to this RMP.	Reflect key changes during RMP update.

ADA = anti-drug antibody; CHMP = Committee for Human Medicinal Products; CSR = clinical study report; DHPC = Direct Healthcare Professional Communication; E.U. = European Union; DLP = data lock point; HLH = haemophagocytic lymphohistiocytosis; ICSR = Individual Case Safety Report; NSCLC = non–small cell lung cancer; PBRER = Period Benefit Risk Evaluation Report; PIL = Patient Information Leaflet; rHuPH20 = recombinant human hyaluronidase enzyme PH20; RMP = Risk Management Plan; SC = subcutaneous; SCARs = Severe Cutaneous Adverse Reactions.

Minor editorial/formatting changes have been undertaken in this RMP.

Other RMP versions under evaluation:

RMP version number: 28.0 (IMbrave050)

Submitted on: 14 August 2023

Procedure Number: EMEA/H/C/004143/II/0081

RMP version number: 31.0 (IMscin002)

Submitted on: 04 July 2024

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Details of Currently Approved RMP:

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Date of approval (opinion date): 08 February 2024

See page 1 for signature and date

Dr. Birgitt Gellert (EU QPPV) | Date

See page 1 for signature and date

PPD , PhD PPD | Date

PART I: PRODUCT OVERVIEW

Table 1 Product Overview

Active Substance(s) (INN or common name)	Atezolizumab
Pharmacotherapeutic group(s) (ATC Code)	L01FF05
Marketing Authorisation Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	Tecentriq
Marketing authorisation procedure	Centralised Authorisation Procedure
Brief description of the product including:	**Chemical Class** Atezolizumab (MPDL3280A) is a humanised immunoglobulin G1 monoclonal antibody
	Summary of mode of action Atezolizumab targets human PD-L1 on tumour-infiltrating immune cells (ICs) and tumour cells (TCs) and inhibits its interaction with its receptors programmed death−1 (PD-1) and B7.1, both of which can provide inhibitory signals to T cells.
	Important information about its composition **Tecentriq Intravenous (IV)** Concentrate for solution for infusion (sterile concentrate). **Tecentriq Subcutaneous (SC)** Solution for injection (subcutaneous use only).
Hyperlink to the Product Information	EU PI

Indication(s) in the EEA	**Current:** **<u>Tecentriq IV</u>** <u>Tecentriq monotherapy</u> • **UC** Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC): – after prior platinum-containing chemotherapy, or – who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%. • **NSCLC** Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with epidermal growth factor receptor (EGFR) mutant or anaplastic lymphoma kinase (ALK)-positive NSCLC should also have received targeted therapies before receiving Tecentriq. Tecentriq as monotherapy is indicated for the first-line (1L) treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥50% TC or ≥10% tumour-infiltrating IC and who do not have EGFR mutant or ALK-positive NSCLC. Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥50% of TC and who do not have EGFR mutant or ALK-positive NSCLC.

	<u>Tecentriq combination</u> • **NSCLC** Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies. Tecentriq, in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC. • **SCLC** Tecentriq, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC). • **TNBC** Tecentriq, in combination with nab-paclitaxel, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression $\geq$1%, and who have not received prior chemotherapy for metastatic disease. • **HCC** Tecentriq, in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

	Tecentriq SC Tecentriq subcutaneous is indicated in all the approved indications of Tecentriq IV.
	Proposed: Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with advanced NSCLC who are ineligible for platinum-based therapy.
Dosage in the EEA	**Current:** **Tecentriq IV** Tecentriq monotherapy The recommended dose of Tecentriq is either: • 840 mg administered IV every two weeks (q2w), or • 1,200 mg administered IV every three weeks (q3w), or • 1,680 mg administered IV every four weeks (q4w). Tecentriq in combination therapy For induction and maintenance phases, the recommended dose of Tecentriq is either: • 840 mg administered IV q2w, or • 1,200 mg administered IV q3w, or • 1,680 mg administered IV q4w. • **1L non-squamous NSCLC** *Tecentriq in combination with bevacizumab, paclitaxel, and carboplatin*: Tecentriq should be administered first when given on the same day. During the induction phase, Tecentriq is administered by IV infusion, followed by bevacizumab, paclitaxel and then carboplatin. During the induction phase, combination partners are administered q3w weeks for four or six cycles. The induction phase is followed by a maintenance phase without chemotherapy in which Tecentriq is

	administered by IV infusion. Bevacizumab is administered q3w. *Tecentriq in combination with nab-paclitaxel and carboplatin:* Tecentriq should be administered first when given on the same day. During the induction phase, Tecentriq is administered by IV infusion, followed by nab-paclitaxel and carboplatin. The combination partners are administered q3w for four or six cycles. For each 21-day cycle, nab-paclitaxel and carboplatin are administered on Day 1. In addition, nab-paclitaxel is administered on Days 8 and 15. The induction phase is followed by a maintenance phase without chemotherapy in which Tecentriq is administered by IV infusion. • **SCLC** *Tecentriq in combination with carboplatin and etoposide:* During the induction phase: On Day 1, Tecentriq is administered by IV infusion followed by carboplatin and then etoposide administration by IV infusion. On Days 2 and 3, etoposide is administered by IV infusion. Combination partners are administered q3w for four cycles. During the maintenance phase (without chemotherapy): Tecentriq is administered by IV infusion. • **TNBC** *Tecentriq in combination with nab-paclitaxel in 1L mTNBC:* Tecentriq should be administered by IV infusion followed by nab-paclitaxel when given on the same day. Nab-paclitaxel should be administered at 100 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle.

	• **HCC** *Tecentriq in combination with bevacizumab:* Tecentriq should be administered by intravenous infusion followed by bevacizumab when given on the same day. Bevacizumab is administered at 15 mg/kg of body weight by IV infusion q3w. **<u>Tecentriq SC</u>** <u>Tecentriq monotherapy</u> The recommended dose of Tecentriq SC is: • 1875 mg administered SC q3w. <u>Tecentriq in combination therapy</u> For induction and maintenance phases, the recommended dose of Tecentriq SC is 1875 mg administered SC q3w. • **1L non-squamous NSCLC** *Tecentriq in combination with bevacizumab, paclitaxel, and carboplatin:* Tecentriq SC should be administered first when given on the same day. During the induction phase, Tecentriq SC is administered subcutaneously, followed by bevacizumab, paclitaxel and then carboplatin. During the induction phase, combination partners are administered q3w for 4 or 6 cycles. The induction phase is followed by a maintenance phase without chemotherapy in which Tecentriq SC is administered subcutaneously. Bevacizumab is administered q3w. *Tecentriq in combination with nab-paclitaxel and carboplatin:* Tecentriq SC should be administered first when given on the same day. During the induction phase, Tecentriq SC is administered subcutaneously, followed by nab-paclitaxel and carboplatin. The combination partners are administered q3w for 4 or 6 cycles. For each 21-day cycle, nab-paclitaxel and carboplatin are administered on Day 1. In addition, nab-paclitaxel is administered on Days 8 and 15.

	The induction phase is followed by a maintenance phase without chemotherapy in which Tecentriq SC is administered subcutaneously. • **SCLC** *Tecentriq in combination with carboplatin and etoposide:* During the induction phase: On Day 1, Tecentriq SC is administered subcutaneously followed by carboplatin and then etoposide administration by IV infusion. On Days 2 and 3, etoposide is administered by IV infusion. Combination partners are administered q3w for 4 cycles. During the maintenance phase (without chemotherapy): Tecentriq SC is administered subcutaneously. • **TNBC** *Tecentriq in combination with nab-paclitaxel in 1L mTNBC:* Tecentriq SC should be administered subcutaneously prior to nab-paclitaxel when given on the same day. Nab-paclitaxel should be administered at 100 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle. • **HCC** *Tecentriq in combination with bevacizumab:* Tecentriq SC should be administered subcutaneously prior to bevacizumab when given on the same day. Bevacizumab is administered at 15 mg/kg of body weight by IV infusion q3w.
	Proposed: Not applicable

Pharmaceutical form(s) and strengths	**Current:** **<u>Tecentriq IV</u>** Concentrate for solution for infusion (sterile concentrate). Strength: 60 mg/mL **<u>Tecentriq SC</u>** Solution for injection (subcutaneous use only) Strength: 125 mg/mL
	Proposed: Not applicable
Is or will the product be subject to additional monitoring in the E.U.?	No

1L = first-line; ALK=anaplastic lymphoma kinase; ATC = Anatomical Therapeutic Chemical; EEA = European Economic Area; EGFR = epidermal growth factor receptor; ES-SCLC = extensive-stage small cell lung cancer; E.U. = European Union; IC = immune cell; IV = intravenous; HCC = hepatocellular carcinoma; INN = International Nonproprietary Name; mTNBC = metastatic triple-negative breast cancer; NSCLC = non–small cell lung cancer; PD-1=programmed death-1; PD-L1 = programmed death-ligand 1; PI = Product Information; q2w = every two weeks; q3w = every three weeks; q4w = every four weeks; RMP = Risk Management Plan; SC = subcutaneous; SCLC=small cell lung cancer; TC = tumour cell; TNBC = triple-negative breast cancer; UC = urothelial carcinoma.

ABBREVIATIONS

Abbreviation	Definition
1L	first-line
2L	second-line
2L+	subsequent lines
3L	third-line
ADA	anti-drug antibody
AE	adverse event
AEGT	adverse event grouping term
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ASR	age standardised rate
CCOD	clinical cutoff date
CI	confidence interval
CL-13	Clone-13
DLP	data lock point
DOT	duration of treatment
EAU	European Association of Urology
ECIS	European Cancer Information System
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EMR	electronic medical records
eNSCLC	early-stage non-small cell lung cancer
ER	estrogen receptor
ES-SCLC	extensive-stage small cell lung cancer
ESMO	European Society for Medical Oncology
E.U.	European Union
E.U.-RMP	EU Risk Management Plan
EV	EudraVigilance
FAERS	FDA Adverse Event Reporting System
FDA	U.S. Food and Drug Administration
FGFR	fibroblast growth factor receptor inhibitors
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HER2	human epidermal growth factor 2

Abbreviation	Definition
HLA	human leukocyte antigen
HLH	hemophagocyctic lymphohistiocytosis
HLT	high level term
HR	hazard ratio
IBD	International Birth Date
IC	tumour-infiltrating immune cell
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IRR	infusion-related reaction
IV	intravenous
KRAS	Kirsten rat sarcoma viral oncogene homologue
LCMV	lymphocytic choriomeningitis virus
MAH	Marketing Authorisation Holder
mBC	metastatic breast cancer
MRI	magnetic resonance imaging
mTNBC	metastatic triple-negative breast cancer
mUC	metastatic urothelial carcinoma
NAFLD	non-alcoholic fatty liver disease
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	non–small cell lung cancer
OR	odds ratio
PARP	poly (ADP-ribose) polymerase
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
PR	progestogen receptor
PT	Preferred Term
q2w	every 2 weeks
q3w	every 3 weeks
q4w	every 4 weeks
RMP	Risk Management Plan
RoW	Rest of World
SAE	serious adverse event
SC	subcutaneous
SCAR	severe cutaneous adverse reaction
SCLC	small cell lung cancer

Abbreviation	Definition
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TC	tumour cell
TKI	tyrosine kinase inhibitor
TNBC	triple-negative breast cancer
TPS	tumour proportion score
UC	urothelial carcinoma
U.S.	United States

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Urothelial Carcinoma (UC)

Incidence

Bladder cancer is the 9th most common malignancy worldwide, making up to 3.1% of all cancer diagnoses (Ferlay et al. 2015). New cases of bladder cancer (both sexes) diagnosed in 2010 in the United States, France, Germany, Italy, Spain, and United Kingdom accounted for almost half of all new cases diagnosed worldwide that year (Fam et al. 2011). Please refer to Table 2 for the incidence of bladder cancer worldwide, in the United States, and in the European Union.

From 1985 to 2005, the incidence of bladder cancer in the United States increased by more than 50% (Jemal et al. 2005; Jemal et al. 2010). The American Cancer Society estimated that in 2015 there were 74,000 new cases in the United States (American Cancer Society 2014).

In the United States and Western Europe, UC (also transitional cell carcinoma) is the predominant histologic type and accounts for approximately 90% of bladder cancers (Ploeg et al. 2009). The majority of patients (70%) present with superficial tumours (stages Ta, T1 or carcinoma in situ), and the rest (30%) present with muscle-invasive disease (T2–4); approximately 4% of all patients with bladder cancer present with de novo metastatic disease (American Cancer Society 2014). Approximately 50%–70% of superficial tumours recur and 10%–20% progress to muscle-invasive disease (Sun and Trinh 2015).

Prevalence

In 2012, the 5-year worldwide prevalence of bladder cancer was 1,319,749, and the 5-year prevalence proportion was 25.4 per 100,000 in both sexes (Bray et al. 2013); see Table 2 for prevalence data worldwide, in the United States, and the European Union.

Table 2 Estimates of Bladder Cancer Incidence, Mortality, and 5-Year Prevalence in 2012: United States, Europe, and Worldwide

Country	Number (Incidence)	Incidence per 100,000 (World age-standardised rate)	Number (Mortality)	Mortality per 100,000 (World age-standardised rate)	5-year Prevalence
Worldwide	429,793	5.3	165,084	1.9	1,319,749
United States	68,639	11.6	16,468	2.4	243,876
European Union (28)	124,188	10.8	40,635	2.9	413,522

Sources: Bray et al. 2013; Ferlay et al. 2015.

Demographics

Bladder cancer mainly occurs in older adults, with the mean and median age at diagnosis of 73 years (American Cancer Society 2014; Howlader et al. 2015). The incidence of bladder cancer increases with age; the incidence in men who are 65 to 69 years old is 142 per 100,000 and increases to 296 per 100,000 in men aged 85 years and over. In women in the same two age groups, the incidence increases from 33 to 74 per 100,000, respectively (Hinotsu et al. 2009).

A review of literature published between 1975 and 2011 showed that women have up to a 4-fold lower incidence of urothelial bladder cancer, but women disproportionately present with more advanced disease than men (Matsushita et al. 2011), and have less favorable outcomes after treatment (Dobruch et al. 2016).

Like age and gender, race and ethnicity are also associated with variations in bladder cancer incidence. In the United States, white males have the highest risk of bladder cancer, with approximately twice the incidence observed in African-American and Hispanic men (Howe et al. 2006).

Natural History of the Indicated Condition in the (Untreated) Population

Mortality and Morbidity

Bladder cancer deaths are ranked 13th among all cancer deaths; an estimated 165,000 deaths were attributed to bladder cancer in 2012, accounting for 2% of all cancer deaths worldwide (Ferlay et al. 2015). Please refer to Table 2 for further details on bladder cancer mortality. The age standardised rate (ASR) of bladder cancer mortality worldwide among males is 3.2 per 100,000, and among females the ASR is 0.9 per 100,000 (Ferlay et al. 2015).

Based on the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) database, the 5-year survival rates range from 98% for Stage 0 to 63% for Stage II and 15% for Stage IV (American Cancer Society 2014).

Pregnancy and Lactation

Bladder cancer during pregnancy is an extremely rare diagnosis. Recently, a study reported that approximately 50 cases have been published as single case reports or case series for pregnancy in bladder cancer patients, including all histologic variants (Rojas et al. 2021).

Risk Factors for the Disease

Smoking is the most important risk factor for bladder cancer, with half of all bladder cancers in both men and women attributed to smoking (American Cancer Society 2014). Epidemiologic evidence suggests that other risk factors for bladder cancer include older age (>45 years); male sex; occupational exposures such as to aromatic amines and polycyclic aromatic hydrocarbons; arsenic; exposure to medications such as phenacetin, cyclophosphamide, and chlornaphazine; and exposure to radiation (Malats and Real 2015). Infection with *Schistosoma hematobium*, a parasite found in Africa and the Middle East associated with schistosomiasis (Chavan et al. 2014), is also a risk factor for bladder cancer (Malats and Real 2015) in those regions. Genetic variants of genes coding for enzymes involved in the metabolism of urothelial carcinogens may contribute to the risk of developing bladder cancer; some of these genes include *GSTM1*, *NAT2*, *UGT1A*, and *SLC14A1* (Malats and Real 2015). Differences in incidence and mortality between men and women may be due to environmental exposure to carcinogens, anatomic and hormonal factors, and unequal access to healthcare (Burger et al. 2013).

The Main Existing Treatment Options

Guidelines for the diagnosis and management of UC issued by the American Urological Association, European Association of Urology (EAU), European Society for Medical Oncology (ESMO), and the National Comprehensive Cancer Network (NCCN) all provide an evidence-based framework, but occasionally vary with respect to issues such as definitions of risk level and management strategies. Based on EAU and NCCN guidelines, treatment of non–muscle invasive disease includes transurethral resection of bladder tumours, followed by intravesical therapy or cystectomy, with the goal of curative intent, reduction of recurrence, and prevention of progression to a more advanced stage. The EAU endorses radical cystectomy as the curative treatment of choice for muscle-invasive disease. In metastatic disease, chemotherapy and/or radiotherapy are used to prolong quantity and quality of life. The NCCN recommends transurethral resection of bladder tumours, partial or radical cystectomy, neoadjuvant and adjuvant chemotherapy, and radiotherapy with curative intent to reduce recurrence, and to prevent progression to advanced disease (NCCN 2017; European Association of Urology [EAU] 2017).

The recommended first-line (1L) chemotherapy regimen partially depends on the presence or absence of medical comorbidities, including cardiac disease and renal function. First-line chemotherapy options include gemcitabine and cisplatin, and dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin. In 2020/2021, avelumab, a

programmed death–ligand 1 (PD-L1) inhibitor, received approval in the United States and E.U. for the maintenance treatment of metastatic urothelial carcinoma (mUC) patients who did not progress following platinum-based chemotherapy (Powles et al. 2020). For patients ineligible for cisplatin, alternate regimens include carboplatin- or taxane-based combination chemotherapy, checkpoint inhibitors (atezolizumab or pembrolizumab) as monotherapy, or single-agent chemotherapy (Bellmunt et al. 2014; EAU 2017, NCCN 2017). However, in the United States, pembrolizumab and atezolizumab have been withdrawn for this indication.

The recommended subsequent lines (2L+) of therapy depend on what was given as 1L. Globally, regimens used in this setting include the checkpoint inhibitors (pembrolizumab, atezolizumab, nivolumab, durvalumab or avelumab), single agent chemotherapy (vinflunine, taxanes, gemcitabine or pemetrexed) and participation in clinical trials (EAU 2017; NCCN 2017). In the European Union, vinflunine, nivolumab, atezolizumab and pembrolizumab were approved in the 2L+ setting (Bellmunt et al. 2009). In the United States, pembrolizumab, atezolizumab, durvalumab, nivolumab, and avelumab were approved in the 2L+ setting in 2017 (NCCN 2017), but in 2021, pembrolizumab, atezolizumab, and durvalumab were withdrawn for this indication.

Important Comorbidities

Table 3 Prevalence of Selected Comorbidities in Bladder Cancer Patients Compared to People without Cancer

Comorbid condition	Prevalence	
	People without cancer, ≥66 years [a] (%)	Metastatic UC, U.S. MarketScan, ≥18 years [b] (%)
COPD	9	22
Diabetes	14	24
Peripheral vascular disease	3	10
Congestive heart failure	7	9
Cerebrovascular disease	5	9

COPD = chronic obstructive pulmonary disease; UC = urothelial carcinoma; U.S. = United States.

[a] Source: Edwards et al. 2014.

[b] Source: Roche internal data analysis, 98% patients ≥40 years old, mean age 68 years.

Table 4 Prevalence of Selected Comorbidities in Bladder Cancer Patients

Comorbid condition	Stage II, III, IV, Netherlands, mean age 70 years [a]	All stages, U.S. ≥55 years [b]
Pulmonary comorbidity	13%	19%
Diabetes	12%	N/A
Hypertension	19%	38%
Cardiovascular disease	31%	N/A
Heart, high impact	N/A	22%
Heart, moderate impact	N/A	22%
Heart, low impact	N/A	17%
Urinary, low impact	N/A	12%
Arthritis	N/A	17%
Previous cancer	N/A	12%
Anaemia	N/A	11%

N/A = not available; U.S. = United States.

Notes:
Heart, high impact = angina, arrhythmia, cardiovascular disease, myocardial infarction, valve disease, or other heart problems under active management or any history of cardiac arrest or congestive heart failure.
Heart, moderate impact = angina, cardiovascular disease, myocardial infarction, or valve disease not under active management.
Heart, low impact = arrhythmia or other heart disease not under active management.
Urinary, low impact = chronic cystitis, nephritis, nephropathy, nephrosis, kidney stones, urinary tract infections, or urinary incontinence.

[a] Source: Goossens-Laan et al. 2014.

[b] Source: Prout et al. 2005.

SI.2 NON-SMALL CELL LUNG CANCER (NSCLC)

Incidence

Lung cancer is the second most common cancer in both men and women. Approximately 2.2 million new cases of lung cancer occurred worldwide in 2020 (accounting for 11.4% of total cancers), with an age-standardised incidence of 22.4 per 100,000 population (GLOBOCAN 2020). Lung cancer is the third most common cancer in Europe, with an age-standardised incidence of 29.4 per 100,000 population in 2020. In the United States, lung cancer is the second most common cancer with over 225,000 new cases in 2020, with an age-standardised incidence of 33.1 per 100,000 population (GLOBOCAN 2020). According to SEER 2020 factsheet, over the preceding 10 years in the United States, the rates for new lung and bronchus cancer cases had been falling on an average of 2.2% each year from 2008-2017 (SEER 2020). The incidence of lung cancer worldwide, in the United States and Europe (available from GLOBOCAN 2020 database and fact sheets, World Health Organization [WHO]) is presented in Table 5.

Approximately 80%–85% of lung cancers are a histological subtype collectively known as NSCLC, which is comprised of lung adenocarcinoma, lung squamous cell carcinoma, and large cell lung carcinoma (Cancer Facts and Figures 2022). Adenocarcinomas account for approximately 40% of all lung cancer cases, followed by squamous cell carcinomas (25%), and large cell carcinomas (10%). A few other subtypes of NSCLC, such as adenosquamous carcinoma and sarcomatoid carcinoma, are less common (American Cancer Society 2021).

Most patients with NSCLC are initially diagnosed with distant metastasis. Using data from the SEER Explorer database, the 5–year (2016–2020) age-adjusted incidence (per 100,000 population) was 10.7 for metastatic adenocarcinoma, 3.4 for metastatic squamous cell carcinoma, and 0.3 for large cell carcinoma for both sexes in the US (SEER 2023). In the United States, a study reported that the total incidence of NSCLC between 2003 and 2012 was lower (34.8 per 100,000 population) than that between 1993 and 2002 (41.3 per 100,000 population) and between 1983 and 1992 (44.6 per 100,000 population) (Wang et al. 2017b). Data collected retrospectively from Swedish and Danish national registries from 2005 to 2015 included total of 30,067 and 31,939 NSCLC patients, respectively, out of which 48.4% and 51.6% had Stage IV disease at diagnosis (Ekman et al. 2021). A study from the United States using SEER database identified 108,464 patients with NSCLC between 2010 and 2014. Among these, 51,788 (47.7%) patients presented with distant metastasis at diagnosis. A total of 8,654 (22.3%), 7,699 (19.9%), 6,109 (15.8%), and 2,264 (5.8%) patients presented with isolated bone, lung, brain, and liver metastasis at the time of diagnosis, respectively (Xu et al. 2019).

Prevalence

The 5-year worldwide prevalence of lung cancer in 2020 was 2,604,791 with 5-year prevalence proportion of 33.4 per 100,000 population for both sexes (GLOBOCAN 2020). In Europe, the 5-year prevalence proportion was 77.8 per 100,000 population, while in the United States, the 5-year prevalence proportion was 89.2 per 100,000 population (GLOBOCAN 2020). The prevalence of lung cancer worldwide, in the United States and Europe (available from GLOBOCAN 2020 database and fact sheets, WHO) is presented in Table 5.

According to SEER Explorer database, in the United States, 310,295 people were living with lung adenocarcinoma diagnosed during the previous 28 years accounting for an age-adjusted prevalence of 0.1% of the U.S. population. For squamous cell carcinoma (n = 102,009) and large cell carcinoma (n = 8106), the age-adjusted prevalence was < 0.1% each of the U.S. population in 2020. For elderly patients (65 years and older), the age-adjusted prevalence of lung adenocarcinoma, squamous cell carcinoma and large cell carcinoma was 0.4%, 0.2%, and < 0.1%, respectively in 2020 (SEER 2023).

Table 5 Estimates of Lung Cancer Incidence, Mortality, and 5-year Prevalence in 2020: Worldwide, Europe, and the United States

Country	Number: (Incidence in million)	Incidence per 100,000 (World age-standardised rate)	Number Mortality	Mortality per 100,000 (World age-standardised rate)	5-year Prevalence (Number)	5-year Prevalence proportion (per 100,000)
Worldwide	2,206,771	22.4	1,796,144	18.0	2,604,791	33.4
United States	227,875	33.1	138,225	18.9	295,263	89.2
Europe	477,534	29.4	384,176	22.6	582,924	77.8

Reference: WHO GLOBOCAN 2020

Demographics

Age: The incidence of NSCLC increases exponentially with advancing age (Table 6). According to the SEER Explorer US database (2015–2020), the annual incidence (per 100,000 population) of metastatic adenocarcinoma increased from 0.9 (in people < 50 years) to 19.0 (50–64 years), to 56.9 (in 65 years and older: 48 in 65–74 years and 66.6 in 75 years and older). In metastatic large cell carcinoma, the rates (per 100,000 population) were 0 (in <50 years), 0.5 (in 50–64 years), 1.3 (>65 years), 1.2 (in 65–74 years), and 1.4 (in 75 years and older), while in metastatic squamous cell carcinoma, the rates were 0.1 (in <50 years), 5.0 (in 50–64 years) and 20.6 (>65 years), 17.6 (in 65–74 years), and 23.8 (in 75 years and older) (SEER 2023).

Table 6 5-Year Age-Specific Incidence (per 100,000) of Metastatic NSCLC Subtype in the United States

	Metastatic Squamous Cell Carcinoma	Metastatic Adenocarcinoma	Metastatic Large Cell Carcinoma
< 50 years	0.1	0.9	0.0
50–64 years	5.0	19.0	0.5
≥65 years	20.6	56.9	1.3
65–74	17.6	48	1.2
≥75+	23.8	66.6	1.4

Source: SEER 2023

Gender: Evidence from the SEER Explorer US database (2016–2020) suggested a slightly higher incidence of adenocarcinoma among males (11.7 per 100,000 population) than females (9.9 per 100,000 population) (Table 7). Similarly for other subtypes, the incidence (per 100,000) in males vs females were 4.9 vs 2.3 (for metastatic squamous cell) and 0.3 vs 0.2 (for metastatic large cell carcinoma) (SEER 2023). A study in England observed 54.8% males and 45.2% females (Belot et al. 2019) in the cohort of 31,351 NSCLC patients identified from the national population-based cancer registry in

2012. Another study in the United States stated that males showed a higher incidence of NSCLC than females in each decade between 1983–2013, whereas the incidence gap between both genders continued to decline. It is noteworthy that the incidence of NSCLC in males decreased dramatically, whereas the incidence of NSCLC in females remained stable across the three decades (Wang et al. 2017b). In elderly patients (65 years and older), the incidence (per 100,000) of metastatic adenocarcinoma in males vs females were 64.9 vs 51 (metastatic adenocarcinoma), 29.1 vs 14 (for metastatic squamous cell) and 1.8 vs 0.9 (for metastatic large cell carcinoma) (SEER 2023).

Table 7 5-Year Gender-Specific Incidence (per 100,000) of Metastatic NSCLC Subtypes

	Metastatic Squamous Cell Carcinoma	Metastatic Adenocarcinoma	Metastatic Large Cell Carcinoma
Males (all ages)	4.9	11.7	0.3
Females (all ages)	2.3	9.9	0.2
Male (≥65 years)	29.1	64.9	1.8
Females (≥65 years)	14	51	0.9

Source: SEER 2023

Race/ethnicity: The incidence of lung adenocarcinoma in all racial groups has increased over time (2013–2017), with Blacks and Whites (including Hispanics) showing a similar incidence of 24.7 per 100,000 population and 24.2 per 100,000 population, respectively, while Non-Hispanic Whites showing the highest incidence (26.0 per 100,000 population). The incidence of squamous cell carcinoma was reported to be slightly higher in Blacks (12.2 per 100,000 population) as compared to Whites (11.4 per 100,000 population). For large cell carcinoma, Blacks (74.9 per 100,000 population) exhibited a slightly higher incidence as compared to Whites (including Hispanics) (71.5 per 100,000 population) (SEER Explorer 2020). In the United States, a study reported that the incidence (per 100,000 population) gap between Whites and Blacks has kept narrowing throughout the three decades (incidence gap: 20.7 in 1983–1992; 15.5 in 1993–2002; 11.5 in 2003–2012) (Wang et al. 2017b).

The incidence of metastatic lung adenocarcinoma in people ≥65 years varied in all racial groups (2016–2020), with non-Hispanic Blacks and non-Hispanic Whites having an incidence of 63.9 per 100,000 population and 59.4 per 100,000 population, respectively (Table 8). The incidence of metastatic squamous cell carcinoma was reported to be similar in non-Hispanic Blacks (26.6 per 100,000 population) as compared to non-Hispanic Whites (22.4 per 100,000 population). The incidence of metastatic large cell carcinoma was reported to be similar in non-Hispanic Blacks (1.6 per 100,000 population) compared to non-Hispanic Whites (1.4 per 100,000 population) (SEER 2023).

Table 8 5-year Race-Specific Incidence (per 100,000) of Metastatic NSCLC Based on Subtypes

	Metastatic Squamous Cell Carcinoma	Metastatic Adenocarcinoma	Metastatic Large Cell Carcinoma
NHA (≥65 years)	11.8	60	0.5
NHB (≥65 years)	26.6	63.9	1.6
NHW (≥65 years)	22.4	59.4	1.4

NHA = Non-Hispanic Asian; NHB = non-Hispanic Black; NHW = non-Hispanic white.
Source: SEER 2023

Natural History of the Indicated Condition in the (Untreated) Population

Mortality and Morbidity

NSCLC is associated with poor survival even when the diagnosis is made at an early stage due to a high risk of micrometastasis. The lung cancer death rate has declined by 56% since 1990 in men and by 32% since 2002 in women due to reductions in smoking, with the pace accelerating in recent years. From 2008 to 2017; the rate decreased by about 5% per year in men and 4% per year in women (Cancer Facts and Figures 2022). Between 2011 and 2016, the 5-year survival rate increased by 0.8% in men compared to 0.9% in women (SEER Explorer 2020).

Lung cancer is the most common cause of death from cancer worldwide and is the leading cause of cancer death in the United States. Globally, it is responsible for nearly one in five cancer-related deaths (approximately 1.8 million deaths; 18.0% of the total cancer deaths). Lung cancer mortality (age-standardised) from GLOBOCAN 2020 fact sheets and database was 18.0 worldwide, 18.9 in the United States, and 22.6 in Europe per 100,000 population (GLOBOCAN 2020). According to European Cancer Information System (ECIS) 2020, lung cancer is the most common cause of cancer-related death in Europe with approximately 384,176 deaths in 2020, accounting for 19.8% of all cancer deaths (ECIS 2020).

According to SEER database factsheets, the overall 5-year relative survival rate for lung and bronchus cancer (2011–2017) was estimated to be 21.7%, while the survival was 59.8% for localised stage, 32.9% for regional, and 6.3% for distant or metastatic stage. In people ≥65 years of age, the 5-year (2013–2019) relative survival for metastatic adenocarcinoma, metastatic squamous cell carcinoma, and metastatic large cell carcinoma was reported as 9.1%, 6.2%, and 5.0% respectively (SEER 2023).

A study identified 1,150,722 NSCLC cases from 2004 to 2013 using The National Cancer Database, United States. The median overall survival for all patients was reported to be 13.1 months; 95% confidence interval (CI) (13.08, 13.17). Median overall survival improved for those diagnosed in 2010–2013 [14.8 months; 95% CI (14.7, 14.9)] as compared to 2004–2009 [12.4 months; 95% CI (12.3, 12.5)] (Lou et al. 2018).

Pregnancy and Lactation

Lung cancer during pregnancy remains a rather uncommon condition with less than 70 cases published up to 2016 (Mitrou et al. 2016). NSCLC is the most common type accounting for about 85% of all cases (mainly adenocarcinoma). Overall survival rates are low. Chemotherapy and/or targeted treatment have been used with poor outcomes. The disease has also been found to affect the products of conception (placenta and fetus) with no short- or long-term consequences for the neonate (Mitrou et al. 2016). A nationwide cohort study from Denmark included 1857 pregnant women with lung cancer and 18,244 pregnant matched cancer-free controls followed up to 2017. The prevalence of single pregnancy loss (cases vs control) had been reported to be in 18.4% vs 18.1%, two pregnancy losses in 3.5% vs 3.9% and ≥3 pregnancy losses in 1.5% vs 1.5% of the total pregnancies (Mikkelsen et al. 2019).

Risk Factors for the Disease

Tobacco smoking remains the main cause of lung cancer and the geographical and temporal patterns of the disease largely reflect tobacco consumption during the previous decades. Both smoking prevention and smoking cessation can lead to a reduction of lung cancers. In countries with active tobacco control measures, the incidence of lung cancer has begun to decline in men and is reaching a plateau for women. Several other factors have been described as lung cancer risk factors, including exposure to asbestos, arsenic, radon and non-tobacco-related polycyclic aromatic hydrocarbons. Hypotheses about indoor air pollution (e.g., coal-fueled stoves and cooking fumes) have been suggested for the relatively high burden of non-smoking-related lung cancer in women in some countries. There is evidence that lung cancer rates are higher in cities than in rural settings but many confounding factors other than outdoor air pollution may be responsible for this pattern (Cancer Facts and Figures 2020).

The Main Existing Treatment Options

Curative intent surgery is the preferred treatment for patients with Stage I and II NSCLC. For patients with Stage I disease, surgical treatment alone is the standard of care. For Stage II to III disease, platinum-based chemotherapy as an adjuvant or neoadjuvant therapy is recommended to improve survival outcomes compared with surgery alone (ESMO 2021; NCCN 2023). Chemotherapy regimens used in the adjuvant and neoadjuvant settings involve platinum-based doublets, which are the same as standard of care drugs used in the metastatic setting. According to NCCN and ESMO guidelines, cisplatin is recommended as the preferred platinum agent and carboplatin is used when cisplatin cannot be tolerated or comorbidities exist. Agents that have been combined with either cisplatin or carboplatin include taxanes, vinorelbine, gemcitabine, etoposide and pemetrexed. For patients with activating EGFR mutations, osimertinib is recommended as adjuvant therapy after surgical resection for those who have previously received adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy (Wu et al. 2020; NCCN 2023). Recently, the NCCN panel recommended atezolizumab as adjuvant therapy following platinum-based chemotherapy for patients

with completely resected Stage IIB to IIIA, Stage IIIB (only T3, N2), or high-risk Stage IIA PD-L1 positive (i.e., ≥1% of tumour cells). The panel added a recommendation for adjuvant pembrolizumab following platinum-based chemotherapy and resection for patients with Stage IIB to IIIA, Stage IIIB (only T3, N2), or high-risk Stage IIA, with the caveat on the unclear benefit seen in patients with PD-L1 <1%. Additionally, nivolumab plus platinum-doublet chemotherapy is recommended as neoadjuvant systemic therapy for patients with resectable (≥4 cm or node positive) NSCLC. For patients with unresectable (Stage III) NSCLC, durvalumab is recommended for the treatment of patients without progression following definitive concurrent platinum-based chemoradiation.

According to the latest ESMO 2023 and NCCN 2023 guidelines on metastatic/advanced NSCLC, systemic therapy recommendations are based on histology and oncogene targets.

Regardless of the histology and in the absence of oncogene targets, single agent pembrolizumab, atezolizumab, and cemiplimab are 1L options for patients with high PD-L1 expression in tumour cells (TPS or TC ≥50%). Atezolizumab is also considered a 1L option for patients with PD-L1 stained tumour infiltrating immune cells (ICs) ≥10% (NCCN 2023; ESMO 2023).

Additional 1L options included in the ESMO 2023 and NCCN 2023 guidelines are:

- Pembrolizumab in combination with pemetrexed and platinum-based chemotherapy in non-squamous NSCLC regardless of PD-L1 status.
- Pembrolizumab in combination with paclitaxel or protein-bound paclitaxel and carboplatin in squamous NSCLC regardless of PD-L1 status.
- Atezolizumab in combination with protein-bound paclitaxel and carboplatin in non-squamous NSCLC regardless of PD-L1 status.
- Atezolizumab and bevacizumab with carboplatin and paclitaxel in non-squamous NSCLC regardless of PD-L1 status.
- Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy in non-squamous NSCLC regardless of PD-L1 expression.
- Nivolumab plus ipilimumab in non-squamous NSCLC patients with PD-L1 expression levels of ≥1% (not EMA approved).
- Platinum-based combination chemotherapy in squamous/non-squamous NSCLC.

In patients with activating EGFR-mutated NSCLC, EGFR tyrosine kinase inhibitors (TKIs) such as afatinib, dacomitinib, erlotinib, gefitinib, and osimertinib are recommended as 1L therapy. The NCCN NSCLC Panel and ESMO guidelines recommend also erlotinib plus ramucirumab or plus bevacizumab as a 1L therapy option for patients with metastatic NSCLC and EGFR exon 19 deletions or L858R mutations (ESMO 2023; NCCN 2023). In patients with ALK-rearranged NSCLC, an ALK-tyrosine

kinase inhibitor (TK)I is recommended as the 1L treatment with alectinib, brigatinib, and lorlatinib as preferred options. In patients with ROS1–rearranged NSCLC, entrectinib, and crizotinib are approved 1L treatment options. In BRAF-mutated NSCLC, patients should be exposed in first- or second-line to combined BRAF/MEK inhibition using dabrafenib plus trametinib, or single agent vemurafenib or dabrafenib if the combination is not tolerated. For patients with NTRK fusions, larotrectinib and entrectinib are approved for the treatment of adult and paediatric patients with solid tumours, including NSCLC. In RET-rearranged NSCLC patients, selpercatinib or pralsetinib are recommended as 1L therapy options. In patients with Kirsten rat sarcoma viral oncogene homologue (KRAS) mutation-positive metastatic NSCLC, platinum-based chemotherapy (± immunotherapy) is a recommended option. In patients with mesenchymal-epithelial transition (MET) exon 14 skipping mutation NSCLC, capmatinib or tepotinib are recommended as 1L options.

Second line treatment options are based on the treatment given in the 1L. The following options are included in the ESMO 2023 and NCCN 2023 guidelines:

- In patients with progression after 1L single-agent immunotherapy or those progressing after 1L therapy for EGFR, ALK or other genomic aberrations, platinum-based chemotherapy doublets are recommended as 2L treatment options.
- For patients with progression during or following platinum-based chemotherapy, the PD-L1 and PD-1 inhibitors (atezolizumab, nivolumab, and pembrolizumab) are recommended; those with EGFR and ALK genomic aberrations should have disease progression on approved therapy for these aberrations prior to receiving these therapies.
- Osimertinib for EGFR-mutated NSCLC patients whose tumours are tested positive for T790M either in liquid biopsy or re-biopsy, if not previously treated with osimertinib.
- Ceritinib and alectinib in patients with ALK-positive advanced NSCLC who are intolerant to, or have progressed under treatment with crizotinib. For patients who have progressed after a second-generation ALK-TKI, the ALK inhibitor lorlatinib is considered a treatment option.
- The NCCN NSCLC Panel recommends mobocertinib as a subsequent therapy option for patients with EGFR exon 20 insertion-positive metastatic NSCLC.
- The NCCN NSCLC Panel recommends sotorasib as a subsequent therapy option for select patients with metastatic NSCLC and KRAS p.G12C mutations who have disease progression after treatment with platinum-based chemotherapy (± immunotherapy).

Important Comorbidities

The comorbidity prevalence data presented in Table 9 are based on retrospective studies that consisted of 31,351 NSCLC patients in England during 2012 and 400 NSCLC patients in Poland from 2012 to 2013.

Table 9 Prevalence of Selected Comorbidities in Patients with NSCLC

Comorbid Conditions	Advanced stage NSCLC, England, mean age: 72.81±10.90 years [a]	All stage, Poland, mean age: 64±7.47 years [b]
Hypertension	N/A	41.6%
COPD	21.5%	21.5%
Ischemic heart disease	N/A	17.3%
Diabetes	N/A	11.0%
Myocardial Infarction	5.4%	9.3%
Peripheral vascular disease	6.4%	8.3%
Cerebrovascular disease	6.1%	NA
Congestive heart failure	5.2%	NA

COPD = chronic obstructive pulmonary disease; N/A = not available; NSCLC = non-small cell lung cancer.

[a] Source: Belot et al. 2019.

[b] Source: Lembicz et al. 2018.

SI.3 TRIPLE-NEGATIVE BREAST CANCER (TNBC)

Incidence

Globally, breast cancer is the third most common cancer overall, with an estimated 1.7 million (95% uncertainty interval, 1.6–1.8 million) incident cases in 2016, and 1 in 20 women developed breast cancer over a lifetime (Fitzmaurice et al. 2017). According to ECIS, breast cancer is the second most common cancer in Europe with approximately 522,513 new cases in 2018, represents around 13.4% of all cancers, accounting for an incidence of 136.0 per 100,000 population (European Commission 2018).

According to SEER, in 2018, breast cancer was estimated to occur in 266,120 patients in the United States, making up to 15.3% of all new cancer cases. Over the last 10 years in the United States, the rates for new female breast cancer cases have been rising on an average of 0.3% each year (National Cancer Institute 2017). Please refer to the incidences of breast cancer worldwide, in the United States, and Europe (available from GLOBOCAN 2012 fact sheets, WHO) and presented in Table 10.

Triple-negative breast cancer (TNBC) is a subtype of breast cancer, in which the expression of all three molecular (progesterone receptor [PR], estrogen receptor [ER] and human epidermal growth factor receptor 2 [HER2]) markers are negative, and it accounts for 10%–20% of all breast cancers (Li et al. 2017). TNBC comprised 170,000 of an estimated 1 million cases of breast cancer diagnosed annually worldwide (Anders and Carey 2009). Cortet et al. (2018) estimated the crude incidence rate of TNBC as 16.48 per 100,000 person-years from 2007 to 2012 using three French registries. The worldwide and European standardised incidence rates of TNBC are 12.0 and 14.85 per 100,000 person-years, respectively (Cortet et al. 2018).

Prevalence

According to the Global Burden of Diseases (GDB) 2016, worldwide prevalence of breast cancer was reported as 8,151,000 (GBD 2016). Per WHO, in 2012, the 5-year worldwide prevalence of breast cancer among females were 6,232,108 with 5-year prevalence proportion of 239.9 per 100,000 (Ferlay 2013). In Europe, 1,814,572 females were living with breast cancer in 2012 with a 5-year prevalence of 553.8 per 100,000 (Ferlay 2013). According to the NCI SEER database, in 2015 there were an estimated 3,418,124 women living with female breast cancer in the United States. (NCI 2017). The prevalence of breast cancer worldwide, in the United States, and Europe (available from GLOBOCAN 2012 fact sheets, WHO) are presented in Table 10.

Table 10 Estimates of Breast Cancer Incidence, Mortality, and 5-Year Prevalence in 2012: Worldwide, Europe, and United States

Country	Number (Incidence in million)	Incidence per 100,000 (World age-standardised rate)	Number (Mortality)	Mortality per 100,000 (World age-standardised rate)	5-year Prevalence (Number)
Worldwide	1,671,149	43.1	521,907	12.9	6,232,108
United States	232,714	92.9	43,909	14.9	970,693
Europe	458,718	69.9	131347	16.1	1,814,572

Source: GLOBOCAN 2012 (Ferlay 2013).

Demographics

The incidence of TNBC is higher among African women of younger age than those of European ancestry (Brewster et al. 2014). In a study by Howlader et al. (2014) using data from 17 population-based cancer registries that participate in the SEER program (consisting of 6193 patients with TNBC), 26% of patients were $<$50 years of age, 41% were of age 50–64 years, 19% were of age 65–74 years, and 14% were $\geq$75 years of age (Howlader et al. 2014). TNBC is often aggressive and is associated with higher mortality than other subtypes of breast cancer. Women of African ancestry have a disproportionately high incidence of TNBC (20%–79%) (Brewster et al. 2014). Racial disparities contribute majorly in terms of breast cancer incidence and survival rate. From U.S. Breast Cancer, facts and figures 2017–2018 by the American Cancer Society, the incidence rates of TNBC was highest among non-Hispanic blacks (24.0 per 100,000), followed by non-Hispanic whites (12.0 per 100,000), American Indians or Hispanic/Latina (10.0 per 100,000), and lowest for Asian/Pacific Islander (8.0 per 100,000) (American Cancer Society 2017).

The age-standardised incidence rates of breast cancer vary nearly four-fold across the world regions, with rates ranging from 27 per 100,000 in Middle Africa and Eastern Asia to 92 in Northern America in 2012 (Ferlay et al. 2013). In Europe, the highest age-standardised incidence rates were observed for Belgium (199.8 per 100,000), followed

by Luxembourg (189.5 per 100,000) and Netherlands (183.0 per 100,000), and lowest for Albania (70.1 per 100,000) in 2018 (ECIS 2018; DeSantis et al. 2016). Using the SEER database 2010, Howlader and colleagues exhibited that age-specific incidence rate of TNBC was highest among non-Hispanic blacks across all age groups with the difference in rates reaching its widest point at ages 60 to 64 (68.9 per 100,000) and 65 to 69 (69.5 per 100,000) years (Howlader et al. 2014).

Natural History of the Indicated Condition in the (Untreated) Population

Mortality and Morbidity

Breast cancer ranks as the fifth cause of death from cancer overall; an estimated 546,000 deaths were attributed to breast cancer in 2016, accounting for 6.1% of all cancer deaths worldwide (Fitzmaurice et al. 2017). It is the most frequent cause of cancer death in women in less developed regions (324,000 deaths, 14.3% of total) and it is the second cause of cancer death in more developed regions (198,000 deaths, 15.4%) after lung cancer (Ferlay et al. 2015). Breast cancer mortality from GLOBOCAN fact sheets 2012 was 12.9 worldwide, 14.9 in the United States, and 16.1 in Europe per 100,000. According to GBD 2016, the ASR of breast cancer mortality worldwide among females is 14.6 per 100,000 person-years (Fitzmaurice et al. 2017).

According to SEER database factsheets, in 2018, deaths due to breast cancer were estimated to be 40,920 (6.7% of all cancer) in United States, while the 5-year survival rates range from 98.7% for localised to 85.3% for regional/locally advanced and 27.0% for distant/ metastatic stages (National Cancer Institute 2017).

Five-year survival rates also tend to be lower for TNBC. In one urban centre with 190 breast cancers cases, 40% of all recurrences occurred in women with TNBC, who were also more likely to die of their disease (odds ratio [OR] 3.7; 95% CI: 1.1, 13.0) (Lund et al. 2008). In the California study (1999–2003), 5-year relative survival was 77% for TNBC versus 93% for all other breast cancers (Bauer et al. 2007). A study of 1601 women diagnosed with breast cancer with a median follow up of 8.1 years found patients with TNBC experienced a higher rate of distant recurrences (hazard ratio [HR] 2.6; 95% CI: 2.0, 3.5) and death (HR 3.2; 95% CI: 2.3, 4.5) within 5 years of diagnosis, as opposed to patients with any breast cancers that were positive for ER, PR or HER2 receptors (Dent et al. 2007).

Pregnancy and Lactation

Evidence of pregnancy cases specifically in early or metastatic breast cancer (mBC) was limited in literature. In a systematic review of 39 studies, 112,840 breast cancer patients were identified of whom a total of 7,505 (6.7%) had a pregnancy after diagnosis (Lambertini et al. 2021). In a meta-analysis of 3 population-based studies comprising of 711 breast cancer patients, the rate of pregnancy was reported to be 3.0% (Gerstl et al. 2018).

Considerable evidence was available for the pregnancy outcomes in overall breast cancer patients. A systematic literature review was conducted to identify studies including patients with pregnancy after breast cancer cumulatively up to October 2020. A total of 39 studies involving 8,093,401 women from the general population (without breast cancer) and 112,840 patients with breast cancer were included. Women with breast cancer were significantly less likely to have a subsequent pregnancy compared to the general population (relative risk: 0.40; 95% CI: 0.32, 0.49). Risks of caesarean section (OR: 1.14; 95% CI: 1.04, 1.25), low birth weight (OR: 1.50; 95% CI: 1.31, 1.73), preterm birth (OR: 1.45; 95% CI: 1.11, 1.88), and small for gestational age (OR: 1.16; 95% CI: 1.01, 1.33) were significantly higher in women with breast cancer, particularly in those with previous chemotherapy exposure, compared with the general population (Lambertini et al. 2021).

Risk Factors for the Disease

Several risk factors are associated with the development of TNBC. Women under the age of 40 years old have a two-fold increased risk for TNBC, and it is more prevalent in non-Hispanic black or Hispanic women. Premenopausal status has been found to correlate with increased risk for basal-like breast cancer, a molecular subtype that significantly overlaps with TNBC (Boyle 2012). The association between obesity and TNBC has been described in several studies and was confirmed in a meta-analysis showing that a body mass index over 30 correlated with an increased risk for TNBC (Pierobon and Frankenfeld 2013). Among parous women, the number of births was positively associated with the risk of TNBC. Oral contraceptive usage $\geq$1 year was associated with a 2.5-fold increased risk of TNBC. Smoking and alcohol consumption have not been associated with increased risk of TNBC (Boyle 2012). Patients of low socioeconomic status had a higher rate of TNBC compared with patients of high or moderate socioeconomic status (Ray and Polite 2010).

The Main Existing Treatment Options

Patients with TNBC do not benefit from hormonal or trastuzumab-based therapy because of the absence of target receptors such as ER, PR, and HER-2. Hence, surgery and chemotherapy, individually or in combination, appear to be the only available modalities. However, some studies have identified certain receptors as targets for new therapeutic drugs. Traditionally radiotherapy is given in TNBC as indicated in other breast cancer subtypes following mastectomy or conservative breast surgery. The therapeutic strategies for the management of TNBC include agents targeting DNA repair complex like (platinum compounds and taxanes), P53 like (taxanes), cell proliferation like (anthracycline containing regimen), and other targeted therapies. Several neoadjuvant studies have sought to determine the additive benefit of incorporating novel chemotherapeutics with standard chemotherapy like anthracycline, taxanes, antimetabolites, platinum agents and novel microtubule stabilising agents (Wahba and El-Hadaad 2015).

Targeted therapy for the treatment of patients with TNBC currently under investigation includes mammalian target of rapamycin (mTOR) inhibitors (everolimus, sirolimus etc.), fibroblast growth factor receptor (FGFR) inhibitors, and EGFR inhibitors (cetuximab, erlotinib etc.). FGFR inhibitors are either FGFR-specific or target FGFR as part of their tyrosine kinase panel in addition to vascular endothelial growth factor receptor inhibition. At least four compounds are currently in clinical trials for TNBC. Cetuximab is a chimeric monoclonal antibody targeting EGFR but elicits little response as single-agent therapy in the setting of advanced TNBC. In recent years, new therapies for TNBC include immunotherapies (so called immune checkpoint inhibitors), drugs that target the androgen receptor, DNA damaging agents, such as platinum drugs, antibody-drug conjugates that deliver drugs to cells that have a specific protein on their surface, drugs that block DNA repair pathways called poly (ADP-ribose) polymerase (PARP) inhibitor (Wahba and El–Hadaad 2015). The PARP inhibitor, olaparib, has been approved by the U.S. Food and Drug Administration (FDA) for treatment of advanced breast cancers with BRCA mutations providing a new treatment option for the 10%–20% of patients with TNBC who harbor a BRCA mutation (FDA 2018).

Tecentriq was approved in the European Union (June 2019) for the treatment of metastatic TNBC. The E.U. indication is as follows:

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

The FDA approved pembrolizumab (Keytruda®) in combination with chemotherapy for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumours express PD-L1 (Combined Positive Score ≥10) as determined by an FDA–approved test in October 2020.

Important Comorbidities

Swede et al. (2016) using the SEER Connecticut Tumor Registry (2000–2007) reported that African-American- women with breast cancer were likely to have a history of hypertension (47.5% vs 30.8%), Type II diabetes (23.3% vs 4.2%), kidney disease (5.0% vs 0.9%), congestive heart disease (3.5% vs 0.9%), myocardial infarction (3.5% vs 1.4%), liver disease (2.5% vs 0.9%), cerebrovascular events (4.5% vs 2.3%) than White women at the time of breast cancer diagnosis. The authors further concluded that the comorbidities at diagnosis exert an independent risk for overall mortality among patients with breast cancer (Swede et al. 2016).

Demographic evaluation of patients with TNBC among 132 Turkish patient population revealed diabetes mellitus (9.1%), hypertension (21.2%), and coronary artery disease (3.0%) as the most common underlying comorbid conditions (Somali et al. 2013).

SI.4 SMALL CELL LUNG CANCER (SCLC)

Incidence

Small cell lung cancer (SCLC) accounts for 15% to 17% of all lung cancers (Wang et al. 2017a). SCLC is the most aggressive subtype of lung cancer and is characterised by a rapid doubling time, high growth fraction, and early widespread metastasis (Wang et al. 2017a). Using data from the SEER program (1992–2010), 51,959 cases of SCLC were diagnosed in the United States, accounting for an incidence of 7.63 per 100,000 person-years (Dores et al. 2015). During 1992–2010, a decreasing trend in the incidence rates was observed for SCLC (annual percent change of −2.74) (Dores et al. 2015). The overall incidence of SCLC per 100,000 decreased each decade to 9.6, 7.8 and 5.8 from 1983 to 2012 in the United States (Wang et al. 2017a). de Jong et al. 2008 reported that between 1989 and 2003, the incidence of SCLC was decreased from 19.5 to 11.2 per 100,000 in Netherlands.

Prevalence

As presented in Section SI. 2.

Demographics

The incidence of SCLC was reported to increase exponentially with advancing age (Wang et al. 2017a). According to a study using the SEER database (1975–2010), the proportion of elderly patients among all cases of SCLC increased from 23% in 1975 to 44% in 2010 in the United States (Abdel-Rahman 2018). A reduction in the incidence (per 100,000 population) of SCLC from 1983 to 2012 (in three decades) in the United States can be seen in most age groups, with large decreases in some groups: from 24.4 to 17.4 to 11.5 in the 50–64 age group and from 48.7 to 43.0 to 33.1 in the 65–79 age group. However, the incidence remained stable in the 0-34 and older than 80 years age groups while the incidence was highest in the 65–79 age group in all three decades (Wang et al. 2017a).

Evidence from the SEER database (1973–2010) suggested a higher incidence of SCLC among males than females (Eskandar et al. 2015). From the U.K. Thames Cancer registry (1970–2007), the age-standardised incidence rates of SCLC in the United Kingdom were estimated to be 6.0 per 100,000 for males and 4.0 per 100,000 in females. The incidence rate of SCLC declined from the 1980s among males, and from the 1990s among females (Riaz et al. 2012). In Switzerland, 2,592 SCLC cases were identified from 1980–2010, the age-standardised incidence rate in men was reported to decrease from 14.1 (1980–1989) to 7.4 (2000–2010) per 100,000 person-years, while there was an increase in the incidence rate from 3.3 (1980–1989) to 3.8 (2000–2010) per 100,000 person-years in women (Oberli et al. 2016). In the United States, incidence differences were observed between sexes, with a higher incidence per 100,000 in males than females (12.9 vs. 7.1 in 1983–1992, 9.2 vs. 6.8 in 1993–2002, and 6.4 vs. 5.4 in 2003–2012) (Wang et al. 2017a).

According to GLOBOCAN 2012, the highest estimated rates (per 100,000) of SCLC worldwide are found in Northern America (33.8) and Northern Europe (23.7) with a relatively high rate in Eastern Asia (19.2) and the lowest rates in Western and Middle Africa (1.1 and 0.8 respectively) (World Health Organization; GLOBOCAN 2012).

The incidence of SCLC was higher in Whites compared with the Black population. Blacks presented with SCLC at a younger age compared with Whites. Women presented with limited-stage SCLC more often than men (26.28% vs 20.75%, respectively) (Eskandar et al. 2015).

Natural History of the Indicated Condition in the (Untreated) Population

Mortality and Morbidity

Patients with SCLC have a poor prognosis. In most cases, death from recurrent disease occurs within 2 years of the initial diagnosis (Janssen-Heijnen et al. 2012).

A total of 106,439 patients with SCLC between 1983 and 2012 at 18 registry sites were identified in the United States, with the five-year survival rate improving from 4.9% to 5.9% to 6.4% each decade (Wang et al. 2017a).

Pregnancy and Lactation

Refer to SI.2 Non-Small Cell Lung Cancer (NSCLC) for epidemiological information related to pregnancy and lactation in lung cancer.

Risk Factors for the Disease

Tobacco smoking is the leading cause of SCLC. The risk increases with both quantity and duration of smoking. Exposure to radon gas released from soil and building materials is thought to be the second-leading cause of SCLC in the United States. Other risk factors include occupational or environmental exposure to asbestos, certain metals (chromium, cadmium, arsenic), some organic chemicals, radiation, air pollution, and diesel exhaust. Some specific occupational exposures that increase the risk include rubber manufacturing, paving, roofing, painting, and chimney sweeping. The risk is also believed to be increased among people with a history of tuberculosis. Genetic susceptibility (e.g., family history) plays a role in the development of SCLC, especially in those who develop the disease at a young age (American Cancer Society; Cancer Facts and Figures 2018).

The Main Existing Treatment Options

Based on NCCN and ESMO guidelines, the current standard-of-care in the 1L treatment of extensive-stage SCLC (ES-SCLC) is cytotoxic chemotherapy consisting of a platinum (carboplatin or cisplatin) plus etoposide for four to six cycles (NCCN 2018, Früh et al. 2013). Combination therapy of irinotecan-cisplatin, gemcitabine-carboplatin and topotecan-cisplatin are alternative options, if etoposide is contraindicated. Thoracic radiotherapy is generally used in ES-SCLC for the palliation of symptoms. The routine use of thoracic consolidative radiotherapy is currently not recommended for all patients

with ES-SCLC, but may be considered in select patients with low-bulk metastatic disease who have a complete or near complete response after initial chemotherapy. Depending on individual patient factors, patients can be considered for prophylactic cranial irradiation or close magnetic resonance imaging (MRI) surveillance.

In 2019, the FDA and the European Union approved Tecentriq for 1L SCLC. The E.U. indication is as follows:

- Tecentriq, in combination with carboplatin and etoposide, is indicated for the first–line treatment of adult patients with ES–SCLC.

Important Comorbidities

Aarts et al. 2015 identified 4,142 SCLC patients from the population-based Netherlands Cancer Registry between 1995 and 2012 and reported multi-morbidity in 36% of the patients. Pulmonary disease was the most common concomitant disease in patients aged ≤ 59 years (16%), followed by hypertension (12%), and cardiac disease (10%). The prevalence of cardiac disease increased strongly with age, being present in 40% of patients with SCLC aged ≥ 80 years. Pulmonary disease and hypertension were the second and third most common comorbid conditions in the elderly group with 33% and 26%, respectively, and a higher proportion of men suffered from comorbidities than women (68% vs. 62%). The common comorbidities in male patients with SCLC include hypertension, cardiac disease, pulmonary disease, and diabetes mellitus, while pulmonary disease remained the most prevalent comorbid disease in females (Aarts et al. 2015).

SI.5 HEPATOCELLULAR CANCER (HCC)

Limited information is available for the European HCC patients and the available data are presented in different subsections below.

Incidence

HCC is the most frequent (75%–85%) subtype of primary liver cancer worldwide with high lethality (Bray et al. 2018). Liver cancer (including intrahepatic bile duct cancers) is the sixth most common cancer worldwide (4.7% of all cancers) with an age-standardised incidence of 9.3 per 100,000 in 2018. In Europe, 82,466 new cases of liver cancer were diagnosed in 2018, accounting for an age-standardised incidence 5.1 per 100,000 population (WHO 2018). The age-standardised incidence of liver cancer worldwide, in Europe, the United States, Asia, and Africa (available from GLOBOCAN, 2018 database and fact sheets, WHO) is presented in Table 11.

In the United States, liver cancer incidence has tripled since 1980, and between 2006 (7.2 per 100,000) and 2015 (9.1 per 100,000) the incidence rate increased by about 3% per year (American Cancer Society 2019). An estimated 37,948 new cases of liver cancer (including intrahepatic bile duct cancers) were diagnosed in the United States during 2018, accounting for an age-standardised incidence of 6.8 per 100,000 population (WHO 2018). According to the SEER Explorer database, in the United

States, the 5-year (2012–2016) age-adjusted incidence of distant/metastatic liver cancer was 1.6 per 100,000 population during this period. The majority of the patients diagnosed with liver cancer presented with localised disease (44.1%), followed by regional (27%) and distant (18%) diseases (SEER Explorer 2019).

According to the population-based data from the U.S. Cancer Statistics registry which covers 97% of the U.S. population, 236,290 HCC cases were diagnosed between 2000 and 2012. The age-adjusted incidence rate for HCC increased from 4.4 per 100,000 (95% CI: 4.3, 4.5) in 2000 to 6.7 per 100,000 (95% CI: 6.6, 6.8) in 2012, representing an average annual percentage change of 3.5% (95% CI: 3.3%, 3.8%) (White et al. 2017).

Prevalence

In 2018, the 5-year worldwide prevalence of liver cancer was 675,210 and the 5-year prevalence proportion was 8.8 per 100,000 for both sexes. The prevalence of liver cancer worldwide, in Europe, the United States, Asia and Africa (available from GLOBOCAN 2018 fact sheets, WHO) is presented in Table 11.

Table 11 Estimates of Liver Cancer Incidence, Mortality, and 5-Year Prevalence in 2018 for Both Sexes and All Ages

Country	Incidence (Number)	Incidence per 100,000 (World age-standardised rate)	Number (Mortality)	Mortality per 100,000 (World age-standardised rate)	5-year Prevalence (Number)	5-year Prevalence (proportion) per 100,000
Worldwide	841,080	9.3	781,631	8.5	675,210	8.8
Europe	82,466	5.1	77,375	4.4	58,477	7.9
United States	37,948	6.8	30,485	4.9	31,023	9.5
Asia	609,596	11.4	566,269	10.5	494,783	10.9
Africa	64,779	8.4	63,562	8.3	56,736	4.4

Source: Bray 2018; WHO 2018.

Demographics

Worldwide in 2018, the age-standardised incidence of liver cancer is typically 2–4 times higher for men than women (13.9 vs 4.9 per 100,000). A similar trend was observed for Europe with an age-standardised incidence of 8.0 per 100,000 for men and 2.7 per 100,000 for women (WHO 2018).

In the United States, HCC is rarely diagnosed before the age of 40 years. After the age of 40 years, the incidence increases with age, reaching a peak between 80–84 years and then decreases after 85 years. The age distribution of HCC varies between regions and countries. In China, the mean age at diagnosis is between 55–59 years; while in Europe and North America it is 63–65 years (Tang et al. 2018).

The incidence of HCC varies widely between geographic regions. Most cases occur in developing countries where hepatitis B virus (HBV) is endemic (Tang et al. 2018). The

age-standardised incidence is highest (more than 13 cases per 100,000 population) in Eastern Asia, South-Eastern Asia, Northern Africa and Micronesia, while the lowest incidence (less than 5 cases per 100,000) have been reported in Central, Eastern, and Northern Europe, and Western and South-Central Asia (WHO 2018).

Within multi-ethnic populations, the incidence of HCC varies by race or ethnicity. In the United States, the 5-year (2012–2016) age-adjusted incidence per 100,000 are highest among Asians and Pacific Islanders and Hispanics (13.6), intermediate among black Americans (10.8), and lower among white Americans (7.0) (SEER Database 2019).

Natural History of the Indicated Condition in the (Untreated) Population

Mortality and Morbidity

Worldwide, liver cancers are the fourth most common cause of cancer-related death with 781,631 deaths (70% in males and 30% in females) accounting for an age-standardised mortality rate of 8.5 (12.7 in males and 4.6 in females) per 100,000 (WHO 2018). The age-standardised mortality due to liver cancer worldwide, in Europe, the United States, Asia, and Africa (available from GLOBOCAN 2018 fact sheets, WHO) is presented in Table 11.

Outcome of the (Untreated) Target Disease

The 5-year (2000–2007) relative survival rate for liver cancer in Europe for individuals aged 15 years and older was approximately 11.7% for all stages (ECIS 2019). According to SEER Explorer database, the 5–year (2009–2015) relative survival rate for liver cancer in the United States was 18.4% (32.6% for localised to 10.8% for regional/locally advanced and 2.4% for distant/ metastatic stages) (SEER Database 2019).

Pregnancy and Lactation

Reported cases of HCC in pregnancy are largely isolated and highly scattered. The rarity of HCC in pregnancy results from a combination of three factors: the male predominance of HCC, the late age at which the tumour usually presents in women, and decreased fertility in women with advanced cirrhosis (hepatitis is a predisposing factor for HCC development) (Lau et al. 1995).

Risk Factors for the Disease

HCC is rare among patients without liver disease. It is twice as common in men as in women. Cirrhosis of any cause increases the risk of HCC, with an annual incidence between 2% and 4%. Worldwide, HBV infection is the main cause of HCC. Dietary exposure to aflatoxin B1 amplifies the risk of HCC among patients with HBV infection, through a specific mutation in TP53 at position 249 (R→S). In Western countries and Japan, the main cause of HCC is hepatitis C virus (HCV) infection. HBV infection has a direct oncogenic effect, regardless of the degree of underlying liver fibrosis, but HCC rarely occurs in HCV-infected patients who do not have advanced fibrosis. The incidence of HCC due to non-alcoholic fatty liver disease (NAFLD) is increasing

worldwide (Villanueva 2019). In a large retrospective cohort study in the United States, annual incidence rate of HCC in patients with NAFLD was estimated at 0.21 per 1000 person-years (compared with 0.02 per 1000 person-years for general population). Patients with NAFLD were at a >7.6-fold higher risk of developing HCC compared with the general population after adjusting for race and features of metabolic syndrome (Kanwal et al. 2018). Alcoholic cirrhosis is another frequent cause of HCC. Smoking and coinfection with the human immunodeficiency virus can also contribute to the development of HCC (Villanueva 2019).

The Main Existing Treatment Options

Early-stage liver cancer can sometimes be treated successfully with surgery to remove part of the liver (few patients have sufficient healthy liver tissue for this option) or liver transplantation (American Cancer Society 2019). According to NCCN 2019 Guidelines, the preferred treatment approach for patients with HCC who are not eligible for surgery or liver transplantation is locoregional therapy (e.g., ablation, arterially directed therapies, and external-beam radiation therapy). Ablation alone may be curative in selected patients with small tumours, whereas embolization is generally not considered curative (Benson et al. 2019). The ESMO 2018 Guidelines state that in patients with advanced/metastatic HCC disease, chemotherapy is not recommended as the standard care of treatment. Patients diagnosed at an advanced stage may be offered targeted therapies or immunotherapy. Among targeted 1L therapies, sorafenib is the standard of care for patients with intermediate/ advanced HCC. Lenvatinib showed non-inferior efficacy compared with sorafenib and can be considered as 1L therapy in patients with advanced HCC. Targeted 2L therapies include regorafenib which is the standard of care for patients with advanced HCC who have tolerated sorafenib but progressed and is recommended in patients with well-preserved liver function. Second-line treatments also include cabozantinib and ramucirumab for patients with progressive disease who have been on one or two systemic therapies with well-preserved liver function. Ramucirumab is considered only in patients with baseline alpha-fetoprotein ≥ 400 ng/mL. Immunotherapeutic approaches involve the use of immune checkpoint inhibitors such as nivolumab and pembrolizumab for patients who are intolerant to, or have progressed under, approved TKIs (Vogel et al. 2018). Nivolumab has been approved by the FDA as a 2L agent for advanced HCC (Marrero et al. 2018). The FDA has granted pembrolizumab an accelerated approval for the treatment of patients with HCC who have previously received sorafenib (Benson et al. 2019). However, both pembrolizumab and nivolumab have pending E.U. approval (Vogel et al. 2018).

Tecentriq was approved by the FDA (May 2020) and in the European Union (September 2020) for the treatment of advanced HCC. The E.U. indication is as follows:

- Tecentriq, in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable HCC who have not received prior systemic therapy.

Important Comorbidities

Table 12 Prevalence of Selected Comorbidities in Patients with HCC

Comorbid condition	Advanced stage Japan, mean age 71±9.5 years [a]	All stages, U.S, mean age 63.1±10.1 years [b]
Diabetes mellitus	45.7%	35.2%
Hypertension	51.5%	57.9%
Cirrhosis	39.5%	N/A
Hyperlipidaemia	14.0%	17.6%
Non-viral hepatitis	15.6%	N/A
Coronary artery disease	N/A	8.4%
COPD	N/A	5.4%

Information on comorbidities was not available for European patients with HCC.

COPD = chronic obstructive pulmonary disease; HCC = hepatocellular carcinoma; N/A = not available, U.S. = United States.

[a] Source: Akada et al. 2019.

[b] Source: Kim et al. 2018.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

The following nonclinical safety and toxicity studies have been conducted with atezolizumab to support use in oncology patients:

- A 15-day repeat-dose pilot study in C57BL/6 and cluster of differentiation-1 (CD-1) mice
- An 8-week repeat-dose study in cynomolgus monkeys with integrated safety pharmacology
- A 26-week repeat-dose study in cynomolgus monkeys with integrated safety pharmacology
- An in vitro cytokine release assay
- An in vitro hemolytic potential assay
- A tissue cross-reactivity analysis of human and cynomolgus monkey tissues

No single-dose toxicity studies were performed or considered necessary. A high dose was investigated with weekly dose administration in the repeat-dose toxicity studies, without morbidity or mortality after the first dose administration.

Repeat-dose toxicity studies were conducted in mice and cynomolgus monkeys. Because the PD-L1/PD-1 pathway is extensively characterised in mice, the mouse was the preferred rodent species to test the toxicity of atezolizumab. Cynomolgus monkeys were chosen because atezolizumab binds to PD-L1 in cynomolgus monkeys and humans with comparable affinity.

Per current International Council for Harmonisation (ICH) ICH S6 (R1) guidance on the preclinical safety evaluation of biotechnology-derived pharmaceuticals (1997 and 2011), no genotoxicity studies were conducted.

The nonclinical safety program demonstrated that weekly intravenous (IV) administration of atezolizumab at dose levels up to 50 mg/kg for up to 26 weeks (cynomolgus monkeys only) was well-tolerated in mice and cynomolgus monkeys. In primate studies, no atezolizumab-related changes in clinical observations, body weight, food consumption, central nervous system, cardiovascular, respiratory safety pharmacology parameters, or clinical pathology endpoints were observed.

The nonclinical safety findings include neuropathy in C57BL/6 mice, and vasculitis and disturbed menstrual cycles in cynomolgus monkeys. The neuropathy and vasculitis are consistent with heightened immune responses, including those to acute microbial and viral infections, and the potential to increase immune-associated inflammatory lesions.

SII.1 NEUROPATHY

After three weekly dose administrations, microscopic findings attributed to atezolizumab were observed in the sciatic nerve. Minimal neuropathy was noted in C57BL/6 mice at terminal (Day 17) and recovery (Day 43) necropsy at both dose levels (10 and 50 mg/kg). No clinical observations were noted with this finding. This minimal neuropathy was attributed to blockade of PD-L1 by atezolizumab as it is consistent with the observation that PD-1–deficient female mice on the same major histocompatibility complex (MHC) H2b haplotype as C57Bl/6 mice (NOD-H2b/b Pdcd1–/– mice) spontaneously develop autoimmune inflammation in multiple tissues, including peripheral nerves, between 20 and 25 weeks of age, whereas no such lesions were observed in age-matched PD-1–sufficient mice (Yoshida et al. 2008).

Relevance to human usage: Yes

Discussion:

PD-L1/PD-1 interactions regulate and maintain peripheral tolerance, and blockade can increase the risk of immune-related adverse events (AE) (Okazaki and Honjo 2007; Keir et al. 2008). Immune related neuropathies including Guillain Barré syndrome, myasthenic syndrome / myasthenia gravis, and facial paresis have been observed at very low rates (refer to Table 49, Table 50, Table 51, Table 52, Table 53, and Table 54) in clinical trials with atezolizumab.

SII.2 VASCULITIS

Atezolizumab-related minimal to mild arteritis/periarteritis within the interstitium of parenchymal organs (heart, kidney, liver, pancreas, and epididymis), or within the submucosa or muscularis of tubular organs, such as the gastrointestinal and female reproductive tracts, was observed after 9 weekly doses of atezolizumab at the terminal phase necropsy (Study Day 60 in 1 of 6 animals in the 15 mg/kg SC and 50 mg/kg IV dose groups, and in 2 of 6 animals in the 50 mg/kg SC dose group) in the 8-week repeat-dose toxicity study (Study 08-1148). Similarly, in the 26-week repeat-dose toxicity study (Study 13-3278), atezolizumab-related anatomic pathology findings were limited to microscopic, minimal to slight, chronic-active, and multifocal arteritis/periarteritis in multiple organs of 2 animals at the terminal phase necropsy. Similar microscopic arterial findings occurred spontaneously in cynomolgus monkeys to the same extent (generally subclinical in severity, similar in tissue distribution) (Beach et al. 1974; Chamanza et al. 2006); however, this finding was considered atezolizumab-related as it occurred only in test article-treated groups, appeared to be dose-related in incidence (high- and mid-dose groups), and occurred at a higher incidence than historical controls at the test facility (historical incidence of approximately 1%).

Relevance to human usage: Yes

Discussion:

The sporadic observation of spontaneous arteritis/periarteritis within various organs in cynomolgus monkeys appeared to be dose related and consistent with deregulation of peripheral tolerance based on the mechanism of action of atezolizumab. It is known that this species may be predisposed to this form of possible autoimmune disorder.

SII.3 MENSTRUAL CYCLE CHANGES

Female and male reproductive organ systems were assessed as part of the 8- and 26–week, repeat-dose studies (Studies 08-1148 and 13-3278, respectively). In the 26–week, repeat-dose toxicity study (Study 13-3278), an effect on menstrual cycles was noted in all female monkeys in the 50 mg/kg dose group, and was characterised by an irregular cycle pattern during the dosing phase with disturbed cycles especially between Weeks 8 and 14. This finding correlated with an absence of fresh corpora lutea in the ovaries (lack of cycling activity) at the time of the terminal phase necropsy. This effect showed reversibility as the 2 females at 50 mg/kg assigned to the recovery period demonstrated a return to normal menstrual cycling by vaginal swab data, and both animals had fresh corpus lutea at the recovery necropsy. There was no effect on the male monkey reproductive organs.

Relevance to human usage: Yes

Discussion:

Reversible menstrual cycle changes were noted in female monkeys at the highest dose group of 50 mg/kg, which is approximately six times the recommended human equivalent dose (based on area under the curve). These findings have not been replicated in human clinical trials and are not considered relevant to the safety profile of atezolizumab at the proposed dose level in humans.

SII.4 DEVELOPMENTAL TOXICITY

Reproductive and developmental toxicity studies with atezolizumab have not been conducted. Several nonclinical studies have demonstrated that the PD-L1/PD-1 signaling pathway is critical in establishing maternal/fetal tolerance, which is essential for embryofetal survival during gestation (Guleria et al. 2005; Habicht et al. 2007; Wafula et al. 2009; D'Addio et al. 2011). Inhibition of the PD-L1/PD-1 pathway has not been reported to result in teratogenic effects and syngeneic homozygous knockout fetuses (PD-L1 or PD-1 knockouts) develop normally and have not shown skeletal or visceral defects. The weight of evidence of the association between PD-L1/PD-1 inhibition and the increased risk of immune-mediated rejection of the developing fetus suggests there is a risk to the human fetus, including embryo lethality.

Relevance to human usage: Yes

Discussion:

No clinical studies have been performed in pregnant women. Women of childbearing potential are advised to use highly effective contraception and take active measures to avoid pregnancy while undergoing atezolizumab treatment, and for at least 5 months after the last dose.

SII.5 MODULATION OF HOST IMMUNE RESPONSE TO ACUTE INFECTION

Initial in vivo studies assessed the efficacy of atezolizumab in mice infected with lymphocytic choriomeningitis virus (LCMV). When anti-PD-L1 was administered during the chronic phase of LCMV Clone-13 (CL-13) infection, the antibody was effective in enhancing T-cell function and reducing viral load without evidence of toxicity. However, blockade of PD-L1 at the peak of the acute T-cell response and concomitant peak viraemia following LCMV CL-13 infection resulted in a mortality rate of 60%–100%. Published and internal data support that these mortalities are not unique to this molecule or pathway, as similar mortalities are observed in this model with other PD-1 and PD-L1 inhibitors as well as IL-2. The data suggest that the mortalities observed in the acute CL-13 infection model are likely mediated by enhanced $CD8^+$ T-cell function in the presence of extremely high viral burden in multiple organs. The unique features of the murine CL-13 infection model contributed significantly to these deaths, and importantly, these features are not represented in known human viral infections.

Relevance to human usage: Yes

Discussion:

This finding has not been replicated in humans and as suggested, it is likely that the unique features of the murine CL-13 infection model contributed significantly to the high mortality rate.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

SIII.1 CLINICAL TRIAL EXPOSURE – MONOTHERAPY

The atezolizumab monotherapy exposure and safety data included in this Risk Management Plan (RMP) are derived from 11 studies: GO28915 (referred to as OAK), GO28754 (referred to as BIRCH), GO29293 (referred to as IMvigor210), GO28753 (referred to as POPLAR), PCD4989g (referred to as GO27831), GO28625 (referred to as FIR), GO29294 (referred to as IMvigor211), GO29431 (referred to as IMpower110), GO29527 (referred to as IMpower010), MO29872 (referred to as IPSOS) and BP40657 (referred to as IMscin001). Brief descriptions of these studies are presented below:

- OAK: A Phase III, global, multicenter, open-label, randomised study to investigate the efficacy and safety of atezolizumab compared with docetaxel in patients with NSCLC after failure of platinum-containing chemotherapy. This study enrolled patients regardless of PD-L1 expression status.
- POPLAR: A Phase II, global, multicenter, open-label, randomised, controlled study designed to evaluate the efficacy and safety of atezolizumab as a single agent compared with docetaxel in patients with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen. This study enrolled patients regardless of PD-L1 expression status.
- BIRCH: A Phase II, global, multicenter, single-arm study of atezolizumab as a single agent in patients with PD-L1 selected locally advanced or metastatic NSCLC.
- IMvigor210: A Phase II, multicenter, two-cohort single-arm trial designed to evaluate the efficacy and safety of atezolizumab in patients with locally advanced or metastatic urothelial cancer.
- FIR: A Phase II, global, multicenter, single-arm trial designed to evaluate the efficacy and safety of atezolizumab as a single agent in patients with locally advanced or metastatic NSCLC who are PD-L1 selected.
- PCD4989g: A Phase Ia, multicenter, first-in-human, open-label, dose-escalation study to evaluate the safety and pharmacokinetics of atezolizumab administered IV as a single agent to patients with locally advanced or metastatic solid tumours or hematologic malignancies.
- IMvigor211: A phase III, open-label, multicenter, randomised study to investigate the efficacy and safety of atezolizumab (MPDL3280A; Anti-PDL1 Antibody) compared with chemotherapy in patients with locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy.
- IMpower110: A Phase III, open-label, randomised study of atezolizumab (anti-PD-L1 antibody) compared with a platinum agent (cisplatin or carboplatin) in combination with either pemetrexed or gemcitabine for PD-L1-selected, chemotherapy-naive patients with Stage IV non-squamous or squamous NSCLC.
- IMpower010: A Phase III, open-label, randomised study to investigate the efficacy and safety of atezolizumab (anti-PD-L1 antibody) compared with best supportive

care following adjuvant cisplatin-based chemotherapy in patients with completely resected Stage IB (tumours ≥4 cm)-Stage IIIA NSCLC.

- IPSOS: A Phase III, open-label, multicenter, randomised study to investigate the efficacy and safety of atezolizumab compared with chemotherapy in patients with treatment-naïve advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC who are deemed unsuitable for platinum-based therapy.
- IMscin001: A Phase Ib/III, randomised study to investigate the pharmacokinetics, efficacy, and safety of atezolizumab SC compared with atezolizumab IV in patients with previously treated locally advanced or metastatic NSCLC.

An overview of key design features of the 11 studies that include atezolizumab monotherapy together with the respective data cut-off dates are provided in Table 13. A total of 4156 patients were treated with atezolizumab IV and 247 patients received atezolizumab SC.

Table 13 Summary of Atezolizumab Monotherapy Studies Included in this Risk Management Plan.

Study No.	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	Data Cutoff Date
Atezolizumab IV Monotherapy					
Lung and Bladder Cancer					
PCD4989g (GO27831)	Phase I, open-label, dose-escalation and dose-expansion stages	Patients with locally advanced or metastatic solid tumours (including UC and NSCLC) and hematologic malignancies.	All patients = 640 UC = 95 NSCLC = 89	UC Cohort: 15 mg/kg and fixed 1200 mg [a] NSCLC Cohort: 1, 10, 15, 20 mg/kg, and 1200mg (fixed dose) All patients: ≤ 1, 3, 10, 15, 20 mg/kg and 1200mg	31 March 2016

Study No.	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	Data Cutoff Date
Lung Cancer (N=2717 [b])					
OAK (GO28915)	Phase III, global, multicentre, open-label, randomised, controlled trial	Patients with locally advanced, metastatic, or recurrent non-squamous and squamous NSCLC who have failed a prior platinum-containing regimen (2L and 3L). Patients were stratified by PD-L1 status (IC0/1/2/3), number of prior chemotherapy regimens (1 vs. 2), histology (non-squamous vs. squamous).	609 patients treated with atezolizumab [c]	Atezolizumab 1200 mg IV q3w vs. Docetaxel 75 mg/m^2 q3w	7 July 2016
BIRCH (GO28754)	Phase II, global, multicentre, three cohort, single-arm trial	Patients with locally advanced or metastatic NSCLC who were treatment-naive in the metastatic setting (1L), or had progressed during or following treatment with one platinum-based regimen (2L), or had progressed during or following at least 2 regimens (3L +), one of which had to have been a platinum-containing regimen for advanced disease. Patients were PD-L1 − selected (TC2/3 or IC2/3).	All patients = 659 Cohort 1 (1L) = 139 Cohort 2 (2L) = 268 Cohort 3 (3L +) = 252	Atezolizumab 1200 mg IV q3w	1 December 2015
POPLAR (GO28753)	Phase II, global, multicentre, open-label, randomised, controlled trial	Patients with locally advanced, metastatic, or recurrent non-squamous and squamous NSCLC who have failed a prior platinum-containing regimen (2L and 3L). Patients were stratified by PD-L1 status (IC0/1/2/3), number of prior chemotherapy regimens (1 vs. 2), and histology (non-squamous vs. squamous).	142 patients treated with atezolizumab [d]	Atezolizumab 1200 mg IV q3w vs. Docetaxel 75 mg/m^2 q3w	1 December 2015

Study No.	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	Data Cutoff Date
FIR (GO28625)	Phase II, global, multicentre, single-arm trial	Patients with locally advanced or metastatic NSCLC who were treatment-naive (in metastatic setting; 1L) or progressed during or after one (2L+) prior platinum-containing regimen. Patients were PD-L1–selected (TC2/3 or IC2/3).	All patients = 137 Cohort 1 (1L) = 31 Cohort 2 (2L+) = 93 Cohort 3 (2L+) [e] = 13	Atezolizumab 1200 mg IV q3w	7 January 2015
GO29431 (IMpower110)	Phase III, global, multicentre, open-label, randomised clinical trial	PD-L1-selected, chemotherapy-naive patients with Stage IV non-squamous or squamous NSCLC.	286 patients treated with atezolizumab [f]	Atezolizumab 1200 mg IV q3w	4 February 2020
IMpower010 (GO29527) [g]	Phase III, global, randomised, multicentre, open-label trial	Patients with Stage IB (tumours ≥4 cm)-Stage IIIA NSCLC following complete resection and adjuvant cisplatin-based chemotherapy. Patients were stratified by sex (female vs. male), tumour histology (squamous vs. non-squamous), extent of disease (Stage IB vs. Stage II vs. Stage IIIA), PD-L1 tumour expression status by IHC (TC2/3 and any IC vs. TC0/1 and IC2/3 vs. TC0/1 and IC0/1).	495 patients treated with atezolizumab	Atezolizumab 1200 mg IV q3w	Interim analysis: 21 January 2021

Study No.	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	Data Cutoff Date
IPSOS (MO29872)	Phase III, global, randomised, multicentre, open-label trial	Patients with treatment-naïve locally advanced or recurrent or metastatic NSCLC who are deemed unsuitable for any platinum-doublet chemotherapy.	300 patients treated with atezolizumab [h]	Atezolizumab 1200 mg IV q3w	30 April 2022
Bladder Cancer (N=983 [i])					
IMvigor210 (GO29293)	Phase II, global, multicentre, two-cohort, single-arm trial	Patients with locally advanced or 1L metastatic (no prior chemotherapy in the metastatic setting and ineligible for cisplatin-based chemotherapy) and 2L+ UC patients (patients who failed a prior platinum-based therapy or progressed within 12 months of a platinum-containing treatment administered in the neoadjuvant or adjuvant setting). Approximately 30% of the patient population in each cohort was planned to be PD–L1 – selected (IC2/3).	All patients = 429 Cohort 1 (1L cis-ineligible) = 119 Cohort 2 (2L +) = 310	Atezolizumab 1200 mg IV q3w	4 July 2016
IMvigor211 (GO29294)	Phase III, global, multicentre, open-label, randomised, controlled trial	Patients with locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy.	459 patients treated with atezolizumab [j]	Atezolizumab 1200 mg IV q3w	13 March 2017

Study No.	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	Data Cutoff Date
Atezolizumab SC Monotherapy					
IMscin001 (BP40657) [k]	Phase Ib/III, randomised, multicentre, open-label trial	Patients with locally advanced or metastatic NSCLC who have failed a prior platinum-containing regimen. If EGFR or ALK+, progression under one or more driver mutation-specific therapy.	247 patients treated with atezolizumab SC in Part 2 of the study	Part 2: Atezolizumab SC 1875 mg q3w	Part 2 (Updated analysis): CCOD: 16 January 2023

1L = first-line; 2L+ = second-line and beyond; ALK = anaplastic lymphoma kinase; CCOD = clinical cutoff date; EGFR = epidermal growth factor receptor; IC = tumour-infiltrating immune cells; IHC = immunohistochemistry; IV = intravenous; NSCLC = non-small cell lung cancer; PD–L1 = programmed death-ligand 1; TC = tumour cell; mUC = metastatic urothelial carcinoma; SC = subcutaneous; UC = urothelial carcinoma; q3w = every 3 weeks.

[a] Equivalent to an average body weight-based dose of 15 mg/kg.

[b] 2628 from OAK, POPLAR, BIRCH, FIR, IMpower110, IMpower010, and IPSOS + 89 from PCD4989g (NSCLC cohort).

[c] 578 patients were treated with docetaxel 75 mg/m^2 q3w in Study OAK.

[d] 135 patients were treated with docetaxel 75 mg/m^2 q3w in Study POPLAR.

[e] 2L+ patients with previously treated brain metastases (Study FIR).

[f] 263 patients were treated with cisplatin or carboplatin combined with either pemetrexed or gemcitabine in IMpower110.

[g] 495 patients randomised to the best supportive care arm had at least one post-baseline safety measurement in IMpower010.

[h] 147 patients were treated with gemcitabine or vinorelbine in Study IPSOS.

[i] 888 from IMvigor210 and IMvigor211+95 from PCD4989g (UC cohort).

[j] 443 patients were treated with Vinflunine 320 mg/m^2 q3w, paclitaxel 175 mg/m^2 q3w, or docetaxel 75 mg/m^2 q3w in Study IMvigor211.

[k] 124 patients treated with atezolizumab IV in the control arm in Part 2 of IMscin001 were not included in the safety-evaluable population of this risk management plan.

The exposure and safety outputs presented in this RMP for the atezolizumab monotherapy clinical trial population are summarised for the IMscin001 (atezolizumab monotherapy SC) population and three pooled atezolizumab monotherapy IV safety populations:

- **All Patients Monotherapy IV:** PCD4989g (all cohorts), OAK (atezolizumab arm only), POPLAR (atezolizumab arm only), BIRCH (all cohorts), FIR (all cohorts), IMvigor210 (Cohorts 1 and 2), IMvigor211 (atezolizumab arm only), IMpower110 (atezolizumab arm only), IMpower010 (atezolizumab arm only), and IPSOS (atezolizumab arm only).
- **All Lung Monotherapy IV:** PCD4989g (NSCLC cohort), OAK (atezolizumab arm only), POPLAR (atezolizumab arm only), BIRCH (all cohorts), FIR (all cohorts), IMpower110 (atezolizumab arm only), IMpower010 (atezolizumab arm only), and IPSOS (atezolizumab arm only).
- **All Bladder Monotherapy IV**: PCD4989g (UC cohort), IMvigor210 (Cohorts 1 and 2), and IMvigor211 (atezolizumab arm only).

Exposure by Dose and Duration

See Table 14. The majority of patients (89.7% [3726/4156]) in the All Patients IV monotherapy population received atezolizumab at a fixed dose of 1200 mg given q3w. The remaining 430 patients (from the Study PCD4989g) received:

- Atezolizumab at a dose of 15 mg/kg q3w (equivalent to 1200 mg for an 80 kg adult patient): 236 patients
- Atezolizumab at a dose of 20 mg/kg q3w: 146 patients
- Atezolizumab at a dose of 10 mg/kg q3w: 36 patients
- Atezolizumab at a dose of $\leq$ 1 mg/kg q3w: 9 patients
- Atezolizumab at a dose of 3 mg/kg q3w: 3 patients.

Table 15 and Table 16 present exposures in Lung monotherapy IV and Bladder monotherapy IV clinical studies, respectively.

See Table 17. In the IMscin001 study, 247 patients received atezolizumab at a fixed dose of 1875 mg SC given q3w.

Table 14 Clinical Trial Exposure by Dose and Duration: All Patients Monotherapy IV

Extent of Exposure by Duration and by Dose, Atezolizumab Infusion
Atezo IV Safety Evaluable Patients
Protocols: GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

	<=1 mg/kg (N=9)	3 mg/kg (N=3)	10 mg/kg (N=36)	15 mg/kg (N=236)	20 mg/kg (N=146)	1200 mg (N=3726)	All Patients IV (N=4156)
Counts of Patients in Treatment duration groups							
0 to <= 3 months	6 (66.7%)	1 (33.3%)	10 (27.8%)	112 (47.5%)	53 (36.3%)	1588 (42.6%)	1770 (42.6%)
>3 months to <= 6 months	1 (11.1%)	0	4 (11.1%)	36 (15.3%)	29 (19.9%)	613 (16.5%)	683 (16.4%)
>6 months to <= 12 months	1 (11.1%)	0	12 (33.3%)	42 (17.8%)	47 (32.2%)	834 (22.4%)	936 (22.5%)
>12 months to <= 18 months	0	0	0	7 (3.0%)	0	383 (10.3%)	390 (9.4%)
>18 months to <= 24 months	0	1 (33.3%)	2 (5.6%)	8 (3.4%)	4 (2.7%)	207 (5.6%)	222 (5.3%)
>24 months	1 (11.1%)	1 (33.3%)	8 (22.2%)	31 (13.1%)	13 (8.9%)	101 (2.7%)	155 (3.7%)
Treatment duration groups in person time (years)							
Total	6.0	6.2	43.6	160.5	97.9	2121.0	2435.1
0 to <= 3 months	0.6	0.2	1.0	11.8	6.6	158.2	178.4
>3 months to <= 6 months	0.3	NE	1.6	12.0	9.8	215.0	238.6
>6 months to <= 12 months	0.7	NE	9.7	32.5	36.1	648.9	727.9
>12 months to <= 18 months	NE	NE	NE	9.2	NE	469.0	478.1
>18 months to <= 24 months	NE	1.8	3.2	13.3	7.1	357.3	382.6
>24 months	4.4	4.2	28.2	81.8	38.3	272.6	429.6

All Patients IV: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS).
NE = 0 years. Percentages are based on the total population, N in the column headers.
Person time is the sum of Atezolizumab Infusion exposure across all patients in years.
Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

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Table 15 Clinical Trial Exposure by Dose and Duration: Lung Monotherapy IV

Extent of Exposure by Duration and by Dose, Atezolizumab Infusion
Lung IV Safety Evaluable Patients
Protocols: GO27831, GO28625, GO28753, GO28754, GO28915, GO29431, GO29527, MO29872

	<=1 mg/kg (N=1)	10 mg/kg (N=11)	15 mg/kg (N=26)	20 mg/kg (N=50)	1200 mg (N=2629)	All Lung IV (N=2717)
Counts of Patients in Treatment duration groups						
0 to <= 3 months	0	5 (45.5%)	11 (42.3%)	20 (40.0%)	995 (37.8%)	1031 (37.9%)
>3 months to <= 6 months	0	0	5 (19.2%)	7 (14.0%)	430 (16.4%)	442 (16.3%)
>6 months to <= 12 months	0	3 (27.3%)	5 (19.2%)	15 (30.0%)	691 (26.3%)	714 (26.3%)
>12 months to <= 18 months	0	0	0	0	294 (11.2%)	294 (10.8%)
>18 months to <= 24 months	0	1 (9.1%)	0	3 (6.0%)	118 (4.5%)	122 (4.5%)
>24 months	1 (100%)	2 (18.2%)	5 (19.2%)	5 (10.0%)	101 (3.8%)	114 (4.2%)
Treatment duration groups in person time (years)						
Total	4.4	11.1	19.1	36.2	1624.7	1695.6
0 to <= 3 months	NE	0.4	1.5	2.6	96.3	100.7
>3 months to <= 6 months	NE	NE	1.6	2.1	150.8	154.5
>6 months to <= 12 months	NE	2.5	3.7	12.0	547.6	565.8
>12 months to <= 18 months	NE	NE	NE	NE	356.5	356.5
>18 months to <= 24 months	NE	1.5	NE	5.3	200.9	207.7
>24 months	4.4	6.7	12.4	14.1	272.6	310.3

All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS).
NE = 0 years. Percentages are based on the total population, N in the column headers.
Person time is the sum of Atezolizumab Infusion exposure across all patients in years.
Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

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Table 16 Clinical Trial Exposure by Dose and Duration: Bladder Monotherapy IV

Extent of Exposure by Duration and by Dose, Atezolizumab Infusion
Bladder IV Safety Evaluable Patients
Protocols: GO27831, GO29293, GO29294

	15 mg/kg (N=86)	1200 mg (N=897)	All Bladder IV (N=983)
Counts of Patients in Treatment duration groups			
0 to <= 3 months	43 (50.0%)	456 (50.8%)	499 (50.8%)
>3 months to <= 6 months	10 (11.6%)	156 (17.4%)	166 (16.9%)
>6 months to <= 12 months	11 (12.8%)	116 (12.9%)	127 (12.9%)
>12 months to <= 18 months	2 (2.3%)	80 (8.9%)	82 (8.3%)
>18 months to <= 24 months	6 (7.0%)	89 (9.9%)	95 (9.7%)
>24 months	14 (16.3%)	0	14 (1.4%)
Treatment duration groups in person time (years)			
Total	64.5	440.9	505.4
0 to <= 3 months	5.0	46.4	51.4
>3 months to <= 6 months	3.5	54.9	58.4
>6 months to <= 12 months	8.7	81.7	90.5
>12 months to <= 18 months	2.6	101.5	104.1
>18 months to <= 24 months	10.2	156.3	166.5
>24 months	34.5	NE	34.5

All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211).
NE = 0 years. Percentages are based on the total population, N in the column headers.
Person time is the sum of Atezolizumab Infusion exposure across all patients in years.
Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Clinical cut-off dates: GO27831:31MAR2016, GO29293:04JUL2016, GO29294:13MAR2017.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/CSRFinal_ICSD/prod/program/t_ex_rmp.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/CSRFinal_ICSD/prod/output/
t_ex_rmp_DOSEU_atezo_dose_30APR2022_29872P.out
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Table 17 Clinical Trial Exposure by Duration: All Patients Monotherapy

Extent of Exposure by Duration and by Indication, Atezolizumab Infusion/Injection
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Counts of Patients in Treatment duration groups					
0 to <= 3 months	1770 (42.6%)	1031 (37.9%)	499 (50.8%)	140 (46.7%)	118 (47.8%)
>3 months to <= 6 months	683 (16.4%)	442 (16.3%)	166 (16.9%)	43 (14.3%)	41 (16.6%)
>6 months to <= 12 months	936 (22.5%)	714 (26.3%)	127 (12.9%)	52 (17.3%)	48 (19.4%)
>12 months to <= 18 months	390 (9.4%)	294 (10.8%)	82 (8.3%)	20 (6.7%)	31 (12.6%)
>18 months to <= 24 months	222 (5.3%)	122 (4.5%)	95 (9.7%)	12 (4.0%)	8 (3.2%)
>24 months	155 (3.7%)	114 (4.2%)	14 (1.4%)	33 (11.0%)	1 (0.4%)
Treatment duration groups in person time (years)					
Total	2435.1	1695.6	505.4	208.9	114.2
0 to <= 3 months	178.4	100.7	51.4	11.4	12.5
>3 months to <= 6 months	238.6	154.5	58.4	15.6	14.5
>6 months to <= 12 months	727.9	565.8	90.5	35.5	33.9
>12 months to <= 18 months	478.1	356.5	104.1	24.1	38.5
>18 months to <= 24 months	382.6	207.7	166.5	20.8	12.8
>24 months	429.6	310.3	34.5	101.4	2.0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
NE = 0 years. Percentages are based on the total population, N in the column headers.
Person time is the sum of Atezolizumab Infusion/Injection exposure across all patients in years.
Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ex_rmp.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/t_ex_rmp_RMPALL_atezo_dur_30APR2022_29872P.out
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Table 18 Clinical Trial Exposure by Age and Gender: All Patients Monotherapy IV

Extent of Exposure by Age Group and Gender, Atezolizumab Infusion
Safety Evaluable Patients
Protocols: GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

	All Patients IV (N=4156)			All Lung IV (N=2717)			All Bladder IV (N=983)		
	Female (N=1454)	Male (N=2702)	Total (N=4156)	Female (N=984)	Male (N=1733)	Total (N=2717)	Female (N=223)	Male (N=760)	Total (N=983)
Counts of Patients by Age groups (years)									
0 - <65	767 (52.8%)	1273 (47.1%)	2040 (49.1%)	518 (52.6%)	859 (49.6%)	1377 (50.7%)	78 (35.0%)	291 (38.3%)	369 (37.5%)
65 - 74	472 (32.5%)	970 (35.9%)	1442 (34.7%)	320 (32.5%)	589 (34.0%)	909 (33.5%)	90 (40.4%)	314 (41.3%)	404 (41.1%)
75 - 84	203 (14.0%)	436 (16.1%)	639 (15.4%)	136 (13.8%)	273 (15.8%)	409 (15.1%)	54 (24.2%)	144 (18.9%)	198 (20.1%)
>=85	12 (0.8%)	23 (0.9%)	35 (0.8%)	10 (1.0%)	12 (0.7%)	22 (0.8%)	1 (0.4%)	11 (1.4%)	12 (1.2%)
Treatment duration (years) in person time by Age groups (years)									
Total	785.9	1649.2	2435.1	580.8	1114.8	1695.6	99.6	405.8	505.4
0 - <65	398.5	760.0	1158.6	300.7	527.6	828.3	31.7	159.3	191.0
65 - 74	263.7	602.2	865.8	189.2	403.5	592.7	39.4	163.1	202.5
75 - 84	117.1	278.8	395.9	84.7	178.6	263.2	28.4	80.3	108.7
>=85	6.6	8.2	14.9	6.3	5.1	11.4	0.1	3.2	3.2

Atezo = Atezolizumab. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
NE = 0 years. Percentages are based on the total population, N in the column headers.
Person time is the sum of Atezolizumab Infusion exposure across all patients in years.

Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ex_rmp.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/t_ex_rmp_RMP1_atezo_agesex_30APR2022_29872P.out
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Table 19 Clinical Trial Exposure by Age and Gender: All Patients IV, IPSOS and IMscin001

Extent of Exposure by Age Group and Gender, Atezolizumab Infusion/Injection
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

	All Patients IV (N=4156)			IPSOS Atezo (N=300)			IMSCIN001 Atezo SC (N=247)		
	Female (N=1454)	Male (N=2702)	Total (N=4156)	Female (N=81)	Male (N=219)	Total (N=300)	Female (N=72)	Male (N=175)	Total (N=247)
Counts of Patients by Age groups (years)									
0 - <65	767 (52.8%)	1273 (47.1%)	2040 (49.1%)	13 (16.0%)	33 (15.1%)	46 (15.3%)	37 (51.4%)	100 (57.1%)	137 (55.5%)
65 - 74	472 (32.5%)	970 (35.9%)	1442 (34.7%)	25 (30.9%)	75 (34.2%)	100 (33.3%)	28 (38.9%)	58 (33.1%)	86 (34.8%)
75 - 84	203 (14.0%)	436 (16.1%)	639 (15.4%)	36 (44.4%)	103 (47.0%)	139 (46.3%)	7 (9.7%)	16 (9.1%)	23 (9.3%)
>=85	12 (0.8%)	23 (0.9%)	35 (0.8%)	7 (8.6%)	8 (3.7%)	15 (5.0%)	0	1 (0.6%)	1 (0.4%)
Treatment duration (years) in person time by Age groups (years)									
Total	785.9	1649.2	2435.1	39.8	169.1	208.9	29.7	84.5	114.2
0 - <65	398.5	760.0	1158.6	2.8	18.6	21.4	15.5	41.8	57.3
65 - 74	263.7	602.2	865.8	7.4	72.2	79.6	12.1	31.5	43.6
75 - 84	117.1	278.8	395.9	24.8	74.5	99.3	2.1	9.7	11.9
>=85	6.6	8.2	14.9	4.9	3.8	8.6	NE	1.4	1.4

Atezo = Atezolizumab, SC = Subcutaneous. All Patients IV: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS).
NE = 0 years. Percentages are based on the total population, N in the column headers.
Person time is the sum of Atezolizumab Infusion/Injection exposure across all patients in years.

Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

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Table 20 Clinical Trial Exposure by Race: All Patients Monotherapy

Extent of Exposure by Race, Atezolizumab Infusion/Injection
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Counts of Patients by Race					
White	3233 (77.8%)	2077 (76.4%)	793 (80.7%)	202 (67.3%)	174 (70.4%)
Black	78 (1.9%)	44 (1.6%)	12 (1.2%)	2 (0.7%)	2 (0.8%)
Asian	567 (13.6%)	480 (17.7%)	74 (7.5%)	74 (24.7%)	47 (19.0%)
Other	278 (6.7%)	116 (4.3%)	104 (10.6%)	22 (7.3%)	24 (9.7%)
Treatment duration in person time by Race (years)					
Total	2435.1	1695.6	505.4	208.9	114.2
White	1894.0	1293.9	402.1	130.2	83.9
Black	48.2	28.1	8.3	1.8	1.4
Asian	346.6	307.0	34.6	60.0	19.1
Other	146.4	66.6	60.4	17.0	9.8

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
NE = 0 years. Percentages are based on the total population, N in the column headers.
Person time is the sum of Atezolizumab Infusion/Injection exposure across all patients in years.

Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ex_rmp.sas
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Table 21 Clinical Trial Exposure by Ethnicity: All Patients Monotherapy

Extent of Exposure by Ethnicity, Atezolizumab Infusion/Injection
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Counts of Patients by Ethnicity					
Hispanic or Latino	186 (4.5%)	136 (5.0%)	29 (3.0%)	47 (15.7%)	61 (24.7%)
Not Hispanic or Latino	3659 (88.0%)	2474 (91.1%)	819 (83.3%)	240 (80.0%)	185 (74.9%)
Not reported	218 (5.2%)	74 (2.7%)	93 (9.5%)	9 (3.0%)	0
Unknown	93 (2.2%)	33 (1.2%)	42 (4.3%)	4 (1.3%)	1 (0.4%)
Treatment duration in person time by Ethnicity (years)					
Total	2435.1	1695.6	505.4	208.9	114.2
Hispanic or Latino	104.7	85.9	11.7	31.7	27.6
Not Hispanic or Latino	2170.1	1542.8	422.4	171.3	86.4
Not reported	110.3	47.3	46.8	5.5	NE
Unknown	50.1	19.6	24.5	0.4	0.2

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
NE = 0 years. Percentages are based on the total population, N in the column headers.
Person time is the sum of Atezolizumab Infusion/Injection exposure across all patients in years.

Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ex_rmp.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/t_ex_rmp_RMPALL_atezo_ethnic_30APR2022_29872P.out
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Special Population Exposure in Monotherapy

All clinical trial development programs have inherent limitations, which can result in limited exposure for special patient populations. The focus of the clinical development program for atezolizumab to date has limited specific exposure data for special population groupings; please refer to Section SIV.3 (Limitations in respect to populations typically under-represented in clinical trial development programs) for further information. However, a significant number of elderly patients have been exposed to atezolizumab monotherapy (see Table 18 and Table 19 for further details). Notably, patients ≥65 years of age make up 50.9% of the All Patients IV monotherapy population (34.7% of patients were aged 65–74 years and 15.4% were 75–84 years, while patients ≥85 years of age make up 0.8%). In the IMscin001 study, 34.8% of patients who received atezolizumab SC were aged 65–74 years, 9.3% were 75–84 years, and 0.4% were ≥ 85 years old.

SIII.2 CLINICAL TRIAL EXPOSURE – COMBINATION THERAPY

The exposure and safety data included in this RMP for combination therapy clinical trial population with atezolizumab are summarised for the following pooled populations:

Lung Cancer (NSCLC+SCLC) Combination Therapy: GO29537 (IMpower130), GO29436 (IMpower150), and GO30081 (IMpower133)

- GO29537 (IMpower130): A Phase III, multicenter, randomized, open-label study, which evaluated safety and efficacy of atezolizumab in combination with carboplatin + nab paclitaxel compared with treatment with carboplatin + nab-paclitaxel in chemotherapy naive patients with Stage IV non-squamous NSCLC.
- GO30081 (IMpower133): A Phase I/III, randomized, double-blind, placebo-controlled study of carboplatin plus etoposide with or without atezolizumab in patients with ES-SCLC.
- GO29436 (IMpower150): A Phase III, open-label, randomized study of atezolizumab in combination with carboplatin + paclitaxel with or without bevacizumab compared with carboplatin + paclitaxel + bevacizumab, in chemotherapy-naive patients with Stage IV non-squamous NSCLC.

Breast Cancer Combination Therapy: WO29522 (IMpassion130)

- WO29522 (IMpassion130): A Phase III, multicenter, randomized, placebo-controlled study of atezolizumab (anti-PD-L1 antibody) in combination with nab paclitaxel compared with placebo with nab paclitaxel for patients with locally advanced or metastatic TNBC who have not received prior systemic therapy for mBC.

Hepatocellular Carcinoma Combination Therapy: YO40245 (IMbrave150; atezolizumab+bevacizumab arm) and GO30140 (Arms A+F1)

- YO40245: A Phase III, open-label, randomized study of atezolizumab in combination with bevacizumab compared with sorafenib in patients with untreated locally advanced or metastatic HCC.
- GO30140: An open-label, multicenter phase Ib study of the safety and efficacy of atezolizumab (anti-PDL1 antibody) administered in combination with bevacizumab and/or other treatments in patients with solid tumours (patients with HCC only from Arms A+F1).

All Patients Combination Therapy: GO29537 (IMpower130), GO29436 (IMpower150), GO30081 (IMpower133), WO29522 (IMpassion130), YO40245 (IMbrave150; atezolizumab+bevacizumab arm), and GO30140 (Arms A+F1).

An overview of key design features of these studies together with the respective data cut-off dates is provided in Table 22.

Table 22 Summary of Studies Included in this RMP for Combination Therapy with Atezolizumab

Indication/ Study No.	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	Data Cutoff Date
Lung cancer (N = 1464)					
IMpower130 (GO29537)	Phase III, multicentre, randomised, open-label study	Chemotherapy-naive patients with Stage IV non-squamous NSCLC	Total: n = 473 patients treated with atezo + carboplatin + nab-paclitaxel (CnP)	atezolizumab 1200 mg IV q3w + carboplatin AUC = 6 IV via infusion over 30 min q3w + nab-paclitaxel 100 mg/m2 via IV infusion over 15–30 min q3w[a]	15 March 2018
IMpower150 (GO29436)	Phase III, open-label, randomised trial	Patients with Stage IV non-squamous NSCLC	Total: n = 793 patients treated with ATZ + CP with/without bevacizumab	atezolizumab 1200 mg IV q21d; bevacizumab – 15 mg/kg q21d	22 January 2018
IMpower133 (GO30081)	Phase I/III, global multicentre, randomised, double-blinded, placebo controlled trial	Patients with extensive-stage small cell lung cancer	Total: n = 198 patients treated with atezo + carboplatin + etoposide	atezolizumab 1200 mg administered via IV infusion q3w + carboplatin 5 mg/mL/min via IV infusion over 30–60 min + etoposide 100 mg/m2 via IV infusion over 60 min	24 April 2018

Table 22 Summary of Studies Included in this RMP for Combination Therapy with Atezolizumab (cont.)

Indication/ Study No.	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	Data Cutoff Date
Breast cancer (N = 452)					
IMpassion130 (WO29522)	Phase III, multicentre, randomised, placebo controlled	Patients with previously untreated unresectable locally advanced or metastatic TNBC	Total: n = 452 patients treated with ATZ + nP	atezolizumab 840 mg IV q2w + nab-paclitaxel 100 mg/m2 IV (3 weeks on, 1 week off)	17 April 2018
Hepatocellular carcinoma (N=493)					
IMbrave150 (YO40245)	Phase III, open-label, randomised, multicentre	Patients with untreated locally advanced or metastatic and/or unresectable HCC	Total: n = 329 patients treated with ATZ + Bev	atezolizumab 1200 mg administered via IV infusion q3w + bevacizumab 15 mg/kg via IV infusion q3w	29 August 2019
GO30140	Phase Ib, open-label, multicentre	Patients with untreated locally advanced or metastatic and/or unresectable HCC	Total: n = 164 patients treated with ATZ + Bev (Arm A = 104 + Arm F1 = 60)	atezolizumab 1200 mg administered via IV infusion q3w + bevacizumab 15 mg/kg via IV infusion q3w	14 June 2019

ATZ/atezo = atezolizumab; AUC = area under the concentration–time curve; Bev = bevacizumab; CnP = carboplatin + nab-paclitaxel; CP = carboplatin+paclitaxel; HCC=hepatocellular carcinoma; IV = intravenous; NSCLC = non-small cell lung cancer; nP = nab-Paclitaxel; q2w = every 2 weeks; q3w/q21d = every 3 weeks/every 21 days; SCLC = small cell lung cancer; TNBC = triple negative breast cancer.

[a] nab-Paclitaxel was also administered on Day 8 and Day 15 of each 21-day cycle.

Table 23 Clinical Trial Exposure to Atezolizumab by Treatment Duration and Dose: Combination Therapy (Pooled)

Extent of Exposure by Duration and by Dose, Atezolizumab
Safety Evaluable Patients
Protocols: YO40245, GO30140, GO29436, GO29537, GO30081, WO29522

	All Patients (N=2409)		
	840 mg (N=452)	1200 mg (N=1957)	Total (N=2409)
Counts of Patients in Treatment duration groups			
0 to <= 3 months	106 (23.5%)	463 (23.7%)	569 (23.6%)
>3 months to <= 6 months	131 (29.0%)	410 (21.0%)	541 (22.5%)
>6 months to <= 12 months	128 (28.3%)	587 (30.0%)	715 (29.7%)
>12 months to <= 18 months	63 (13.9%)	323 (16.5%)	386 (16.0%)
>18 months to <= 24 months	16 (3.5%)	119 (6.1%)	135 (5.6%)
>24 months	8 (1.8%)	55 (2.8%)	63 (2.6%)
Treatment duration groups in person time (years)			
Total	273.4	1328.6	1602.0
0 to <= 3 months	12.9	43.6	56.5
>3 months to <= 6 months	48.5	150.4	198.9
>6 months to <= 12 months	92.4	416.9	509.2
>12 months to <= 18 months	74.5	391.8	466.3
>18 months to <= 24 months	27.0	204.6	231.6
>24 months	18.1	121.3	139.5

GO29436(IMPOWER150 Arms A+B) + GO29537(IMPOWER130 Arm A)+ GO30081(IMPOWER133 ARM A)+ YO40245(Arm A) + GO30140(Arms A+F1) + WO29522(IMPASSION130 Arm A).
NE = 0 years. Percentages are based on the total population, N in the column headers.
Person time is the sum of Atezolizumab exposure across all patients in years. Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Clinical cut-off dates: YO40245:29AUG2019, GO30140:14JUN2019, GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, WO29522:17APR2018

Program: root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018_ICSD/prod/program/t_ex_rmp.sas
Output: root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018_ICSD/prod/output/t_ex_rmp_RMPALL_atezo_dosea_29AUG2019_40245P.out
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Table 24 Clinical Trial Exposure to Atezolizumab by Treatment Duration and Dose: Combination Therapy (Stratified by Indications)

Extent of Exposure by Duration and by Dose, Atezolizumab
Safety Evaluable Patients
Protocols: YO40245, GO30140, GO29436, GO29537, GO30081, WO29522

	Lung (N=1464)		Breast (N=452)		HCC (N=493)	
	1200 mg (N=1464)	Total (N=1464)	840 mg (N=452)	Total (N=452)	1200 mg (N=493)	Total (N=493)
Counts of Patients in Treatment duration groups						
0 to <= 3 months	347 (23.7%)	347 (23.7%)	106 (23.5%)	106 (23.5%)	116 (23.5%)	116 (23.5%)
>3 months to <= 6 months	321 (21.9%)	321 (21.9%)	131 (29.0%)	131 (29.0%)	89 (18.1%)	89 (18.1%)
>6 months to <= 12 months	356 (24.3%)	356 (24.3%)	128 (28.3%)	128 (28.3%)	231 (46.9%)	231 (46.9%)
>12 months to <= 18 months	276 (18.9%)	276 (18.9%)	63 (13.9%)	63 (13.9%)	47 (9.5%)	47 (9.5%)
>18 months to <= 24 months	116 (7.9%)	116 (7.9%)	16 (3.5%)	16 (3.5%)	3 (0.6%)	3 (0.6%)
>24 months	48 (3.3%)	48 (3.3%)	8 (1.8%)	8 (1.8%)	7 (1.4%)	7 (1.4%)
Treatment duration groups in person time (years)						
Total	1038.0	1038.0	273.4	273.4	290.5	290.5
0 to <= 3 months	31.5	31.5	12.9	12.9	12.1	12.1
>3 months to <= 6 months	117.9	117.9	48.5	48.5	32.5	32.5
>6 months to <= 12 months	247.4	247.4	92.4	92.4	169.4	169.4
>12 months to <= 18 months	336.8	336.8	74.5	74.5	55.0	55.0
>18 months to <= 24 months	199.9	199.9	27.0	27.0	4.7	4.7
>24 months	104.6	104.6	18.1	18.1	16.8	16.8

Lung: GO29436(IMPOWER150 Arms A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arms A+F1).
Breast: WO29522(IMPASSION130 Arm A).
NE = 0 years. Percentages are based on the total population, N in the column headers.
Person time is the sum of Atezolizumab exposure across all patients in years. Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Clinical cut-off dates: YO40245:29AUG2019, GO30140:14JUN2019, GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, WO29522:17APR2018

Program: root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018_ICSD/prod/program/t_ex_rmp.sas
Output: root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018_ICSD/prod/output/t_ex_rmp_RMP1_atezo_dosea_29AUG2019_40245P.out
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Table 25 Exposure to Atezolizumab by Age and Gender: Combination Therapy (Pooled)

Extent of Exposure by Age Group and Gender, Atezolizumab
Safety Evaluable Patients
Protocols: YO40245, GO30140, GO29436, GO29537, GO30081, WO29522

	All Patients (N=2409)		
	Female (N=1125)	Male (N=1284)	Total (N=2409)
Counts of Patients by Age groups (years)			
< 65	716 (63.6%)	693 (54.0%)	1409 (58.5%)
65 - 74	324 (28.8%)	452 (35.2%)	776 (32.2%)
75 - 84	82 (7.3%)	128 (10.0%)	210 (8.7%)
>=85	3 (0.3%)	11 (0.9%)	14 (0.6%)
Treatment duration in person time by Age groups (years)			
Total	758.4	843.6	1602.0
< 65	466.3	454.5	920.8
65 - 74	233.3	295.7	529.0
75 - 84	58.0	89.1	147.1
>=85	0.8	4.3	5.1

GO29436(IMPOWER150 Arms A+B) + GO29537(IMPOWER130 Arm A)+ GO30081(IMPOWER133 ARM A)+
YO40245(Arm A) + GO30140(Arms A+F1) + WO29522(IMPASSION130 Arm A).
NE = 0 years. Percentages are based on the total population, N in the column headers.
Person time is the sum of Atezolizumab exposure across all patients in years.
Clinical cut-off dates: YO40245:29AUG2019, GO30140:14JUN2019, GO29436:22JAN2018,
GO29537:15MAR2018, GO30081:24APR2018, WO29522:17APR2018

Program: root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018_ICSD/prod/
program/t_ex_rmp.sas
Output: root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018_ICSD/prod/
output/t_ex_rmp_RMPALL_atezo_agesex_29AUG2019_40245P.out
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Table 26 Exposure to Atezolizumab by Age and Gender: Combination Therapy (Stratified by Indications)

Extent of Exposure by Age Group and Gender, Atezolizumab
Safety Evaluable Patients
Protocols: YO40245, GO30140, GO29436, GO29537, GO30081, WO29522

	Lung (N=1464)			Breast (N=452)			HCC (N=493)		
	Female (N=591)	Male (N=873)	Total (N=1464)	Female (N=449)	Male (N=3)	Total (N=452)	Female (N=85)	Male (N=408)	Total (N=493)
Counts of Patients by Age groups (years)									
< 65	329 (55.7%)	455 (52.1%)	784 (53.6%)	346 (77.1%)	2 (66.7%)	348 (77.0%)	41 (48.2%)	236 (57.8%)	277 (56.2%)
65 - 74	214 (36.2%)	336 (38.5%)	550 (37.6%)	82 (18.3%)	1 (33.3%)	83 (18.4%)	28 (32.9%)	115 (28.2%)	143 (29.0%)
75 - 84	47 (8.0%)	76 (8.7%)	123 (8.4%)	21 (4.7%)	0	21 (4.6%)	14 (16.5%)	52 (12.7%)	66 (13.4%)
>=85	1 (0.2%)	6 (0.7%)	7 (0.5%)	0	0	0	2 (2.4%)	5 (1.2%)	7 (1.4%)
Treatment duration in person time by Age groups (years)									
Total	435.6	602.5	1038.0	272.6	0.8	273.4	50.2	240.3	290.5
< 65	238.3	318.6	556.9	203.0	0.5	203.5	25.1	135.3	160.4
65 - 74	159.3	223.6	382.9	58.0	0.3	58.3	16.0	71.7	87.8
75 - 84	38.0	58.7	96.7	11.6	NE	11.6	8.4	30.4	38.9
>=85	0.1	1.5	1.6	NE	NE	NE	0.7	2.8	3.5

Lung: GO29436(IMPOWER150 Arms A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arms A+F1).
Breast: WO29522(IMPASSION130 Arm A).
NE = 0 years. Percentages are based on the total population, N in the column headers.
Person time is the sum of Atezolizumab exposure across all patients in years.
Clinical cut-off dates: YO40245:29AUG2019, GO30140:14JUN2019, GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, WO29522:17APR2018

Program: root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018_ICSD/prod/program/t_ex_rmp.sas
Output: root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018_ICSD/prod/output/t_ex_rmp_RMP1_atezo_agesex_29AUG2019_40245P.out
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Table 27 Exposure to Atezolizumab by Race: Combination Therapy

Extent of Exposure by Race, Atezolizumab
Safety Evaluable Patients
Protocols: YO40245, GO30140, GO29436, GO29537, GO30081, WO29522

	All Patients (N=2409)	Lung (N=1464)	Breast (N=452)	HCC (N=493)
Counts of Patients by Race				
White	1684 (69.9%)	1225 (83.7%)	306 (67.7%)	153 (31.0%)
Black	73 (3.0%)	30 (2.0%)	30 (6.6%)	13 (2.6%)
Asian	539 (22.4%)	149 (10.2%)	84 (18.6%)	306 (62.1%)
Other	113 (4.7%)	60 (4.1%)	32 (7.1%)	21 (4.3%)
Treatment duration in person time by Race (years)				
Total	1602.0	1038.0	273.4	290.5
White	1147.4	873.0	187.5	87.0
Black	47.6	22.4	14.8	10.4
Asian	334.5	99.4	54.6	180.4
Other	72.5	43.3	16.5	12.7

Lung: GO29436(IMPOWER150 Arms A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arms A+F1).
Breast: WO29522(IMPASSION130 Arm A).
NE = 0 years. Percentages are based on the total population, N in the column headers.
Person time is the sum of Atezolizumab exposure across all patients in years.
Clinical cut-off dates: YO40245:29AUG2019, GO30140:14JUN2019, GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, WO29522:17APR2018

Program: root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018_ICSD/prod/program/t_ex_rmp.sas
Output: root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018_ICSD/prod/output/
t_ex_rmp_RMP_atezo_race_29AUG2019_40245P.out
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Table 28 Exposure to Atezolizumab by Ethnicity

Extent of Exposure by Ethnicity, Atezolizumab
Safety Evaluable Patients
Protocols: YO40245, GO30140, GO29436, GO29537, GO30081, WO29522

	All Patients (N=2409)	Lung (N=1464)	Breast (N=452)	HCC (N=493)
Counts of Patients by Ethnicity				
n	2409	1464	452	493
Hispanic or Latino	176 (7.3%)	104 (7.1%)	59 (13.1%)	13 (2.6%)
Not Hispanic or Latino	2104 (87.3%)	1276 (87.2%)	371 (82.1%)	457 (92.7%)
Not reported	78 (3.2%)	59 (4.0%)	10 (2.2%)	9 (1.8%)
Unknown	51 (2.1%)	25 (1.7%)	12 (2.7%)	14 (2.8%)
Treatment duration in person time by Ethnicity (years)				
Total	1602.0	1038.0	273.4	290.5
Hispanic or Latino	121.0	82.8	31.2	7.0
Not Hispanic or Latino	1393.1	894.1	229.2	269.9
Not reported	54.6	42.1	7.0	5.6
Unknown	33.2	19.1	6.0	8.1

Lung: GO29436(IMPOWER150 Arms A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arms A+F1).
Breast: WO29522(IMPASSION130 Arm A).
NE = 0 years. Percentages are based on the total population, N in the column headers.
Person time is the sum of Atezolizumab exposure across all patients in years.
Clinical cut-off dates: YO40245:29AUG2019, GO30140:14JUN2019, GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, WO29522:17APR2018

Program: root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018_ICSD/prod/program/t_ex_rmp.sas
Output: root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018_ICSD/prod/output/t_ex_rmp_RMP_atezo_ethnic_29AUG2019_40245P.out
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Special Population Exposure in Combination Therapy

All clinical trial development programs have inherent limitations, which can result in limited exposure for special patient populations. The focus of the clinical development program for atezolizumab to date has limited specific exposure data for special population groups; please refer to Section SIV.3 (Limitations in respect to populations typically under-represented in clinical trial development programs) for further information. Nevertheless, a significant number of elderly patients have been exposed to atezolizumab (given in combination), see Table 25 for further details. Notably, patients ≥65 years of age make up 41.5 % of the All Patients Combination therapy population (32.2% of patients were aged 65–74 years and 8.7% were 75–84 years, while patients ≥85 years of age make up 0.6%).

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 29 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Atezolizumab is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.	Patients with hypersensitivity to atezolizumab or any excipient cannot be treated or continue treatment.	No	Hypersensitivity is listed as a contraindication in E.U. SmPC.
Pregnant or lactating patients	Based on the critical role that PD-L1/PD-1 pathway plays in the maintenance of maternal-fetal tolerance, it is recommended that atezolizumab not be administered to pregnant women.	No	Section 4.6 of the E.U. SmPC advises women of childbearing potential to use effective contraception during treatment with atezolizumab and up to 5 months after the last dose of atezolizumab. Section 4.6 of the E.U. SmPC advises nursing mothers that atezolizumab is a monoclonal antibody and is expected to be present in the first milk and at low levels afterwards, and thus a risk for newborns/infants cannot be excluded. Also, a decision must be made to either discontinue breastfeeding or discontinue atezolizumab therapy.
History or risk of systemic autoimmune disease, pulmonary fibrosis, organizing pneumonia, and drug-induced pneumonitis	Based on the mechanism of action, it was anticipated that atezolizumab may be associated with immune-mediated adverse reactions similar to those observed in autoimmune disease as well as inflammatory lung diseases	No	Patients with well-controlled Type 1 DM and autoimmune related hypothyroidism (receiving stable dose of replacement hormone) were not excluded from the studies included in this RMP.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
	similar to interstitial lung disease. Patients with autoimmune diseases as well as inflammatory lung diseases were excluded from clinical studies as it was not known whether use of atezolizumab in these patients is associated with exacerbation of the existing autoimmune condition.		Section 4.4 of the E.U. SmPC describes warnings and precautions in special populations, and describes patients who were excluded from clinical trials, including those with a history of autoimmune disease. Section 4.4 of the E.U. SmPC also contains special warnings and precautions relevant to immune-mediated pneumonitis, including management guidelines.
Patients with active hepatitis B or hepatitis C virus, patients who are positive for HIV, and patients with active tuberculosis.	These patients were excluded to minimise the effects and possible complications of synergistic immunologic stimulation by atezolizumab and infection	No	No specific warning or exclusion included in the E.U. SmPC as there has been no evidence that atezolizumab worsens any viral or bacterial infections. Patients with HCV and HBV have been included in the development program for HCC without complications due to their viral status.
Severe infections within 4 weeks prior to starting study treatment, including but not limited to hospitalisation for complications of infection, bacteraemia, or severe pneumonia. Signs or symptoms of infections within 2 weeks prior to starting study treatment. Received therapeutic oral or IV antibiotics within 2 weeks prior to starting study treatment	Patients with severe active infections were excluded to minimise the effects and possible complications of synergistic immunologic stimulation by atezolizumab and infection.	No	During the course of the development program, patients have experienced severe infections including sepsis and have been able to continue treatment. No specific warning or exclusion included in the E.U. SmPC as there has been no evidence that atezolizumab worsens any viral or bacterial infections.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Administration of a live, attenuated vaccine within 4 weeks before starting study treatment or anticipation that such a live vaccine will be required while receiving atezolizumab treatment	Both atezolizumab and live vaccines are designed to provoke an immunologic response. Administration of live attenuated vaccines was excluded to minimise the theoretical effects of excessive synergistic immunologic stimulation by atezolizumab and the vaccine, which could result in severe immune adverse events and confound the interpretation of safety results.	No	No specific warning or exclusion criterion included in the E.U. SmPC since patients are exposed to live pathogens on a regular basis via their activities of daily living. There has been no evidence that atezolizumab worsens any viral or bacterial infections, or that any excessive synergistic immunologic stimulation by atezolizumab occurs in the presence of pathogens.
Prior allogeneic stem cell or solid organ transplant	Patients undergoing these procedures generally require long-term treatment with immunosuppressant drugs and were excluded since inclusion could confound interpretation of the trial efficacy data.	No	Given the life-threatening nature of the proposed indications, treatment with atezolizumab should be an option for such patients.
Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within the previous 3 months, unstable arrhythmias, or unstable angina	Impaired end-organ function and associated clinical complications may impair the patient's ability to receive an adequate course of treatment.	No	No specific warning or exclusion included in the E.U. SmPC since it is considered part of routine oncology practice to assess a patient's fitness for treatment.
Uncontrolled or symptomatic hypercalcaemia	Hypercalcaemia is a sign of poor prognosis that could confound interpretation of trial efficacy data.	No	No specific warning or exclusion included in the E.U. SmPC since it is considered part of routine oncology practice to assess a patient's fitness for treatment.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Known active or untreated central nervous system (CNS) metastases or leptomeningeal disease	Patients with CNS metastases or leptomeningeal disease may experience a number of disease related signs and symptoms which could confound interpretation of trial safety data. Leptomeningeal disease is also an indicator of poor prognostic outcomes which could confound interpretation of trial efficacy data. However, the FIR study (GO28625) included a cohort of 13 patients with previously treated brain metastases, and the safety profile in these patients was acceptable with no unexpected safety concerns.	No	No specific warning or exclusion is included in the E.U. SmPC since it is considered part of routine oncology practice to assess a patient's fitness for treatment.
Malignancies other than UC or NSCLC within 5 years prior to starting study treatment, with the exception of those with negligible risk of metastasis or death treated with expected curative outcome.	Such patients were excluded from clinical trials because relapse or progression of the other malignancy could confound interpretation of trial efficacy data.	No	No specific warning or exclusion is included in the E.U. SmPC. Given the life-threatening nature of the proposed indications, treatment with atezolizumab should be an option for such patients.
Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures	Such patients are generally associated with a poor prognosis and were excluded since inclusion could confound interpretation of trial efficacy data.	No	No specific warning or exclusion is included in the E.U. SmPC since it is considered part of routine oncology practice to assess a patient's fitness for treatment.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Patients with severe reactions to other PD-1/PD-L1 immune checkpoint inhibitors.	Such patients were excluded from clinical trials because use of other immune checkpoint inhibitors could confound interpretation of trial safety and efficacy data.	No	No specific warning or exclusion is included in the E.U. SmPC and this exclusion is mentioned in the description of studies.
Treatment with systemic immunomodulatory agents at least 4 weeks or five half-lives of the drug, prior to starting study treatment	Administration of immunomodulatory agents could result in synergistic interactions with atezolizumab which could have resulted in complications and confounded the interpretation of trial safety and efficacy data.	No	Section 4.4 of the E.U. SmPC describes patients excluded from clinical trials, including those who have received systemic immune-stimulatory agents or systemic immunosuppressive medications prior to study entry. Given the life-threatening nature of the proposed indications, treatment with atezolizumab should be an option for such patients.
Treatment with systemic corticosteroids or other immunosuppressive medications within two weeks prior to starting study treatment	Atezolizumab is designed to enhance the immune response to tumour cells. Use of immunosuppressive medications could have confounded interpretation of trial safety and efficacy data	No	Section 4.5 of the E.U. SmPC mentions avoidance of systemic corticosteroids or immunosuppressants before starting atezolizumab due to their pharmacodynamic and potential efficacy effects. However, this section also mentions that systemic corticosteroids or other immunosuppressants can be used after starting atezolizumab to treat immune-mediated adverse reactions.

CNS = central nervous system; DM = diabetes mellitus; E.U. = European Union; HBV = Hepatitis B virus; HCC = hepatocellular carcinoma; HCV = Hepatitis C virus; HIV=human immunodeficiency virus; IV = intravenous; NSCLC =non-small cell lung cancer; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; RMP = Risk Management Plan; SmPC = Summary of Product Characteristics; UC = urothelial carcinoma.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development program for atezolizumab may not detect certain types of adverse reactions such as those with a long latency, or those caused by prolonged or cumulative exposure.

The clinical development program for atezolizumab SC started with Study BP40657 (IMscin001). The primary analysis of this study (Clinical cutoff date [CCOD]: 26 April 2022) and the updated analysis (CCOD: 16 January 2023) showed the overall safety profile of atezolizumab SC monotherapy is comparable to the safety profile of atezolizumab IV. The safety profile of atezolizumab SC in combination therapies has not been investigated yet.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Information available for use of atezolizumab in populations typically under-represented in clinical development program is provided in Table 30; additional details for use in pregnancy and lactation are presented in Use in Pregnancy and Lactation.

Table 30 Exposure of Special Populations Included or Not in the Clinical Trial Development Program

Type of special population	Exposure
Children	Sixty-nine paediatric patients with previously treated solid tumours enrolled in Study GO29664 were exposed to atezolizumab IV (2 patients aged <2 years, 29 patients aged $2-<12$ years and 38 patients aged $12-<18$ years). With the exception of this (completed) study, paediatric patients have been excluded from the clinical development program. Because of the small number of paediatric patients exposed to atezolizumab, the safety profile in this population is not fully known.
Elderly	**Monotherapy:** Patients 65 years of age and older have been included in atezolizumab monotherapy IV and SC clinical studies ($n=2116$ and $n=110$, respectively), and they represent a significant proportion of the exposed patient population (refer to Table 18 and Table 19 for exposure by age). The small number of

Type of special population	Exposure
	patients in the ≥85 years age category (n=35 patients in monotherapy IV clinical studies and 1 patient in monotherapy SC clinical study), limits meaningful conclusion regarding the safety profile of atezolizumab in this population. **Combination therapy:** Patients 65 years of age and older (n=1000) have been included in atezolizumab clinical studies, and they represent a significant proportion of the exposed population (refer to Table 25 for exposure by age). The small number of patients in the ≥ 85 years age category (n=14), limits meaningful conclusion regarding the safety profile of atezolizumab in this population.
Pregnant or breastfeeding women	Not included in the clinical development program.
Patients with hepatic impairment	In the popPK analysis, there were no clinically important differences in the clearance of atezolizumab between patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 to 1.5 × ULN and any AST) or moderate hepatic impairment (bilirubin > 1.5 to 3 × ULN and any AST) hepatic impairment. Hepatic impairment was defined by the NCI criteria of hepatic dysfunction.
Patients with renal impairment	In the popPK analysis, no clinically important differences in the clearance of atezolizumab were found in patients with mild (eGFR 60 to 89 mL/min/1.73 m^2; n = 208) or moderate (eGFR 30 to 59 mL/min/1.73 m^2; n = 116) renal impairment compared to patients with normal (eGFR ≥ 90 mL/min/1.73 m^2; n = 140) renal function. Only a few patients had severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2; n = 8). At this time, the effect of severe renal impairment on the pharmacokinetics of atezolizumab is unknown.
Cardiovascular disease	Not included in the clinical development program.

Type of special population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Population with relevant different ethnic origin	After adjusting for covariate effects in the final popPK model [b], neither race (Asian, n = 17; Black, n = 15; White, n = 375) nor ethnicity (Hispanic, n = 16; Not Hispanic, n = 364; Unknown, n = 92) was a significant covariate on the pharmacokinetics of atezolizumab or had clinically relevant effects on atezolizumab clearance. Across the development program, Caucasian patients accounted for a majority of the population.

AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; IV = intravenous; NCI = National Cancer Institute; popPK = population pharmacokinetic; ULN = upper limit of normal.

Use in Pregnancy and Lactation

No clinical studies have been performed with atezolizumab in pregnant women.

Based on the critical role that PD-L1/PD-1 pathway plays in the maintenance of maternal-fetal tolerance, it is recommended that atezolizumab not be administered to pregnant women. Section 4.6 of the E.U. Summary of Product Characteristics (SmPC) advises women of childbearing potential to use effective contraception during treatment with atezolizumab to avoid pregnancy while undergoing atezolizumab treatment, and up to 5 months after the last dose of atezolizumab (see information for important potential risk 'embryo-fetal toxicity' in SVII.3.1, Section 4). Section 4.6 of the E.U. SmPC also advises nursing mothers that atezolizumab is a monoclonal antibody and is expected to be present in the first milk and at low levels afterwards, and thus a risk for newborns/infants cannot be excluded. A decision must be made to either discontinue breastfeeding or discontinue atezolizumab therapy.

The detailed evaluation of pregnancy and lactation cases with atezolizumab available to the marketing authorisation holder (MAH) is presented in Periodic Benefit Risk Evaluation Report 1122480 (reporting interval 18 May 2022 to 17 May 2023) in Section 15.2 and a detailed summary of MAH review of available epidemiological information of pregnancy rates and adverse pregnancy outcomes in the approved indications for atezolizumab is presented in Section 5.2.3.

Interval and cumulative data of the pregnancy outcome (Overall Exposure, Exposure by Parents [mother and father], and Exposure by Source) is presented in Annex 7 of the RMP.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 POST-AUTHORISATION EXPOSURE

SV.1.1 Method Used to Calculate Exposure

All TNBC exposures described in this section are for mBC (1L PD-L1+ metastatic TNBC) unless otherwise specified.

United States

The number of patients exposed to atezolizumab (Tecentriq) was estimated based on milligrams of atezolizumab sold. This exposure covers atezolizumab sold through 30 April 2023, the closest date for which data are available. The average milligram per patient is based on the approved dose of 1200 mg flat dose q3w until disease progression as well as 840 mg dose every 2 weeks (q2w) until disease progression.

The split between indications is estimated based on IQVIA claims data showing the split of Tecentriq utilisation and validated through Flatiron electronic medical records (EMR) data, quarterly chart audit data, and qualitative and quantitative market research projects. Tecentriq was approved in 1L melanoma in the United States on 30 July 2020, but use in this indication has been negligible and as a result was not quantified in this report.

The gender and age estimate percentage are based on the mUC Tecentriq Chart Audit, metastatic NSCLC Tecentriq Chart Audit, SCLC, HCC, and early-stage NSCLC incidence from epidemiology, and TNBC Chart Audit. The data have a large confidence interval due to small sample size but is the best estimate the MAH can have at the moment. The current sample size of these chart trackers represents < 1% of the total mUC, NSCLC, early-stage NSCLC, TNBC, HCC, and SCLC patients treated.

Average dose

- Atezolizumab has been approved for 3 dosing schedules across all approved indications: 840 mg q2w, 1200 mg q3w, and 1680 mg every 4 weeks (q4w).
- The use of q2w and q4w dosing schedules is currently very limited, except for TNBC where the initial approval was for q2w dosing.

Duration of treatment

- Duration of treatment (DOT) is informed by:
  - For mUC: clinical trial data from IMvigor210 cohort 2 study. Weekly duration includes an estimated persistence factor of 71% in 1L/2L and 57% in 3L after four quarters of treatment (based on Tecentriq mUC claims data, compared to clinical trial data).

- For 2L NSCLC: clinical trial data from POPLAR study. Weekly duration includes an estimated persistence factor of 71% after two quarters of treatment (based on 2L+ nivolumab EMR data, compared to clinical trial data).
- For 1L NSCLC, clinical trial data from IMpower150. Weekly duration includes an estimated persistence rate of 77%.
- For early-stage non-small cell lung cancer (eNSCLC): clinical trial data from IMpower010 study. Weekly duration includes an estimated persistence rate of 90%.
- For SCLC: clinical trial data from IMpower133 study. Weekly duration includes an estimated persistence rate of 85%.
- For TNBC: clinical trial data from IMpassion130 study. Weekly duration includes an estimated persistence rate of 80%.
- For HCC: clinical trial data from IMbrave150 study. Weekly duration includes an estimated persistence rate of 80%.

- The estimated compliance rate is 95% for 2L+ NSCLC and eNSCLC (analog-based), 92% for mUC (claims-based), 80% for 1L NSCLC (analog-based), 90% for SCLC (analog-based), 85% for TNBC (analog-based), and 85% for HCC (analog-based).

Genentech Access to Care Foundation

Data includes patients who received Tecentriq through the Genentech Access to Care Foundation. These patients are part of marketing experience (not pre-marketing access).

European Economic Area (EEA)

The methodology for the EEA is the same as for the Rest of World (RoW) region.

Rest of World

RoW includes all regions outside of the United States, EEA, and Japan.

Patient Volume Calculation

The number of patients exposed to Tecentriq was estimated based on the number of milligrams of product distributed to healthcare providers. The total milligrams are converted to patient numbers by estimating the average milligrams per patient per course of treatment. The average milligrams per patient per course of treatment were calculated based on estimating the average days on therapy and the equivalent dose per day. The equivalent dose per day is calculated based on the dose per infusion, frequency of infusions, and compliance with recommended dosing schedule.

Data Period

The volume sold by Roche is sourced from Roche supply chain and financial systems (Controlling Profitability Analysis [COPA]). The sales data are available on a monthly basis; therefore, the exposure is available from the International Birth Date (IBD) to the nearest point of data lock point ([DLP], i.e., 17 May 2023). The month end cut-offs slightly change commercial patient exposure relative to using the exact mid-month DLP.

Indications

- The non-clinical trial (post-authorisation) exposure split by indication is based on a global summary of country-level data. The exact source of data varies by country, but represents the best available estimate. Indication splits differ by geography due to differences in indication approval / access timelines and physician adoption.

Average daily dose

- For TNBC: The recommended dose was initially 840 mg q2w.
- All other indications: The most common dose is 1200 mg q3w. Alternative dosing schedules (840 mg q2w and 1680 mg q4w) are available, but adoption has been very limited, so patient volume for these dosing schedules were not calculated.

Duration of treatment

The DOT, compliance, and persistence are based on current global forecast assumptions.

Segment Splits

The split by age and gender is estimated based on U.S. chart audits and epidemiology data.

Japan

Tecentriq was approved in Japan for the following indications:

- 2L+NSCLC (approved 19 January 2018) with dose of 1200 mg q3w.
- 1L NSCLC has the following approval dates in the below indications with dose of 1200 mg q3w.
  - Tecentriq in combination with bevacizumab, paclitaxel, and carboplatin—IMpower150 (approved 21 December 2018).
  - Tecentriq in combination with cisplatin or carboplatin and pemetrexed—IMpower132 (approved 22 November 2019).
  - Tecentriq in combination with nab-paclitaxel and carboplatin—IMpower130 (approved 22 November 2019).

  - Tecentriq monotherapy for PD-L1 positive 1L NSCLC—IMpower110 (approved date 25 December 2020).
  - Tecentriq monotherapy for PD-L1 positive adjuvant NSCLC— (approved date 26 May 2023).

- SCLC (approved 22 August 2019) with dose of 1200 mg q3w, in combination with carboplatin and etoposide.
- PD-L1 positive 1L mTNBC (approved 20 September 2019, launched 27 November 2019) with dose of 840 mg q2w, in combination with nab-paclitaxel.
- HCC (approved 25 September 2020) with a dose of 1200 mg q3w, in combination with bevacizumab.

Since only the active pharmaceutical ingredient quantity sold was available, the total patient exposure for Japan has been calculated using the same assumptions that were used for RoW/EEA. Indication splits are based on sales forecasts.

SV.1.2 Exposure

Since the IBD of 18 May 2016 and until 17 May 2023, an estimated cumulative total of 433,872 patients have received atezolizumab from marketing experience; see Annex 7 for further details.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Drugs that have a potential for misuse for illegal purposes are expected to share general characteristics such as psychoactive, stimulant, or sedative effects, or less commonly, anabolic effects or enhancement of haemoglobin levels. Nonclinical tests have not shown that atezolizumab binds to or activates receptors associated with psychostimulatory effects or dependency. Therefore, the potential for atezolizumab to be misused for illegal purposes is low.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

Not applicable.

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Not applicable.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

The frequency, severity, seriousness and outcomes for the important identified and potential risks are presented in two tables for each risk:

- The monotherapy table for each risk includes the atezolizumab All Patients IV Monotherapy population (N=4156), the all Lung IV Monotherapy population (N=2717), the all Bladder IV Monotherapy population (N=983), and IMscin001 (SC monotherapy) population, and are based on atezolizumab-treated, safety-evaluable patients enrolled in IMvigor211 (N=459), OAK (N=609), IMvigor210 (N=429), POPLAR (N=142), BIRCH (N=659), FIR (N=137), all cohorts of Study PCD4989g (N=640), IMpower110 (N=286), IMpower010 (N=495), IPSOS (N=300) and IMscin001 (N=247). One pooled safety population including 4156 patients is discussed in this RMP. This monotherapy pooled population provides the largest

dataset to evaluate the clinical safety of atezolizumab monotherapy in patients with NSCLC (N=2717), UC (N=983) and other solid tumours such as renal cell carcinoma, TNBC, melanoma, head and neck, colorectal cancer, gastric, and ovarian from Study PCD4989g (N = 456).

- The combination therapy table for each risk includes the pooled safety population (N=2409), presented by indication: 1464 patients with Lung cancer (1266 patients with NSCLC [793 patients from IMpower150 and 473 patients from IMpower130 studies]+198 patients with SCLC [from IMpower133 study]); 452 patients with breast cancer (from IMpassion130 study); and 493 patients with HCC (YO40245 [329 patients] and GO30140 [164 patients]).

INFORMATION ON IMPORTANT IDENTIFIED RISKS

1. IMMUNE-MEDIATED ADVERSE REACTIONS

1.1 HEPATITIS

Hepatitis: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions Standardised MedDRA Query (SMQ; narrow), Hepatitis non-infectious SMQ (narrow), Liver related investigations, signs and symptoms SMQ (narrow).

Potential mechanisms:

The use of atezolizumab to block the inhibitory immune checkpoint molecule PD-L1, serves to increase a baseline T-cell-specific immune response that turns the immune system against the tumour. However, a disruption in the functioning of immune checkpoint molecules can lead to imbalances in immunologic tolerance that results in an unchecked immune response. This may clinically manifest with autoimmune-like/inflammatory side-effects, which can cause collateral damage to normal organ systems and tissues (Naidoo et al. 2015).

Evidence source(s) and strength of evidence:

Clinical trial data

Characterisation of the risk:

See Table 31 and Table 32. There are no clinically relevant differences in the frequency of the hepatic events between the monotherapy IV and IMscin001 (SC monotherapy) populations. The majority of the events were Grade 1 or 2 in severity.

In the All Patients combination therapy populations, a higher frequency was observed in the HCC combination therapy population, which was likely associated with the underlying disease under study. Overall, the majority of hepatic events observed were Grade 1–2 and non-serious liver enzyme elevations across the monotherapy populations and the combination therapy populations.

Risk factors and risk groups:

There are no identified risk factors for the development of immune-mediated hepatitis in atezolizumab–treated patients.

Preventability:

There are currently no reliable predictors of susceptibility of individual patients to development of immune-mediated hepatitis following atezolizumab therapy. Sections 4.2 and 4.4 of the E.U. SmPC provide management guidelines to reduce the potential for negative outcomes in patients experiencing this event.

Impact on the benefit-risk balance of the product:

The liver function test abnormalities reported in clinical trials were mainly mild to moderate in severity. However, severe immune-mediated hepatitis including fatal outcome has been observed and therefore the impact on individual patients could potentially be significant.

A patient card will be provided to reduce the severity of immune-mediated hepatitis by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and timely intervention. This will reduce the impact of immune-mediated hepatitis on the benefit–risk balance of the product.

Public health impact:

Patients receiving chemotherapy, targeted agents, and immunotherapies are already at risk of developing hepatotoxicity. Given the low frequency of serious events, coupled with the responsiveness to treatment with corticosteroids, the impact on public health of immune-mediated hepatitis is considered low.

Table 31 Immune-Mediated Hepatitis: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Hepatitis (Diagnosis and Lab Abnormalities)

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	499 (12.0%)	317 (11.7%)	108 (11.0%)	32 (10.7%)	29 (11.7%)
95% CI for % of patients with at least one AE	(11.03%, 13.03%)	(10.48%, 12.93%)	(9.10%, 13.11%)	(7.41%, 14.72%)	(8.01%, 16.43%)
Overall total number of events	1006	614	235	56	62
No. of Patients with at least one AE by Worst Grade					
Grade 1	222 (5.3%)	162 (6.0%)	39 (4.0%)	16 (5.3%)	12 (4.9%)
Grade 2	112 (2.7%)	73 (2.7%)	19 (1.9%)	10 (3.3%)	9 (3.6%)
Grade 3	138 (3.3%)	66 (2.4%)	45 (4.6%)	4 (1.3%)	8 (3.2%)
Grade 4	24 (0.6%)	14 (0.5%)	5 (0.5%)	1 (0.3%)	0
Grade 5	3 (<0.1%)	2 (<0.1%)	0	1 (0.3%)	0
No. of Patients with at least one Serious AE	55 (1.3%)	30 (1.1%)	19 (1.9%)	4 (1.3%)	1 (0.4%)
Number of patients with at least one AE by outcome					
Fatal outcome	3 (0.6%)	2 (0.6%)	0	1 (3.1%)	0
Unresolved	164 (32.9%)	75 (23.7%)	48 (44.4%)	10 (31.3%)	14 (48.3%)
Recovering/Resolving	23 (4.6%)	18 (5.7%)	2 (1.9%)	4 (12.5%)	6 (20.7%)
Recovered/Resolved	360 (72.1%)	247 (77.9%)	72 (66.7%)	20 (62.5%)	17 (58.6%)
Resolved with sequelae	9 (1.8%)	5 (1.6%)	2 (1.9%)	0	1 (3.4%)
Unknown outcome	4 (0.8%)	2 (0.6%)	1 (0.9%)	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/
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24JUN2024 20:15
Adapted from t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out

Table 32 Immune-Mediated Hepatitis: Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Hepatitis (Diagnosis and Lab Abnormalities)

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	416 (17.3%)	156 (10.7%)	191 (38.7%)	69 (15.3%)
95% CI for % of patients with at least one AE	(15.78%, 18.84%)	(9.12%, 12.35%)	(34.42%, 43.20%)	(12.08%, 18.92%)
Overall total number of events	879	299	439	141
No. of Patients with at least one AE by Worst Grade				
Grade 1	147 (6.1%)	73 (5.0%)	44 (8.9%)	30 (6.6%)
Grade 2	96 (4.0%)	32 (2.2%)	49 (9.9%)	15 (3.3%)
Grade 3	142 (5.9%)	43 (2.9%)	80 (16.2%)	19 (4.2%)
Grade 4	22 (0.9%)	6 (0.4%)	12 (2.4%)	4 (0.9%)
Grade 5	9 (0.4%)	2 (0.1%)	6 (1.2%)	1 (0.2%)
No. of Patients with at least one Serious AE	73 (3.0%)	19 (1.3%)	48 (9.7%)	6 (1.3%)
Number of patients with at least one AE by outcome				
Fatal outcome	9 (2.2%)	2 (1.3%)	6 (3.1%)	1 (1.4%)
Unresolved	158 (38.0%)	41 (26.3%)	97 (50.8%)	20 (29.0%)
Recovering/Resolving	25 (6.0%)	8 (5.1%)	16 (8.4%)	1 (1.4%)
Recovered/Resolved	294 (70.7%)	115 (73.7%)	122 (63.9%)	57 (82.6%)
Resolved with sequelae	5 (1.2%)	3 (1.9%)	1 (0.5%)	1 (1.4%)
Unknown outcome	9 (2.2%)	1 (0.6%)	7 (3.7%)	1 (1.4%)

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/
t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out
02DEC2022 22:08
Adapted from t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out

1.2 PNEUMONITIS

Pneumonitis: Interstitial lung disease SMQ (narrow)

Potential mechanisms:

Inhibition of PD-L1 modifies the regulation of the immune system, which may cause changes in peripheral tolerance, and can lead to immune–mediated inflammation or autoimmune-like side effects in susceptible tissues.

Evidence source(s) and strength of evidence:

Clinical trial data

Characterisation of the risk:

See Table 33 and Table 34. There are no clinically relevant differences in the frequency of this event among the IV monotherapy, IMscin001 (SC monotherapy) and the combination therapy populations. While the frequency of the event in the combination therapy populations was similar to the NSCLC monotherapy population, the majority of the events were Grade 1–2 in severity.

Risk factors and risk groups:

General factors that may be associated with an increased risk of drug-induced interstitial lung disease include: older age, male sex, pre-existing lung disease, smoking, prior radiation therapy, prior or concomitant treatment with medications with known pulmonary toxicity (e.g., some antimicrobial, anti-inflammatory and cardiovascular agents, biologics, and chemotherapeutics), inflammatory conditions (e.g., rheumatoid arthritis and inflammatory bowel disease). The underlying malignant disease itself may also increase the risk of pneumonitis and be a confounder of diagnosis (Barber et al. 2011; Schwaiblmair et al. 2012).

There are currently no known risk factors that may predispose individual patients to develop immune-mediated pneumonitis following treatment with atezolizumab.

Preventability:

Although patients with NSCLC have an increased risk of developing pneumonitis, there are no reliable predictors of susceptibility of individual patients to this risk following exposure to atezolizumab. Sections 4.2 and 4.4 of the E.U. SmPC provide guidelines to monitor and manage pneumonitis to reduce the potential for negative outcomes in patients experiencing this event.

Impact on the benefit-risk balance of the product:

Even though the incidence of pneumonitis in clinical trials was low and most events were of mild to moderate severity, the impact on patients' quality of life can be considerable as it usually requires hospitalisation and can potentially lead to a fatal outcome.

A patient card will be provided to reduce the severity of immune-mediated pneumonitis by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and timely intervention. This will reduce the impact of immune-mediated pneumonitis on the benefit–risk balance of the product.

Public health impact:

The potential public health impact of immune-mediated pneumonitis is considered low. Patients receiving chemotherapy, targeted agents, and immunotherapies are already at risk of developing pneumonitis and the frequency observed in clinical trials with atezolizumab remains low.

Table 33 Immune-Mediated Pneumonitis: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Pneumonitis

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	134 (3.2%)	103 (3.8%)	20 (2.0%)	13 (4.3%)	5 (2.0%)
95% CI for % of patients with at least one AE	(2.71%, 3.81%)	(3.10%, 4.58%)	(1.25%, 3.12%)	(2.33%, 7.30%)	(0.66%, 4.66%)
Overall total number of events	152	118	23	15	6
No. of Patients with at least one AE by Worst Grade					
Grade 1	37 (0.9%)	24 (0.9%)	6 (0.6%)	1 (0.3%)	3 (1.2%)
Grade 2	53 (1.3%)	43 (1.6%)	8 (0.8%)	3 (1.0%)	2 (0.8%)
Grade 3	32 (0.8%)	27 (1.0%)	4 (0.4%)	6 (2.0%)	0
Grade 4	9 (0.2%)	6 (0.2%)	2 (0.2%)	2 (0.7%)	0
Grade 5	3 (<0.1%)	3 (0.1%)	0	1 (0.3%)	0
No. of Patients with at least one Serious AE	61 (1.5%)	50 (1.8%)	8 (0.8%)	9 (3.0%)	0
Number of patients with at least one AE by outcome					
Fatal outcome	3 (2.2%)	3 (2.9%)	0	1 (7.7%)	0
Unresolved	26 (19.4%)	19 (18.4%)	5 (25.0%)	1 (7.7%)	1 (20.0%)
Recovering/Resolving	10 (7.5%)	10 (9.7%)	0	0	1 (20.0%)
Recovered/Resolved	99 (73.9%)	75 (72.8%)	15 (75.0%)	10 (76.9%)	3 (60.0%)
Resolved with sequelae	1 (0.7%)	0	1 (5.0%)	0	0
Unknown outcome	1 (0.7%)	1 (1.0%)	0	1 (7.7%)	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/
t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out
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Adapted from t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out

Table 34 Immune-Mediated Pneumonitis: Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Pneumonitis

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	94 (3.9%)	72 (4.9%)	7 (1.4%)	15 (3.3%)
95% CI for % of patients with at least one AE	(3.16%, 4.75%)	(3.87%, 6.15%)	(0.57%, 2.90%)	(1.87%, 5.41%)
Overall total number of events	99	75	7	17
No. of Patients with at least one AE by Worst Grade				
Grade 1	26 (1.1%)	20 (1.4%)	0	6 (1.3%)
Grade 2	47 (2.0%)	34 (2.3%)	5 (1.0%)	8 (1.8%)
Grade 3	14 (0.6%)	12 (0.8%)	1 (0.2%)	1 (0.2%)
Grade 4	3 (0.1%)	3 (0.2%)	0	0
Grade 5	4 (0.2%)	3 (0.2%)	1 (0.2%)	0
No. of Patients with at least one Serious AE	28 (1.2%)	25 (1.7%)	3 (0.6%)	0
Number of patients with at least one AE by outcome				
Fatal outcome	4 (4.3%)	3 (4.2%)	1 (14.3%)	0
Unresolved	24 (25.5%)	18 (25.0%)	2 (28.6%)	4 (26.7%)
Recovering/Resolving	10 (10.6%)	9 (12.5%)	1 (14.3%)	0
Recovered/Resolved	55 (58.5%)	42 (58.3%)	3 (42.9%)	10 (66.7%)
Resolved with sequelae	3 (3.2%)	1 (1.4%)	0	2 (13.3%)
Unknown outcome	1 (1.1%)	1 (1.4%)	0	0

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/
t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out
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Adapted from t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out.

1.3 COLITIS

Colitis: HLT Colitis (excluding infective)

Potential mechanisms:

Inhibition of PD-L1 modifies the regulation of the immune system, which may cause changes in peripheral tolerance, and can lead to immune-mediated inflammation or autoimmune-like side effects in susceptible tissues.

Evidence source(s) and strength of evidence:

Clinical trial data

Characterisation of the risk:

See Table 35 and Table 36. No events of colitis were reported in the IMscin001 (SC monotherapy) population. There are no clinically relevant differences in the frequency of this event among the IV monotherapy and combination therapy populations.

Risk factors and risk groups:

There are currently no known risk factors that may predispose individual patients to develop immune-mediated colitis following treatment with atezolizumab.

Preventability:

Although there is no possible way to predict which patients may be more susceptible to developing immune-mediated colitis, Sections 4.2 and 4.4 of the E.U. SmPC provide monitoring and management guidelines to reduce the potential for negative outcomes in patients experiencing this event.

Impact on the benefit-risk balance of the product:

Immune-mediated colitis may be prolonged, affect activities of daily living, require hospitalisation and if left untreated can potentially lead to severe outcomes such as bowel perforation or peritonitis; therefore, the impact to the individual patient is considered significant.

A patient card will be provided to reduce the severity of immune-mediated colitis by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and timely intervention. This will reduce the impact of immune-mediated colitis on the benefit–risk balance of the product.

Public health impact:

Given the low rate of immune-mediated colitis (generally responsive to corticosteroids) and the fact that patients with advanced malignancies are at risk for serious gastrointestinal toxicities from both their disease and other available treatments, the overall impact on public health is considered low.

Table 35 Immune-Mediated Colitis: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Colitis

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	44 (1.1%)	25 (0.9%)	16 (1.6%)	3 (1.0%)	0
95% CI for % of patients with at least one AE	(0.77%, 1.42%)	(0.60%, 1.36%)	(0.93%, 2.63%)	(0.21%, 2.89%)	(0.00%, 1.48%)
Overall total number of events	57	31	21	4	0
No. of Patients with at least one AE by Worst Grade					
Grade 1	6 (0.1%)	4 (0.1%)	2 (0.2%)	0	0
Grade 2	14 (0.3%)	11 (0.4%)	3 (0.3%)	1 (0.3%)	0
Grade 3	24 (0.6%)	10 (0.4%)	11 (1.1%)	2 (0.7%)	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
No. of Patients with at least one Serious AE	21 (0.5%)	7 (0.3%)	11 (1.1%)	1 (0.3%)	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	13 (29.5%)	6 (24.0%)	6 (37.5%)	0	0
Recovering/Resolving	2 (4.5%)	2 (8.0%)	0	0	0
Recovered/Resolved	32 (72.7%)	18 (72.0%)	11 (68.8%)	3 (100%)	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	1 (2.3%)	0	1 (6.3%)	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
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Adapted from t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out

Table 36 Immune-Mediated Colitis: Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Colitis

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	36 (1.5%)	22 (1.5%)	9 (1.8%)	5 (1.1%)
95% CI for % of patients with at least one AE	(1.05%, 2.06%)	(0.94%, 2.27%)	(0.84%, 3.44%)	(0.36%, 2.56%)
Overall total number of events	40	23	9	8
No. of Patients with at least one AE by Worst Grade				
Grade 1	5 (0.2%)	2 (0.1%)	2 (0.4%)	1 (0.2%)
Grade 2	11 (0.5%)	4 (0.3%)	4 (0.8%)	3 (0.7%)
Grade 3	16 (0.7%)	13 (0.9%)	2 (0.4%)	1 (0.2%)
Grade 4	4 (0.2%)	3 (0.2%)	1 (0.2%)	0
Grade 5	0	0	0	0
No. of Patients with at least one Serious AE	21 (0.9%)	14 (1.0%)	4 (0.8%)	3 (0.7%)
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	9 (25.0%)	5 (22.7%)	3 (33.3%)	1 (20.0%)
Recovering/Resolving	1 (2.8%)	1 (4.5%)	0	0
Recovered/Resolved	24 (66.7%)	15 (68.2%)	6 (66.7%)	3 (60.0%)
Resolved with sequelae	1 (2.8%)	0	0	1 (20.0%)
Unknown outcome	1 (2.8%)	1 (4.5%)	0	0

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/
t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out
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Adapted from t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out.

1.4 PANCREATITIS

Pancreatitis: Atezolizumab pancreatitis adverse event grouping term (AEGT, Atezolizumab) -22 Jul 2015 Consisting of the Acute pancreatitis SMQ (narrow) plus the following MedDRA Preferred Terms (PTs): Amylase abnormal, amylase increased, autoimmune pancreatitis, lipase abnormal, lipase increased.

Potential mechanisms:

Inhibition of PD-L1 modifies the regulation of the immune system, which may cause changes in peripheral tolerance, and can lead to immune-mediated inflammation or autoimmune-like side effects in susceptible tissues.

Evidence source(s) and strength of evidence:

Clinical trial data

Characterisation of the risk:

See Table 37 and Table 38. No events of pancreatitis were reported in the IMscin001 (SC monotherapy) population. There are no clinically relevant differences in the frequency of this event among the IV monotherapy and the combination therapy populations. The majority of the events across all populations were non-serious elevations in lipase and amylase.

Risk factors and risk groups:

Female sex, younger age, and pre-existing inflammatory bowel disease may be associated with an increased risk of drug-induced pancreatitis (Nitsche et al. 2012; Vinklerova et al. 2010). There are currently no known risk factors that may predispose individual patients to develop immune-mediated pancreatitis following treatment with atezolizumab.

Preventability:

Although there is no possible way to predict patients who may be more susceptible to developing immune-mediated pancreatitis, Sections 4.2 and 4.4 of the E.U. SmPC provide monitoring and management guidelines to reduce the potential for negative outcomes in patients experiencing this event.

Impact on the benefit-risk balance of the product:

Immune-mediated pancreatitis may be prolonged, require hospitalisation with the administration of high doses of corticosteroids and may lead to the discontinuation of atezolizumab treatment; therefore, the impact to the individual patient is considered significant.

A patient card will be provided to reduce the severity of immune-mediated pancreatitis by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and timely intervention. This will reduce the impact of immune-mediated pancreatitis on the benefit–risk balance of the product.

Public health impact:

Given the low rates of pancreatitis and the responsiveness of immune-mediated AEs to steroids, the impact on public health is considered low.

Table 37 Immune-Mediated Pancreatitis: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Pancreatitis

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	24 (0.6%)	16 (0.6%)	7 (0.7%)	3 (1.0%)	0
95% CI for % of patients with at least one AE	(0.37%, 0.86%)	(0.34%, 0.95%)	(0.29%, 1.46%)	(0.21%, 2.89%)	(0.00%, 1.48%)
Overall total number of events	34	23	7	8	0
No. of Patients with at least one AE by Worst Grade					
Grade 1	1 (<0.1%)	1 (<0.1%)	0	0	0
Grade 2	5 (0.1%)	3 (0.1%)	2 (0.2%)	1 (0.3%)	0
Grade 3	13 (0.3%)	10 (0.4%)	3 (0.3%)	2 (0.7%)	0
Grade 4	5 (0.1%)	2 (<0.1%)	2 (0.2%)	0	0
Grade 5	0	0	0	0	0
No. of Patients with at least one Serious AE	8 (0.2%)	5 (0.2%)	3 (0.3%)	1 (0.3%)	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	5 (20.8%)	2 (12.5%)	3 (42.9%)	1 (33.3%)	0
Recovering/Resolving	1 (4.2%)	1 (6.3%)	0	0	0
Recovered/Resolved	19 (79.2%)	14 (87.5%)	4 (57.1%)	3 (100%)	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
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24JUN2024 20:15
Adapted from t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out

Table 38 Immune-Mediated Pancreatitis: Frequency, Severity, Seriousness, and Outcomes - Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Pancreatitis

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	24 (1.0%)	11 (0.8%)	11 (2.2%)	2 (0.4%)
95% CI for % of patients with at least one AE	(0.64%, 1.48%)	(0.38%, 1.34%)	(1.12%, 3.96%)	(0.05%, 1.59%)
Overall total number of events	27	12	12	3
No. of Patients with at least one AE by Worst Grade				
Grade 1	5 (0.2%)	3 (0.2%)	2 (0.4%)	0
Grade 2	7 (0.3%)	2 (0.1%)	4 (0.8%)	1 (0.2%)
Grade 3	11 (0.5%)	6 (0.4%)	4 (0.8%)	1 (0.2%)
Grade 4	1 (<0.1%)	0	1 (0.2%)	0
Grade 5	0	0	0	0
No. of Patients with at least one Serious AE	5 (0.2%)	3 (0.2%)	2 (0.4%)	0
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	5 (20.8%)	3 (27.3%)	1 (9.1%)	1 (50.0%)
Recovering/Resolving	1 (4.2%)	0	1 (9.1%)	0
Recovered/Resolved	17 (70.8%)	8 (72.7%)	8 (72.7%)	1 (50.0%)
Resolved with sequelae	1 (4.2%)	0	1 (9.1%)	0
Unknown outcome	1 (4.2%)	0	0	1 (50.0%)

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/
t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out
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1.5 ENDOCRINOPATHIES

Endocrinopathies: Diabetes Mellitus, Hypothyroidism, Hyperthyroidism, Adrenal Insufficiency, Hypophysitis

1.5.1 Diabetes Mellitus

Diabetes Mellitus: Atezolizumab Diabetes/diabetic ketoacidosis (excludes hyperglycaemia) AEGT (Atezolizumab) -11 August 2017. Consisting of the following MedDRA PTs: Latent autoimmune diabetes in adults, Diabetes mellitus, Diabetic hyperglycaemic coma, Ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Fulminant type 1 diabetes mellitus, Diabetic coma, Diabetic ketoacidosis, Type 1 diabetes mellitus.

Potential mechanisms:

Inhibition of PD-L1 modifies the regulation of the immune system, which may cause changes in peripheral tolerance, and can lead to immune-mediated inflammation or autoimmune-like side effects in susceptible tissues.

Evidence source(s) and strength of evidence:

Clinical trial data

Characterisation of the risk:

See Table 39 and Table 40. No events of diabetes mellitus were reported in the IMscin001 (SC monotherapy) population. There are no clinically relevant differences in the frequency of this event among the IV monotherapy and combination therapy populations. A higher frequency of diabetes mellitus was observed in the Study IPSOS population compared to the monotherapy populations. This higher frequency in the Study IPSOS population may be partly due to the elderly population with a median age of 75 years. Out of the 4 patients in Study IPSOS with an event of diabetes mellitus, 2 patients had pre-existing diabetes and one event was not resolved. The remaining 2 patients developed diabetic ketoacidosis, with one of them as a new onset event. Both events were resolved but with sequelae in the new-onset patient. One patient who received atezolizumab for UC experienced a new onset of diabetes mellitus that led to hospitalisation for diabetic ketoacidosis. The diabetic ketoacidosis has resolved, and this patient's diabetes mellitus is considered resolved with sequelae as the patient is insulin dependent. An event of diabetic ketoacidosis also occurred in the TNBC (Breast) combination therapy population, however, this patient had a history of diabetes and the event was assessed as not related to study treatment by the investigator.

Risk factors and risk groups:

An Italian study of adults between age 30 and 49 years found that the risk of type 1 diabetes was almost two times higher in males compared with females (rate ratio 1.70 [95% CI 1.21 – 2.38]) (Bruno et al. 2005). There are currently no known risk factors that may predispose individual patients to develop immune-mediated diabetes following treatment with atezolizumab.

Preventability:

Although there is no possible way to predict which patients may be more susceptible to developing immune-mediated diabetes, Sections 4.2 and 4.4 of the E.U. SmPC provide monitoring and management guidelines to reduce the potential for negative outcomes in patients experiencing this event.

Impact on the benefit-risk balance of the product:

Since diabetes is associated with significant comorbidities, may require life-long treatment with insulin and, if undiagnosed, may lead to diabetic ketoacidosis, the impact on the individual patient is considered significant.

A patient card will be provided to reduce the severity of immune-mediated diabetes mellitus by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and timely intervention. This will reduce the impact of immune-mediated diabetes mellitus on the benefit–risk balance of the product.

Public health impact:

The rate of diabetes in atezolizumab patients remains low. Once diagnosed, diabetes can be easily managed, therefore the impact on public health is considered low.

Table 39 Immune-Mediated Diabetes Mellitus: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Diabetes Mellitus

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	22 (0.5%)	17 (0.6%)	3 (0.3%)	4 (1.3%)	0
95% CI for % of patients with at least one AE	(0.33%, 0.80%)	(0.36%, 1.00%)	(0.06%, 0.89%)	(0.36%, 3.38%)	(0.00%, 1.48%)
Overall total number of events	24	18	4	4	0
No. of Patients with at least one AE by Worst Grade					
Grade 1	7 (0.2%)	6 (0.2%)	0	1 (0.3%)	0
Grade 2	5 (0.1%)	4 (0.1%)	0	1 (0.3%)	0
Grade 3	8 (0.2%)	5 (0.2%)	3 (0.3%)	1 (0.3%)	0
Grade 4	2 (<0.1%)	2 (<0.1%)	0	1 (0.3%)	0
Grade 5	0	0	0	0	0
No. of Patients with at least one Serious AE	7 (0.2%)	5 (0.2%)	2 (0.2%)	2 (0.7%)	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	10 (45.5%)	7 (41.2%)	2 (66.7%)	1 (25.0%)	0
Recovering/Resolving	2 (9.1%)	2 (11.8%)	0	0	0
Recovered/Resolved	9 (40.9%)	6 (35.3%)	2 (66.7%)	2 (50.0%)	0
Resolved with sequelae	3 (13.6%)	3 (17.6%)	0	1 (25.0%)	0
Unknown outcome	0	0	0	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/
t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out
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Adapted from t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out

Table 40 Immune-Mediated Diabetes Mellitus: Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Diabetes Mellitus

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	18 (0.7%)	7 (0.5%)	10 (2.0%)	1 (0.2%)
95% CI for % of patients with at least one AE	(0.44%, 1.18%)	(0.19%, 0.98%)	(0.98%, 3.70%)	(0.01%, 1.23%)
Overall total number of events	19	7	10	2
No. of Patients with at least one AE by Worst Grade				
Grade 1	1 (<0.1%)	0	1 (0.2%)	0
Grade 2	11 (0.5%)	5 (0.3%)	6 (1.2%)	0
Grade 3	3 (0.1%)	0	2 (0.4%)	1 (0.2%)
Grade 4	3 (0.1%)	2 (0.1%)	1 (0.2%)	0
Grade 5	0	0	0	0
No. of Patients with at least one Serious AE	3 (0.1%)	1 (<0.1%)	1 (0.2%)	1 (0.2%)
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	12 (66.7%)	6 (85.7%)	5 (50.0%)	1 (100%)
Recovering/Resolving	1 (5.6%)	0	1 (10.0%)	0
Recovered/Resolved	5 (27.8%)	1 (14.3%)	3 (30.0%)	1 (100%)
Resolved with sequelae	1 (5.6%)	0	1 (10.0%)	0
Unknown outcome	0	0	0	0

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/
t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out
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Adapted from t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out.

1.5.2 Hypothyroidism

Hypothyroidism: Hypothyroidism SMQ (wide)

Potential mechanisms:

Inhibition of PD-L1 modifies the regulation of the immune system, which may cause changes in peripheral tolerance, and can lead to immune-mediated inflammation or autoimmune-like side effects in susceptible tissues.

Evidence source(s) and strength of evidence:

Clinical trial data

Characterisation of the risk:

See Table 41 and Table 42. There are no clinically relevant differences in the frequency of this event among the Lung IV monotherapy, the Bladder IV monotherapy and the IMscin001 (SC monotherapy) populations. A higher frequency of hypothyroidism was observed in the Lung IV monotherapy population, subset (IMpower010) and combination therapy populations (Lung, Breast, and HCC), compared to the Lung and Bladder IV monotherapy populations. This higher frequency may partly be the result of more frequent thyroid function testing implemented in these studies versus the requirement in the Lung and Bladder IV monotherapy clinical trials established earlier. The initial requirement for the studies that comprise the Lung and Bladder IV monotherapy populations (excluding IMpower010) was thyroid function testing at screening, and then only if clinically indicated. An increase in the frequency of testing was implemented across atezolizumab study protocols after the initiation and/or completion of these monotherapy trials. Due to the increased frequency of collection of thyroid function tests, more asymptomatic AEs of thyroid function test abnormalities and hypothyroidism were identified and reported. Overall, the majority of events were Grade 1or 2, non-serious, manageable and very rarely led to atezolizumab discontinuation.

Risk factors and risk groups:

There are no known risk factors associated with the development of immune-mediated hypothyroidism in individual atezolizumab–treated patients.

Preventability:

Although there is currently no way to predict which patients may be more susceptible to developing hypothyroidism, Section 4.4 of the E.U. SmPC provides a warning to monitor patients for signs and symptoms of endocrinopathies, and to monitor thyroid function. Management guidelines are also provided in Sections 4.2 and 4.4 of the E.U. SmPC to reduce the potential for negative outcomes in patients experiencing this event.

Impact on the benefit-risk balance of the product:

Although the clinical manifestations of hypothyroidism are variable and can be challenging to diagnose, hypothyroidism can be controlled with oral medication. Therefore, the impact on patients in the proposed indications is not considered significant.

A patient card will be provided to reduce the severity of immune-mediated hypothyroidism by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and timely intervention. This will reduce the impact of immune-mediated hypothyroidism on the benefit–risk balance of the product.

Public health impact:

Because hypothyroidism can be easily managed with oral medication, the potential impact on public health is low.

Table 41 Immune-Mediated Hypothyroidism: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Hypothyroidism

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	292 (7.0%)	219 (8.1%)	46 (4.7%)	27 (9.0%)	26 (10.5%)
95% CI for % of patients with at least one AE	(6.27%, 7.85%)	(7.06%, 9.15%)	(3.45%, 6.19%)	(6.01%, 12.82%)	(6.99%, 15.04%)
Overall total number of events	339	260	49	34	31
No. of Patients with at least one AE by Worst Grade					
Grade 1	128 (3.1%)	105 (3.9%)	16 (1.6%)	14 (4.7%)	10 (4.0%)
Grade 2	158 (3.8%)	111 (4.1%)	27 (2.7%)	13 (4.3%)	16 (6.5%)
Grade 3	6 (0.1%)	3 (0.1%)	3 (0.3%)	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
No. of Patients with at least one Serious AE	8 (0.2%)	4 (0.1%)	3 (0.3%)	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	163 (55.8%)	114 (52.1%)	30 (65.2%)	10 (37.0%)	8 (30.8%)
Recovering/Resolving	30 (10.3%)	26 (11.9%)	3 (6.5%)	4 (14.8%)	10 (38.5%)
Recovered/Resolved	122 (41.8%)	100 (45.7%)	14 (30.4%)	14 (51.9%)	9 (34.6%)
Resolved with sequelae	2 (0.7%)	2 (0.9%)	0	0	0
Unknown outcome	3 (1.0%)	2 (0.9%)	1 (2.2%)	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/
t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out
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Adapted from t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out

Table 42 Immune-Mediated Hypothyroidism: Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Hypothyroidism

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	312 (13.0%)	185 (12.6%)	49 (9.9%)	78 (17.3%)
95% CI for % of patients with at least one AE	(11.64%, 14.36%)	(10.98%, 14.45%)	(7.44%, 12.93%)	(13.89%, 21.06%)
Overall total number of events	355	210	52	93
No. of Patients with at least one AE by Worst Grade				
Grade 1	150 (6.2%)	91 (6.2%)	24 (4.9%)	35 (7.7%)
Grade 2	157 (6.5%)	89 (6.1%)	25 (5.1%)	43 (9.5%)
Grade 3	5 (0.2%)	5 (0.3%)	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
No. of Patients with at least one Serious AE	7 (0.3%)	6 (0.4%)	0	1 (0.2%)
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	163 (52.2%)	95 (51.4%)	30 (61.2%)	38 (48.7%)
Recovering/Resolving	39 (12.5%)	28 (15.1%)	5 (10.2%)	6 (7.7%)
Recovered/Resolved	122 (39.1%)	71 (38.4%)	14 (28.6%)	37 (47.4%)
Resolved with sequelae	5 (1.6%)	5 (2.7%)	0	0
Unknown outcome	2 (0.6%)	0	1 (2.0%)	1 (1.3%)

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out
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1.5.3 Hyperthyroidism

Hyperthyroidism: Hyperthyroidism SMQ (narrow)

Potential mechanisms:

Inhibition of PD-L1 modifies the regulation of the immune system, which may cause changes in peripheral tolerance, and can lead to immune-mediated inflammation or autoimmune-like side effects in susceptible tissues.

Evidence source(s) and strength of evidence:

Clinical trial data

Characterisation of the risk:

See Table 43 and Table 44. There are no clinically relevant differences in the frequency of this event among the IV monotherapy, IMscin001 (SC monotherapy), and combination therapy populations. Numerically higher rates noted for IMpower010 and combination therapy populations could partly be due to increased frequency of thyroid function testing requirements in these studies compared to the earlier studies in the Lung and Bladder IV monotherapy populations. Overall, the events were generally Grade 1 or 2 in severity and non-serious.

Risk factors and risk groups:

There are no known risk factors associated with the development of immune-mediated hyperthyroidism in atezolizumab–treated patients.

Preventability:

Although there is currently no way to predict which patients may be more susceptible to developing hyperthyroidism, Section 4.4 of the E.U. SmPC provides a warning to monitor patients for signs and symptoms of endocrinopathies and to monitor thyroid function. Management guidelines are also provided in Sections 4.2 and 4.4 of the E.U. SmPC to reduce the potential for negative outcomes.

Impact on the benefit-risk balance of the product:

Although hyperthyroidism can be challenging to diagnose, events of low grade intensity, were identified and therefore the impact on individual patients is low.

A patient card will be provided to reduce the severity of immune-mediated hyperthyroidism by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and

timely intervention. This will reduce the impact of immune-mediated hyperthyroidism on the benefit-risk balance of the product.

Public health impact:

Given the absence of severe cases, the impact on public health is considered low.

Table 43 Immune-Mediated Hyperthyroidism: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Hyperthyroidism

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	81 (1.9%)	68 (2.5%)	10 (1.0%)	7 (2.3%)	5 (2.0%)
95% CI for % of patients with at least one AE	(1.55%, 2.42%)	(1.95%, 3.16%)	(0.49%, 1.86%)	(0.94%, 4.75%)	(0.66%, 4.66%)
Overall total number of events	88	75	10	10	5
No. of Patients with at least one AE by Worst Grade					
Grade 1	46 (1.1%)	40 (1.5%)	4 (0.4%)	4 (1.3%)	2 (0.8%)
Grade 2	32 (0.8%)	26 (1.0%)	5 (0.5%)	3 (1.0%)	3 (1.2%)
Grade 3	3 (<0.1%)	2 (<0.1%)	1 (0.1%)	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
No. of Patients with at least one Serious AE	1 (<0.1%)	0	1 (0.1%)	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	25 (30.9%)	22 (32.4%)	3 (30.0%)	0	2 (40.0%)
Recovering/Resolving	5 (6.2%)	5 (7.4%)	0	1 (14.3%)	0
Recovered/Resolved	49 (60.5%)	39 (57.4%)	7 (70.0%)	5 (71.4%)	3 (60.0%)
Resolved with sequelae	2 (2.5%)	2 (2.9%)	0	1 (14.3%)	0
Unknown outcome	1 (1.2%)	1 (1.5%)	0	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/
t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out
24JUN2024 20:15
Adapted from t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out

Table 44 Immune-Mediated Hyperthyroidism: Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Hyperthyroidism

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	97 (4.0%)	61 (4.2%)	16 (3.2%)	20 (4.4%)
95% CI for % of patients with at least one AE	(3.28%, 4.89%)	(3.20%, 5.32%)	(1.87%, 5.22%)	(2.72%, 6.75%)
Overall total number of events	103	65	17	21
No. of Patients with at least one AE by Worst Grade				
Grade 1	65 (2.7%)	41 (2.8%)	10 (2.0%)	14 (3.1%)
Grade 2	28 (1.2%)	18 (1.2%)	5 (1.0%)	5 (1.1%)
Grade 3	4 (0.2%)	2 (0.1%)	1 (0.2%)	1 (0.2%)
Grade 4	0	0	0	0
Grade 5	0	0	0	0
No. of Patients with at least one Serious AE	1 (<0.1%)	0	0	1 (0.2%)
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	18 (18.6%)	10 (16.4%)	4 (25.0%)	4 (20.0%)
Recovering/Resolving	4 (4.1%)	4 (6.6%)	0	0
Recovered/Resolved	73 (75.3%)	46 (75.4%)	12 (75.0%)	15 (75.0%)
Resolved with sequelae	2 (2.1%)	1 (1.6%)	0	1 (5.0%)
Unknown outcome	0	0	0	0

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/
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1.5.4 Adrenal Insufficiency

Adrenal Insufficiency: Atezolizumab comprehensive adrenal insufficiency search (22 July 2015) consisting of the following terms:
ACTH stimulation test abnormal, Addison's disease, Adrenal androgen deficiency, Adrenal atrophy, Adrenal insufficiency, Adrenal insufficiency neonatal, Adrenal suppression, Adrenalitis, Adrenocortical insufficiency acute, Adrenocortical insufficiency neonatal, Adrenocorticotropic hormone deficiency, Adrenogenital syndrome, Aldosterone urine abnormal, Aldosterone urine decreased, Apituitarism, Biopsy adrenal gland abnormal, Blood aldosterone abnormal, Blood aldosterone decreased, Blood corticosterone decreased, Blood corticosterone abnormal, Blood corticotropin abnormal, Blood corticotropin decreased, Blood corticotropin increased, Corticotropin-releasing hormone stimulation test, Cortisol decreased, Cortisol free urine decreased, Dexamethasone suppression test, Dexamethasone suppression test positive, Glucocorticoid deficiency, Glucocorticoids abnormal, Glucocorticoids decreased, Hydroxycorticosteroids urine abnormal, Hydroxycorticosteroids urine decreased, Hypoaldosteronism, Hypothalamic pituitary adrenal axis suppression, Immune-mediated adrenal insufficiency, Mineralocorticoid deficiency, Pregnenolone deficiency, Primary adrenal insufficiency, Scan adrenal gland abnormal, Secondary adrenocortical insufficiency, Serum free cortisol decreased, Steroid withdrawal syndrome, Triple A syndrome, Urine cortisol/creatinine ratio abnormal, Urine cortisol/creatinine ratio decreased.

Potential mechanisms:

Inhibition of PD-L1 modifies the regulation of the immune system, which may cause changes in peripheral tolerance, and can lead to immune-mediated inflammation or autoimmune-like side effects in susceptible tissues.

Evidence source(s) and strength of evidence:

Clinical trial data

Characterisation of the risk:

See Table 45 and Table 46. There are no clinically relevant differences in the frequency of the events among the IV monotherapy, IMscin001 (SC monotherapy), and combination therapy populations.

Risk factors and risk groups:

There are no known risk factors associated with the development of immune-mediated adrenal insufficiency in atezolizumab-treated patients.

Preventability:

Although there is currently no way to predict which patients may be more susceptible to developing adrenal insufficiency, Section 4.4 of the E.U. SmPC provides a warning to monitor patients for signs and symptoms of endocrinopathies and to monitor thyroid function. Management guidelines are also provided in Sections 4.2 and 4.4 of the E.U. SmPC to reduce the potential for negative outcomes.

Impact on the benefit-risk balance of the product:

Although adrenal insufficiency is potentially lethal if unrecognised, it is easily diagnosed and manageable with treatment. For this reason, the impact on individual patients is considered low.

A patient card will be provided to reduce the severity of immune-mediated adrenal insufficiency by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and timely intervention. This will reduce the impact of immune-mediated adrenal insufficiency on the benefit–risk balance of the product.

Public health impact:

Given the scarcity of this event, and the simplicity of treatment, the potential impact on public health is low.

Table 45 Immune-Mediated Adrenal Insufficiency: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Adrenal Insufficiency

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	22 (0.5%)	16 (0.6%)	2 (0.2%)	1 (0.3%)	1 (0.4%)
95% CI for % of patients with at least one AE	(0.33%, 0.80%)	(0.34%, 0.95%)	(0.02%, 0.73%)	(0.01%, 1.84%)	(0.01%, 2.23%)
Overall total number of events	25	19	2	1	1
No. of Patients with at least one AE by Worst Grade					
Grade 1	5 (0.1%)	5 (0.2%)	0	0	0
Grade 2	12 (0.3%)	9 (0.3%)	1 (0.1%)	1 (0.3%)	1 (0.4%)
Grade 3	4 (<0.1%)	2 (<0.1%)	0	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
No. of Patients with at least one Serious AE	6 (0.1%)	5 (0.2%)	0	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	12 (54.5%)	9 (56.3%)	1 (50.0%)	0	1 (100%)
Recovering/Resolving	2 (9.1%)	2 (12.5%)	0	0	0
Recovered/Resolved	9 (40.9%)	6 (37.5%)	1 (50.0%)	0	0
Resolved with sequelae	1 (4.5%)	1 (6.3%)	0	1 (100%)	0
Unknown outcome	0	0	0	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/
t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out
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Adapted from t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out

Table 46 Immune-Mediated Adrenal Insufficiency: Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Adrenal Insufficiency

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	22 (0.9%)	14 (1.0%)	2 (0.4%)	6 (1.3%)
95% CI for % of patients with at least one AE	(0.57%, 1.38%)	(0.52%, 1.60%)	(0.05%, 1.46%)	(0.49%, 2.87%)
Overall total number of events	25	16	2	7
No. of Patients with at least one AE by Worst Grade				
Grade 1	6 (0.2%)	5 (0.3%)	0	1 (0.2%)
Grade 2	11 (0.5%)	7 (0.5%)	1 (0.2%)	3 (0.7%)
Grade 3	5 (0.2%)	2 (0.1%)	1 (0.2%)	2 (0.4%)
Grade 4	0	0	0	0
Grade 5	0	0	0	0
No. of Patients with at least one Serious AE	10 (0.4%)	5 (0.3%)	2 (0.4%)	3 (0.7%)
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	12 (54.5%)	9 (64.3%)	1 (50.0%)	2 (33.3%)
Recovering/Resolving	2 (9.1%)	1 (7.1%)	1 (50.0%)	0
Recovered/Resolved	8 (36.4%)	3 (21.4%)	0	5 (83.3%)
Resolved with sequelae	2 (9.1%)	2 (14.3%)	0	0
Unknown outcome	0	0	0	0

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/
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Adapted from t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out.

1.5.5 Hypophysitis

Hypophysitis: HLT Hypothalamic and pituitary disorders NEC

Potential mechanisms:

Inhibition of PD-L1 modifies the regulation of the immune system, which may cause changes in peripheral tolerance, and can lead to immune-mediated inflammation or autoimmune-like side effects in susceptible tissues.

Evidence source(s) and strength of evidence:

Clinical trial data

Characterisation of the risk:

See Table 47 and Table 48. No events of hypophysitis were reported in IMscin001 (SC monotherapy), Bladder IV monotherapy, Breast (TNBC) combination therapy, and HCC combination therapy populations. There are no clinically relevant differences in the frequency of the event between the NSCLC IV monotherapy and Lung combination therapy (NSCLC, SCLC) populations.

There was one additional patient in the monotherapy population from Study PCD4989g who experienced hypophysitis. This patient is not reflected in Table 47, as the event term “intracranial mass” was not included in the MedDRA search methodology for hypophysitis. This case concerned a patient treated with atezolizumab for UC, who experienced the event of “intracranial mass”. Based on the clinical presentation, endocrine function results, MRI results, and response to steroid treatment, this event is compatible with a diagnosis of hypophysitis.

Risk factors and risk groups:

There are no known risk factors associated with the development of immune-mediated hypophysitis in atezolizumab-treated patients.

Preventability:

Although there is currently no way to predict which patients may be more susceptible to developing hypophysitis, Section 4.4 of the E.U. SmPC provides a warning to monitor patients for signs and symptoms of endocrinopathies and to monitor thyroid function. Management guidelines are also provided in Sections 4.2 and 4.4 of the E.U. SmPC to reduce the potential for negative outcomes.

Impact on the benefit-risk balance of the product:

Although hypophysitis is potentially lethal if unrecognised, it is easily diagnosed and manageable with treatment. For this reason, the impact on individual patients is considered low.

A patient card will be provided to reduce the severity of immune-mediated hypophysitis by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and timely intervention. This will reduce the impact of immune-mediated hypophysitis on the benefit–risk balance of the product.

Public health impact:

Given the rarity of this event, and the appropriate guidance for monitoring and managing these events, the public health impact is expected to be limited.

Table 47 Immune-Mediated Hypophysitis: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Hypophysitis

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	6 (0.1%)	5 (0.2%)	0	0	0
95% CI for % of patients with at least one AE	(0.05%, 0.31%)	(0.06%, 0.43%)	(0.00%, 0.37%)	(0.00%, 1.22%)	(0.00%, 1.48%)
Overall total number of events	7	6	0	0	0
No. of Patients with at least one AE by Worst Grade					
Grade 1	2 (<0.1%)	1 (<0.1%)	0	0	0
Grade 2	3 (<0.1%)	3 (0.1%)	0	0	0
Grade 3	1 (<0.1%)	1 (<0.1%)	0	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
No. of Patients with at least one Serious AE	2 (<0.1%)	2 (<0.1%)	0	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	3 (50.0%)	3 (60.0%)	0	0	0
Recovering/Resolving	1 (16.7%)	1 (20.0%)	0	0	0
Recovered/Resolved	3 (50.0%)	2 (40.0%)	0	0	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/
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Table 48 Immune-Mediated Hypophysitis: Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Hypophysitis

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	7 (0.3%)	7 (0.5%)	0	0
95% CI for % of patients with at least one AE	(0.12%, 0.60%)	(0.19%, 0.98%)	(0.00%, 0.75%)	(0.00%, 0.81%)
Overall total number of events	7	7	0	0
No. of Patients with at least one AE by Worst Grade				
Grade 1	2 (<0.1%)	2 (0.1%)	0	0
Grade 2	4 (0.2%)	4 (0.3%)	0	0
Grade 3	1 (<0.1%)	1 (<0.1%)	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
No. of Patients with at least one Serious AE	2 (<0.1%)	2 (0.1%)	0	0
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	2 (28.6%)	2 (28.6%)	0	0
Recovering/Resolving	3 (42.9%)	3 (42.9%)	0	0
Recovered/Resolved	2 (28.6%)	2 (28.6%)	0	0
Resolved with sequelae	0	0	0	0
Unknown outcome	0	0	0	0

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
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1.6 NEUROPATHIES

Neuropathies: Guillain-Barré Syndrome, Myasthenic Syndrome / Myasthenia Gravis, Facial Paresis

1.6.1 Guillain-Barré Syndrome

Guillain-Barré Syndrome: Guillain-Barre SMQ (narrow)

Potential mechanisms:

Inhibition of PD-L1 modifies the regulation of the immune system, which may cause changes in peripheral tolerance, and can lead to immune-mediated inflammation or autoimmune-like side effects in susceptible tissues.

Evidence source(s) and strength of evidence:

Clinical trial data

Characterisation of the risk:

See Table 49 and Table 50. No events of immune-mediated Guillain-Barré syndrome were observed in the Bladder IV monotherapy, IMscin001 (SC monotherapy), and Breast (TNBC) combination therapy populations. There are no clinically relevant differences in the frequency of the event between the NSCLC IV monotherapy, Lung combination therapy populations, and HCC combination therapy population.

Risk factors and risk groups:

There are no known risk factors associated with the development of immune-mediated Guillain-Barré syndrome in atezolizumab-treated patients.

Preventability:

There are currently no reliable predictors of which patients may be susceptible to the development of Guillain-Barré syndrome following atezolizumab therapy. Section 4.4 of the E.U. SmPC provides a warning to monitor patients for signs and symptoms, and Sections 4.2 and 4.4 of the E.U. SmPC advise to discontinue treatment for any grade of Guillain-Barré syndrome.

Impact on the benefit-risk balance of the product:

Guillain-Barré syndrome is an acute monophasic illness causing a rapidly progressive polyneuropathy with symptoms ranging from weakness to paralysis. Given the potential for respiratory muscle involvement with life-threatening consequences, the impact on individual patients could potentially be severe.

A patient card will be provided to reduce the severity of immune-mediated Guillain-Barré Syndrome by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and timely intervention. This will reduce the impact of immune-mediated Guillain-Barré Syndrome on the benefit–risk balance of the product.

Public health impact:

Given the rarity of this event, and the appropriate guidance for monitoring and managing these events, the public health impact is expected to be limited.

Table 49 Immune-Mediated Guillain-Barre Syndrome: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Guillain-Barre Syndrome

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	6 (0.1%)	6 (0.2%)	0	0	0
95% CI for % of patients with at least one AE	(0.05%, 0.31%)	(0.08%, 0.48%)	(0.00%, 0.37%)	(0.00%, 1.22%)	(0.00%, 1.48%)
Overall total number of events	6	6	0	0	0
No. of Patients with at least one AE by Worst Grade					
Grade 1	0	0	0	0	0
Grade 2	1 (<0.1%)	1 (<0.1%)	0	0	0
Grade 3	5 (0.1%)	5 (0.2%)	0	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
No. of Patients with at least one Serious AE	4 (<0.1%)	4 (0.1%)	0	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	3 (50.0%)	3 (50.0%)	0	0	0
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	3 (50.0%)	3 (50.0%)	0	0	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
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Adapted from t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out

Table 50 Immune-Mediated Guillain-Barre Syndrome: Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Guillain-Barre Syndrome

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	2 (<0.1%)	1 (<0.1%)	1 (0.2%)	0
95% CI for % of patients with at least one AE	(0.01%, 0.30%)	(0.00%, 0.38%)	(0.01%, 1.12%)	(0.00%, 0.81%)
Overall total number of events	2	1	1	0
No. of Patients with at least one AE by Worst Grade				
Grade 1	0	0	0	0
Grade 2	0	0	0	0
Grade 3	2 (<0.1%)	1 (<0.1%)	1 (0.2%)	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
No. of Patients with at least one Serious AE	2 (<0.1%)	1 (<0.1%)	1 (0.2%)	0
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	1 (50.0%)	1 (100%)	0	0
Recovering/Resolving	0	0	0	0
Recovered/Resolved	0	0	0	0
Resolved with sequelae	1 (50.0%)	0	1 (100%)	0
Unknown outcome	0	0	0	0

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/
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1.6.2 Myasthenic Syndrome / Myasthenia Gravis

Myasthenic Syndrome / Myasthenia Gravis: HLT Myasthenia gravis and related conditions

Potential mechanisms:

Inhibition of PD-L1 modifies the regulation of the immune system, which may cause changes in peripheral tolerance, and can lead to immune-mediated inflammation or autoimmune-like side effects in susceptible tissues.

Evidence source(s) and strength of evidence:

Clinical trial data

Characterisation of the risk:

See Table 51 and Table 52. Two cases of myasthenic syndrome / myasthenia gravis syndrome were identified; one case occurred in the Renal Cell Carcinoma monotherapy population and one fatal case occurred in the Lung IV monotherapy subset population (Study IPSOS). The fatal myasthenia gravis event occurred in a patient with no relevant medical history after receiving five doses of atezolizumab. No events of myasthenic syndrome / myasthenia gravis syndrome were reported in the Bladder IV monotherapy, IMscin001 (SC monotherapy), Lung combination therapy, Breast (TNBC) combination therapy, and HCC combination therapy populations.

Risk factors and risk groups:

There are no known risk factors associated with the development of immune-mediated myasthenic syndrome / myasthenia gravis in atezolizumab-treated patients.

Preventability:

There are currently no reliable predictors of which individual patients may be susceptible to the development of this risk following atezolizumab therapy. Section 4.4 of the E.U. SmPC provides a warning to monitor patients for signs and symptoms and Sections 4.2 and 4.4 of the E.U. SmPC advice to discontinue treatment for any grade of myasthenic syndrome / myasthenia gravis.

Impact on the benefit-risk balance of the product:

Myasthenic syndrome / myasthenia gravis is manifested by worsening contractile force of the skeletal muscles, has the potential to interfere with activities of daily living, and can lead to the life-threatening condition of myasthenic crisis. This event may thus have a significant impact on the individual patient's quality of life.

A patient card will be provided to reduce the severity of immune-mediated myasthenic syndrome / myasthenia gravis by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and timely intervention. This will reduce the impact of immune-mediated myasthenic syndrome / myasthenia gravis on the benefit-risk balance of the product.

Public health impact:

Given the rarity of this event, the public health impact is expected to be minimal.

Table 51 Immune-Mediated Myasthenic Syndrome / Myasthenia Gravis: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Myasthenia Gravis

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	2 (<0.1%)	1 (<0.1%)	0	1 (0.3%)	0
95% CI for % of patients with at least one AE	(0.01%, 0.17%)	(0.00%, 0.20%)	(0.00%, 0.37%)	(0.01%, 1.84%)	(0.00%, 1.48%)
Overall total number of events	2	1	0	1	0
No. of Patients with at least one AE by Worst Grade					
Grade 1	0	0	0	0	0
Grade 2	1 (<0.1%)	0	0	0	0
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Grade 5	1 (<0.1%)	1 (<0.1%)	0	1 (0.3%)	0
No. of Patients with at least one Serious AE	2 (<0.1%)	1 (<0.1%)	0	1 (0.3%)	0
Number of patients with at least one AE by outcome					
Fatal outcome	1 (50.0%)	1 (100%)	0	1 (100%)	0
Unresolved	1 (50.0%)	0	0	0	0
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	0	0	0	0	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/
t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out
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Adapted from t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out

Table 52 Immune-Mediated Myasthenic Syndrome / Myasthenia Gravis: Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Myasthenia Gravis

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	0	0	0	0
95% CI for % of patients with at least one AE	(0.00%, 0.15%)	(0.00%, 0.25%)	(0.00%, 0.75%)	(0.00%, 0.81%)

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/
t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out
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Adapted from t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out.

1.6.3 Facial Paresis

Facial paresis: PT Facial paresis

Potential mechanisms:

Inhibition of PD-L1 modifies the regulation of the immune system which may cause changes in peripheral tolerance, and can lead to immune-mediated inflammation or autoimmune-like side effects in susceptible tissues, endoneurial microvasculature inflammation may cause neurotoxicity secondary to local edema leading to neural compression.

Evidence source(s) and strength of evidence:

Based on a comprehensive analysis of cases retrieved from the Roche global drug safety database reported with facial paresis in patients who received treatment with atezolizumab, as well as available data from the clinical database, FDA Adverse Event Reporting System (FAERS) and EudraVigilance (EV) databases, preclinical studies, published literature and considering the plausible mechanism of action and the class effect of similar-in-class drugs, a causal association between atezolizumab and facial paresis has been established.

Characterisation of the risk:

See Table 53 and Table 54. No events of immune-mediated facial paresis were observed in the Lung IV monotherapy, Bladder IV monotherapy, and IMscin001 (SC monotherapy) populations. One event of immune-mediated facial paresis was reported in the atezolizumab combination therapy population (<0.1%).

Risk factors and risk groups:

There are no identified risk factors for the development of immune-mediated facial paresis in atezolizumab treated patients.

Preventability:

There are currently no reliable predictors of which individual patients may be susceptible to the development of this risk following atezolizumab therapy. Sections 4.2 and 4.4 of the E.U. SmPC provide management guidelines to reduce the potential for negative outcomes.

Impact on the benefit-risk balance of the product:

Facial paresis may lead to complications such as exposure keratitis, dryness of cornea, corneal ulcerations, and hyperkinetic complications such as hemifacial spasm, facial

asymmetry, and synkinesis. Therefore, the impact on the individual patient is potentially severe.

A patient card will be provided to reduce the severity of immune-mediated facial paresis by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and timely intervention. This will reduce the impact of immune-mediated facial paresis on the benefit–risk balance of the product.

Public health impact:

Given the rarity of this event, the public health impact is expected to be minimal.

Table 53 Immune-Mediated Facial Paresis: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Facial Paresis

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	0	0	0	0	0
95% CI for % of patients with at least one AE	(0.00%, 0.09%)	(0.00%, 0.14%)	(0.00%, 0.37%)	(0.00%, 1.22%)	(0.00%, 1.48%)
Overall total number of events	0	0	0	0	0
No. of Patients with at least one AE by Worst Grade					
Grade 1	0	0	0	0	0
Grade 2	0	0	0	0	0
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
No. of Patients with at least one Serious AE	0	0	0	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	0	0	0	0	0
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	0	0	0	0	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.
Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out
24JUN2024 20:15
Adapted from t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out

Table 54 Immune-Mediated Facial Paresis: Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Facial Paresis

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	1 (<0.1%)	1 (<0.1%)	0	0
95% CI for % of patients with at least one AE	(0.00%, 0.23%)	(0.00%, 0.38%)	(0.00%, 0.75%)	(0.00%, 0.81%)
Overall total number of events	1	1	0	0
No. of Patients with at least one AE by Worst Grade				
Grade 1	0	0	0	0
Grade 2	1 (<0.1%)	1 (<0.1%)	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	0	0	0	0
Recovering/Resolving	0	0	0	0
Recovered/Resolved	1 (100%)	1 (100%)	0	0
Resolved with sequelae	0	0	0	0
Unknown outcome	0	0	0	0

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/
t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out
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1.7 MYELITIS

Myelitis: Acute flaccid myelitis, acute necrotizing myelitis, myelitis, myelitis transverse, noninfectious myelitis, paraneoplastic myelopathy.

Potential mechanisms:

Inhibition of PD-L1 modifies the regulation of the immune system which may cause changes in peripheral tolerance, and can lead to immune-mediated inflammation or autoimmune-like side effects in susceptible tissues including the spinal cord.

Evidence source(s) and strength of evidence:

Based on a comprehensive analysis of cases retrieved from the Roche global drug safety database reported with myelitis and related events in patients who received treatment with atezolizumab, as well as available data from the clinical database, FAERS and EV databases, preclinical studies, published literature and considering the plausible mechanism of action and the class effect of similar-in-class drugs, a causal association between atezolizumab and myelitis has been established.

Characterisation of the risk:

See Table 55 and Table 56. Two events of immune-mediated myelitis from the same patient were reported in the Lung IV monotherapy population (<0.1%). No events of immune-mediated myelitis were observed in the Bladder IV monotherapy, IMscin001 (SC monotherapy), and combination therapy populations.

Risk factors and risk groups:

There are no identified risk factors for the development of immune-mediated myelitis in atezolizumab treated patients.

Preventability:

There are currently no reliable predictors of which individual patients may be susceptible to the development of this risk following atezolizumab therapy. Sections 4.2 and 4.4 of the E.U. SmPC provide management guidelines to reduce the potential for negative outcomes.

Impact on the benefit-risk balance of the product:

Myelitis is characterised by partial or bilateral deficiencies, progressive muscular weakness, sensory abnormalities, and bowel/bladder dysfunction. Therefore, the impact on the individual patient is potentially severe.

A patient card will be provided to reduce the severity of immune-mediated myelitis by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and timely intervention. This will reduce the impact of immune-mediated myelitis on the benefit–risk balance of the product.

Public health impact:

Given the rarity of this event, the public health impact is expected to be minimal.

Table 55 Immune-Mediated Myelitis: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Myelitis

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	1 (<0.1%)	1 (<0.1%)	0	0	0
95% CI for % of patients with at least one AE	(0.00%, 0.13%)	(0.00%, 0.20%)	(0.00%, 0.37%)	(0.00%, 1.22%)	(0.00%, 1.48%)
Overall total number of events	2	2	0	0	0
No. of Patients with at least one AE by Worst Grade					
Grade 1	0	0	0	0	0
Grade 2	0	0	0	0	0
Grade 3	1 (<0.1%)	1 (<0.1%)	0	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
No. of Patients with at least one Serious AE	1 (<0.1%)	1 (<0.1%)	0	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	1 (100%)	1 (100%)	0	0	0
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	0	0	0	0	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/
t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out
24JUN2024 20:15
Adapted from t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out

Table 56 Immune-Mediated Myelitis: Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Myelitis

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	0	0	0	0
95% CI for % of patients with at least one AE	(0.00%, 0.15%)	(0.00%, 0.25%)	(0.00%, 0.75%)	(0.00%, 0.81%)

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/
t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out
02DEC2022 22:08
Adapted from t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out.

1.8 MENINGOENCEPHALITIS

Meningoencephalitis: Noninfectious meningitis SMQ (narrow), Noninfectious encephalitis SMQ (narrow)

Potential mechanisms:

Inhibition of PD-L1 modifies the regulation of the immune system, which may cause changes in peripheral tolerance, and can lead to immune-mediated inflammation or autoimmune-like side effects in susceptible tissues.

Evidence source(s) and strength of evidence:

Clinical trial data

Characterisation of the risk:

See Table 57 and Table 58. No events of immune-mediated meningoencephalitis were observed in the Bladder IV monotherapy and IMscin001 (SC monotherapy) populations. There were no clinically relevant differences in the frequency of this event among the Lung IV monotherapy population, Lung combination therapy, Breast (TNBC) combination therapy, and HCC combination therapy populations. The majority of events were Grades 1–3 in severity, with the majority of events resolved by the time of the data cut.

Risk factors and risk groups:

There are no known risk factors associated with the development of immune-mediated meningoencephalitis in atezolizumab-treated patients.

Preventability:

There are currently no reliable predictors of which individual patients may be susceptible to the development of immune-mediated meningoencephalitis following atezolizumab therapy. Sections 4.2 and 4.4 of the E.U. SmPC provide management guidelines to reduce the potential for negative outcomes.

Impact on the benefit-risk balance of the product:

Meningoencephalitis has the capacity to lead to permanent neurologic damage. Therefore, the impact on the individual patient is potentially significant.

A patient card will be provided to reduce the severity of immune-mediated meningoencephalitis by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier

diagnosis and timely intervention. This will reduce the impact of immune-mediated meningoencephalitis on the benefit–risk balance of the product.

Public health impact:

Given the rarity of this event, the public health impact is expected to be minimal.

Table 57 Immune-Mediated Meningoencephalitis: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Meningoencephalitis

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	17 (0.4%)	13 (0.5%)	0	0	0
95% CI for % of patients with at least one AE	(0.24%, 0.65%)	(0.26%, 0.82%)	(0.00%, 0.37%)	(0.00%, 1.22%)	(0.00%, 1.48%)
Overall total number of events	17	13	0	0	0
No. of Patients with at least one AE by Worst Grade					
Grade 1	5 (0.1%)	3 (0.1%)	0	0	0
Grade 2	3 (<0.1%)	3 (0.1%)	0	0	0
Grade 3	8 (0.2%)	6 (0.2%)	0	0	0
Grade 4	1 (<0.1%)	1 (<0.1%)	0	0	0
Grade 5	0	0	0	0	0
No. of Patients with at least one Serious AE	11 (0.3%)	9 (0.3%)	0	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	1 (5.9%)	1 (7.7%)	0	0	0
Recovering/Resolving	2 (11.8%)	2 (15.4%)	0	0	0
Recovered/Resolved	14 (82.4%)	10 (76.9%)	0	0	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
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24JUN2024 20:15
Adapted from t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out

Table 58 Immune-Mediated Meningoencephalitis: Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Meningoencephalitis

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	10 (0.4%)	4 (0.3%)	1 (0.2%)	5 (1.1%)
95% CI for % of patients with at least one AE	(0.20%, 0.76%)	(0.07%, 0.70%)	(0.01%, 1.12%)	(0.36%, 2.56%)
Overall total number of events	10	4	1	5
No. of Patients with at least one AE by Worst Grade				
Grade 1	5 (0.2%)	2 (0.1%)	0	3 (0.7%)
Grade 2	2 (<0.1%)	0	0	2 (0.4%)
Grade 3	3 (0.1%)	2 (0.1%)	1 (0.2%)	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
No. of Patients with at least one Serious AE	3 (0.1%)	2 (0.1%)	1 (0.2%)	0
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	3 (30.0%)	1 (25.0%)	0	2 (40.0%)
Recovering/Resolving	0	0	0	0
Recovered/Resolved	7 (70.0%)	3 (75.0%)	1 (100%)	3 (60.0%)
Resolved with sequelae	0	0	0	0
Unknown outcome	0	0	0	0

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/
t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out
02DEC2022 22:08
Adapted from t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out.

1.9 MYOCARDITIS

Myocarditis: Atezolizumab Myocarditis Immune-Related AEGT consisting of the following MedDRA PTs: Autoimmune myocarditis, chronic myocarditis, eosiniphilic myocarditis, giant cell myocarditis, hypersensitivity myocarditis, immune-mediated myocarditis, myocarditis

Potential mechanisms:

Inhibition of PD-L1 modifies the regulation of the immune system which may cause changes in peripheral tolerance, and can lead to immune-mediated inflammation or autoimmune-like side effects in susceptible tissues.

Evidence source(s) and strength of evidence:

Clinical trial data

Characterisation of the risk:

See Table 59 and Table 60. No events of immune-mediated myocarditis were observed in the Bladder IV monotherapy, IMscin001 (SC monotherapy), Lung combination therapy, and Breast (TNBC) combination therapy populations. There are no clinically relevant differences in the frequency of this event between Lung IV monotherapy and HCC combination therapy populations. Within the Lung IV monotherapy population (including Study IPSOS), four events of myocarditis were identified, of which one was fatal. The fatal myocarditis event occurred in a patient with paroxysmal atrial fibrillation, hypertension, diabetes, and hyperlipidaemia after receiving 2 doses of atezolizumab. Endomyocardial biopsy revealed myocarditis on a background of cardiac transthyretin amyloidosis. Within the IPSOS study, one case of Grade 2 myocarditis was identified in a patient with sinus tachycardia that led to treatment interruption. The patient was treated with oral corticosteroids and the event resolved after 40 days.

Risk factors and risk groups:

There are no known risk factors associated with the development of immune-mediated myocarditis in atezolizumab-treated patients.

Preventability:

There are currently no reliable predictors of which individual patients may be susceptible to the development of this risk following atezolizumab therapy. Sections 4.2 and 4.4 of the E.U. SmPC provide management guidelines to reduce the potential for negative outcomes.

Impact on the benefit-risk balance of the product:

Myocarditis has the potential to be fatal; therefore, the impact on the individual patient is potentially significant.

A patient card will be provided to reduce the severity of immune-mediated myocarditis by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and timely intervention. This will reduce the impact of immune-mediated myocarditis on the benefit–risk balance of the product.

Public health impact:

Given the rarity of this event, the public health impact is expected to be minimal.

Table 59 Immune-Mediated Myocarditis: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Myocarditis

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	4 (<0.1%)	4 (0.1%)	0	1 (0.3%)	0
95% CI for % of patients with at least one AE	(0.03%, 0.25%)	(0.04%, 0.38%)	(0.00%, 0.37%)	(0.01%, 1.84%)	(0.00%, 1.48%)
Overall total number of events	4	4	0	1	0
No. of Patients with at least one AE by Worst Grade					
Grade 1	1 (<0.1%)	1 (<0.1%)	0	0	0
Grade 2	1 (<0.1%)	1 (<0.1%)	0	1 (0.3%)	0
Grade 3	1 (<0.1%)	1 (<0.1%)	0	0	0
Grade 4	0	0	0	0	0
Grade 5	1 (<0.1%)	1 (<0.1%)	0	0	0
No. of Patients with at least one Serious AE	3 (<0.1%)	3 (0.1%)	0	1 (0.3%)	0
Number of patients with at least one AE by outcome					
Fatal outcome	1 (25.0%)	1 (25.0%)	0	0	0
Unresolved	0	0	0	0	0
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	3 (75.0%)	3 (75.0%)	0	1 (100%)	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
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Adapted from t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out

Table 60 Immune-Mediated Myocarditis: Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Myocarditis

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	1 (<0.1%)	0	1 (0.2%)	0
95% CI for % of patients with at least one AE	(0.00%, 0.23%)	(0.00%, 0.25%)	(0.01%, 1.12%)	(0.00%, 0.81%)
Overall total number of events	1	0	1	0
No. of Patients with at least one AE by Worst Grade				
Grade 1	1 (<0.1%)	0	1 (0.2%)	0
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	1 (100%)	0	1 (100%)	0
Recovering/Resolving	0	0	0	0
Recovered/Resolved	0	0	0	0
Resolved with sequelae	0	0	0	0
Unknown outcome	0	0	0	0

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/
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1.10 NEPHRITIS

Nephritis: HLT Nephritis NEC, HLT Glomerulonephritis and nephrotic syndrome

Potential mechanisms:

Immune checkpoint inhibitors may cause changes in peripheral tolerance which can lead to immune-mediated inflammation or autoimmune-like side effects in susceptible tissues.

Evidence source(s) and strength of evidence:

Clinical trial data.

Characterisation of the risk:

See Table 61 and Table 62. No events of immune-mediated nephritis were observed in the Bladder IV monotherapy and IMscin001 (SC monotherapy) populations. There are no clinically relevant differences in the frequency of this event among the Lung IV monotherapy and combination therapy populations.

Risk factors and risk groups:

Risk factors include certain infections, drugs (including antibiotics, non-steroidal anti-inflammatory drugs, proton pump inhibitors) and autoimmune diseases such as Sjögren's syndrome, and immunoglobulin G4 related disease (Muriithi et al. 2014). The risk factors that may predispose individual patients to developing immune-mediated nephritis following therapy with immune checkpoint inhibitors are unknown.

Preventability:

There are currently no reliable predictors of which individual patients may or may not be susceptible to the development of immune-mediated nephritis following atezolizumab therapy. Sections 4.2 and 4.4 of the E.U. SmPC provide guidelines to adequately manage this risk.

Impact on the benefit-risk balance of the product:

Nephritis has the capacity to lead to permanent kidney injury or renal failure. Therefore, the impact on the individual patient is potentially severe.

A patient card will be provided to reduce the severity of immune-mediated nephritis by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and timely intervention. This will reduce the impact of immune-mediated nephritis on the benefit-risk balance of the product.

Public health impact:

Given the low rates of nephritis observed in drugs of the same class, the impact on public health is expected to be low.

Table 61 Immune-Mediated Nephritis: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Nephritis

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	3 (<0.1%)	3 (0.1%)	0	0	0
95% CI for % of patients with at least one AE	(0.01%, 0.21%)	(0.02%, 0.32%)	(0.00%, 0.37%)	(0.00%, 1.22%)	(0.00%, 1.48%)
Overall total number of events	3	3	0	0	0
No. of Patients with at least one AE by Worst Grade					
Grade 1	1 (<0.1%)	1 (<0.1%)	0	0	0
Grade 2	1 (<0.1%)	1 (<0.1%)	0	0	0
Grade 3	1 (<0.1%)	1 (<0.1%)	0	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
No. of Patients with at least one Serious AE	1 (<0.1%)	1 (<0.1%)	0	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	2 (66.7%)	2 (66.7%)	0	0	0
Recovering/Resolving	1 (33.3%)	1 (33.3%)	0	0	0
Recovered/Resolved	0	0	0	0	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
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24JUN2024 20:15
Adapted from t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out

Table 62 Immune-Mediated Nephritis: Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Nephritis

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	13 (0.5%)	9 (0.6%)	3 (0.6%)	1 (0.2%)
95% CI for % of patients with at least one AE	(0.29%, 0.92%)	(0.28%, 1.16%)	(0.13%, 1.77%)	(0.01%, 1.23%)
Overall total number of events	14	9	3	2
No. of Patients with at least one AE by Worst Grade				
Grade 1	0	0	0	0
Grade 2	6 (0.2%)	4 (0.3%)	1 (0.2%)	1 (0.2%)
Grade 3	7 (0.3%)	5 (0.3%)	2 (0.4%)	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
No. of Patients with at least one Serious AE	6 (0.2%)	5 (0.3%)	1 (0.2%)	0
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	6 (46.2%)	3 (33.3%)	2 (66.7%)	1 (100%)
Recovering/Resolving	1 (7.7%)	0	1 (33.3%)	0
Recovered/Resolved	6 (46.2%)	5 (55.6%)	0	1 (100%)
Resolved with sequelae	1 (7.7%)	1 (11.1%)	0	0
Unknown outcome	0	0	0	0

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/
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Adapted from t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out.

1.11 MYOSITIS

Myositis: HLT ‘Muscle infections and inflammations’, HLT ‘Muscular autoimmune disorders’ excluding PTs with ‘myasthen*’ (Myasthen* means PTs start with "myasthen", for example, Myasthenia gravis, Myasthenia gravis crisis, Myasthenia gravis neonatal, Myasthenic syndrome), Rhabdomyolysis/myopathy SMQ (narrow)

Potential mechanisms:

Inhibition of PD-L1 modifies the regulation of the immune system, which may cause changes in peripheral tolerance, and can lead to immune-mediated inflammation or autoimmune-like side effects in susceptible tissues.

Evidence source(s) and strength of evidence:

Clinical trial data.

Characterisation of the risk:

See Table 63 and Table 64. No events of immune-mediated myositis were observed in the IMscin001 (SC monotherapy) population. There are no clinically relevant differences in the frequency of this event among the IV monotherapy and the combination therapy populations.

Risk factors and risk groups:

Like other autoimmune diseases, genes and environment/lifestyle factors are likely to contribute to susceptibility to myositis. Multiple independent associations within the human leukocyte antigen (HLA) 8.1 ancestral haplotype are the strongest genetic risk factors for idiopathic inflammatory myopathies. Epidemiological data support a role for infections, prior lung disease, physical exertion, collagen implants, exposure to ultraviolet radiation and smoking in the development of inflammatory myopathies. Females were found to be more prone to develop polymyositis and dermatomyositis, while males were more prone to develop inclusion body myositis. Drugs such as statins, D-penicillamine, interferon-α, and procainamide were found to be associated with myositis. The risk of developing myositis is found to increase with age and peaks in patients aged 50 – 79 years (Svensson et al. 2017).

Preventability:

While older patients have an increased risk of developing myositis, there are no reliable predictors of susceptibility of individual patients to this risk following exposure to atezolizumab. Sections 4.2 and 4.4 of the E.U. SmPC provide guidelines to monitor and manage immune-mediated myositis to reduce the potential for negative outcomes in patients experiencing this event.

Impact on the benefit-risk balance of the product:

Myositis has the capacity to lead to serious complications such as rhabdomyolysis or myocarditis. Therefore, the impact on the individual patient is potentially severe.

A patient card will be provided to reduce the severity of immune-mediated myositis by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and timely intervention. This will reduce the impact of immune-mediated myositis on the benefit-risk balance of the product.

Public health impact:

Given the low rates of myositis observed in drugs of the same class, the impact on public health is expected to be low.

Table 63 Immune-Mediated Myositis: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Myositis (Myositis+Rhabdomyolysis)

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	18 (0.4%)	11 (0.4%)	6 (0.6%)	0	0
95% CI for % of patients with at least one AE	(0.26%, 0.68%)	(0.20%, 0.72%)	(0.22%, 1.32%)	(0.00%, 1.22%)	(0.00%, 1.48%)
Overall total number of events	22	13	8	0	0
No. of Patients with at least one AE by Worst Grade					
Grade 1	4 (<0.1%)	3 (0.1%)	1 (0.1%)	0	0
Grade 2	9 (0.2%)	6 (0.2%)	2 (0.2%)	0	0
Grade 3	3 (<0.1%)	1 (<0.1%)	2 (0.2%)	0	0
Grade 4	2 (<0.1%)	1 (<0.1%)	1 (0.1%)	0	0
Grade 5	0	0	0	0	0
No. of Patients with at least one Serious AE	5 (0.1%)	2 (<0.1%)	3 (0.3%)	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	5 (27.8%)	3 (27.3%)	2 (33.3%)	0	0
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	14 (77.8%)	8 (72.7%)	5 (83.3%)	0	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	1 (5.6%)	1 (9.1%)	0	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/
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Table 64 Immune-Mediated Myositis: Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Myositis (Myositis+Rhabdomyolysis)

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	11 (0.5%)	7 (0.5%)	3 (0.6%)	1 (0.2%)
95% CI for % of patients with at least one AE	(0.23%, 0.82%)	(0.19%, 0.98%)	(0.13%, 1.77%)	(0.01%, 1.23%)
Overall total number of events	14	10	3	1
No. of Patients with at least one AE by Worst Grade				
Grade 1	1 (<0.1%)	1 (<0.1%)	0	0
Grade 2	5 (0.2%)	4 (0.3%)	1 (0.2%)	0
Grade 3	4 (0.2%)	2 (0.1%)	1 (0.2%)	1 (0.2%)
Grade 4	1 (<0.1%)	0	1 (0.2%)	0
Grade 5	0	0	0	0
No. of Patients with at least one Serious AE	2 (<0.1%)	0	1 (0.2%)	1 (0.2%)
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	2 (18.2%)	1 (14.3%)	0	1 (100%)
Recovering/Resolving	2 (18.2%)	2 (28.6%)	0	0
Recovered/Resolved	8 (72.7%)	5 (71.4%)	3 (100%)	0
Resolved with sequelae	0	0	0	0
Unknown outcome	0	0	0	0

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/
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1.12 SEVERE CUTANEOUS ADVERSE REACTIONS

Severe cutaneous adverse reactions (SCARs): Severe cutaneous adverse reactions (SMQ; narrow).

Potential mechanisms:

Inhibition of PD-L1 modifies the regulation of the immune system, which may cause changes in peripheral tolerance, and can lead to immune-mediated inflammation or autoimmune-like side effects in susceptible tissues.

Evidence source(s) and strength of evidence:

Based on a comprehensive analysis of all the cases retrieved from the Roche global drug safety database reported under the SMQ (narrow) 'severe cutaneous adverse reactions' in patients who received treatment with atezolizumab as well as available data from the clinical database, literature (Zhao et al. 2018; Raschi et al. 2019; Jimenez et al. 2020), and EV database with a cut-off date of 31 July 2020 and considering the plausible mechanism of action and background of SCARs as a known class effect, a causal association between atezolizumab and SCARs has been established. As such, SCARs is updated from a potential risk to an important identified risk.

Characterisation of the risk:

See Table 65 and Table 66. There are no clinically relevant differences in the frequency of this event among all the monotherapy and the combination therapy populations. The majority of the dermatological events identified with the SMQ were Grade 1 or 2,non-serious across the IV monotherapy and combination therapy populations, and resolved by the time of the data cut-off date. Within the IMscin001 (SC monotherapy) population, two events of immune-mediated SCARs were reported, of which one was fatal. The fatal event occurred in a patient with worsening of the underlying condition of rash and pruritus, no further information was available prior to death. The other event was Grade 3, deemed related to concomitant medication by the investigator.

Risk factors and risk groups:

There are currently no known risk factors associated with the development of SCARs in atezolizumab-treated patients.

Preventability:

There are currently no reliable predictors of which individual patients may be susceptible to the development of SCARs following atezolizumab therapy. Sections 4.2 and 4.4 of the E.U. SmPC provide management guidelines to reduce the potential for negative outcomes.

Impact on the benefit-risk balance of the product:

SCARs are rare but potentially fatal skin toxicities; therefore, the impact on the individual patient is potentially significant.

Public health impact:

Given the low rates of SCARs observed in drugs of the same class, the impact on public health is expected to be low.

Table 65 Immune-Mediated Severe Cutaneous Adverse Reactions: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Severe Cutaneous Reactions

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	26 (0.6%)	16 (0.6%)	8 (0.8%)	0	2 (0.8%)
95% CI for % of patients with at least one AE	(0.41%, 0.92%)	(0.34%, 0.95%)	(0.35%, 1.60%)	(0.00%, 1.22%)	(0.10%, 2.89%)
Overall total number of events	30	20	8	0	2
No. of Patients with at least one AE by Worst Grade					
Grade 1	14 (0.3%)	9 (0.3%)	4 (0.4%)	0	0
Grade 2	7 (0.2%)	4 (0.1%)	2 (0.2%)	0	0
Grade 3	4 (<0.1%)	3 (0.1%)	1 (0.1%)	0	1 (0.4%)
Grade 4	0	0	0	0	0
Grade 5	1 (<0.1%)	0	1 (0.1%)	0	1 (0.4%)
No. of Patients with at least one Serious AE	4 (<0.1%)	2 (<0.1%)	2 (0.2%)	0	2 (0.8%)
Number of patients with at least one AE by outcome					
Fatal outcome	1 (3.8%)	0	1 (12.5%)	0	1 (50.0%)
Unresolved	6 (23.1%)	4 (25.0%)	2 (25.0%)	0	0
Recovering/Resolving	2 (7.7%)	1 (6.3%)	1 (12.5%)	0	1 (50.0%)
Recovered/Resolved	17 (65.4%)	11 (68.8%)	4 (50.0%)	0	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/
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Table 66 Immune-Mediated Severe Cutaneous Adverse Reactions Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Severe Cutaneous Reactions

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	14 (0.6%)	12 (0.8%)	0	2 (0.4%)
95% CI for % of patients with at least one AE	(0.32%, 0.97%)	(0.42%, 1.43%)	(0.00%, 0.75%)	(0.05%, 1.59%)
Overall total number of events	15	13	0	2
No. of Patients with at least one AE by Worst Grade				
Grade 1	7 (0.3%)	5 (0.3%)	0	2 (0.4%)
Grade 2	4 (0.2%)	4 (0.3%)	0	0
Grade 3	3 (0.1%)	3 (0.2%)	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
No. of Patients with at least one Serious AE	3 (0.1%)	3 (0.2%)	0	0
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	0	0	0	0
Recovering/Resolving	1 (7.1%)	1 (8.3%)	0	0
Recovered/Resolved	13 (92.9%)	11 (91.7%)	0	2 (100%)
Resolved with sequelae	0	0	0	0
Unknown outcome	0	0	0	0

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
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1.13 PERICARDIAL DISORDERS

Pericardial Disorders: Autoimmune pericarditis, cardiac tamponade, pericarditis, pericarditis constrictive, pericardial disease and pericardial effusion.

Potential mechanisms:

Inhibition of PD-L1 modifies the regulation of the immune system which may cause changes in peripheral tolerance, and can lead to immune-mediated inflammation or autoimmune-like side effects in susceptible tissues.

Evidence source(s) and strength of evidence:

Based on a comprehensive analysis of all the cases retrieved from the Roche global drug safety database reported with the PTs autoimmune pericarditis, cardiac tamponade, pericarditis, pericarditis constrictive, pericardial disease and pericardial effusion in patients who received treatment with atezolizumab as well as available data from the clinical database, FAERS and EV databases, published literature with a cut-off date of 29 April 2022 and considering the plausible mechanism of action and the class effect of similar-in-class drugs, a causal association between atezolizumab and pericardial disorders has been established.

Characterisation of the risk:

See Table 67 and Table 68. No events of pericardial disorders were observed in the IMscin001 (SC monotherapy) population. The overall incidence of pericardial disorders was low in both IV monotherapy and combination therapy populations, with a higher frequency of immune-mediated pericardial disorders observed in patients treated with atezolizumab IV monotherapy (1.2% vs 0.7%). Two fatal events (cardiac tamponade n = 1, constrictive pericarditis n = 1) were observed within the Lung IV monotherapy population, and the events occurred in patients with contributory risk factors for the development of the pericardial disorder.

Risk factors and risk groups:

The development of immune-mediated pericardial disorders may be higher in patients with lung, breast, and oesophageal carcinoma due to direct local extension to the parietal pericardium and in patients treated with chest radiotherapy (Burazor et al. 2013).

Preventability:

There are currently no reliable predictors of which individual patients may be susceptible to the development of this risk following atezolizumab therapy. Sections 4.2 and 4.4 of the E.U. SmPC provide management guidelines to reduce the potential for negative outcomes.

Impact on the benefit-risk balance of the product:

Pericardial disorders could be life-threatening; therefore, the impact on the individual patient is potentially significant.

A patient card will be provided to reduce the severity of immune-mediated pericardial disorders by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and timely intervention. This will reduce the impact of immune-mediated pericardial disorders on the benefit–risk balance of the product.

Public health impact:

Given the rarity of this event, the public health impact is expected to be minimal.

Table 67 Immune-Mediated Pericardial Disorders: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Immune-Mediated Pericardial Disorders

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	48 (1.2%)	40 (1.5%)	5 (0.5%)	1 (0.3%)	0
95% CI for % of patients with at least one AE	(0.85%, 1.53%)	(1.05%, 2.00%)	(0.17%, 1.18%)	(0.01%, 1.84%)	(0.00%, 1.48%)
Overall total number of events	55	47	5	1	0
No. of Patients with at least one AE by Worst Grade					
Grade 1	7 (0.2%)	6 (0.2%)	1 (0.1%)	0	0
Grade 2	16 (0.4%)	12 (0.4%)	3 (0.3%)	1 (0.3%)	0
Grade 3	7 (0.2%)	6 (0.2%)	1 (0.1%)	0	0
Grade 4	16 (0.4%)	14 (0.5%)	0	0	0
Grade 5	2 (<0.1%)	2 (<0.1%)	0	0	0
No. of Patients with at least one Serious AE	27 (0.6%)	22 (0.8%)	3 (0.3%)	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	2 (4.2%)	2 (5.0%)	0	0	0
Unresolved	15 (31.3%)	12 (30.0%)	3 (60.0%)	0	0
Recovering/Resolving	6 (12.5%)	5 (12.5%)	1 (20.0%)	1 (100%)	0
Recovered/Resolved	26 (54.2%)	22 (55.0%)	1 (20.0%)	0	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	1 (2.1%)	1 (2.5%)	0	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
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Table 68 Immune-Mediated Pericardial Disorders: Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Immune-Mediated Pericardial Disorders

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	16 (0.7%)	14 (1.0%)	1 (0.2%)	1 (0.2%)
95% CI for % of patients with at least one AE	(0.38%, 1.08%)	(0.52%, 1.60%)	(0.01%, 1.12%)	(0.01%, 1.23%)
Overall total number of events	20	18	1	1
No. of Patients with at least one AE by Worst Grade				
Grade 1	3 (0.1%)	2 (0.1%)	1 (0.2%)	0
Grade 2	2 (<0.1%)	2 (0.1%)	0	0
Grade 3	5 (0.2%)	4 (0.3%)	0	1 (0.2%)
Grade 4	6 (0.2%)	6 (0.4%)	0	0
Grade 5	0	0	0	0
No. of Patients with at least one Serious AE	10 (0.4%)	9 (0.6%)	0	1 (0.2%)
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	5 (31.3%)	4 (28.6%)	1 (100%)	0
Recovering/Resolving	0	0	0	0
Recovered/Resolved	10 (62.5%)	9 (64.3%)	0	1 (100%)
Resolved with sequelae	2 (12.5%)	2 (14.3%)	0	0
Unknown outcome	0	0	0	0

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
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1.14 HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Hemophagocytic lymphohistiocytosis (HLH): PT Haemophagocytic lymphohistiocytosis

Potential mechanisms:

Inhibition of PD-L1 modifies the regulation of the immune system which may cause changes in peripheral tolerance, and can lead to immune-mediated inflammation or autoimmune-like side effects.

Evidence source(s) and strength of evidence:

Based on comprehensive review of the company global safety database including HLH cases received up to 17 October 2022, considering the mechanism of action, and known class effect of similar-in-class drugs, a causal association between atezolizumab and HLH has been established.

Characterisation of the risk:

See Table 69 and Table 70. Two events of HLH were reported from one patient in the Lung IV monotherapy population (<0.1%). No events of HLH were observed in the Bladder IV monotherapy, IMscin001 (SC monotherapy), and combination therapy populations.

Risk factors and risk groups:

There are no identified risk factors for the development of HLH in atezolizumab treated patients.

Preventability:

There are currently no reliable predictors of which individual patients may be susceptible to the development of this risk following atezolizumab therapy. Sections 4.2 and 4.4 of the E.U. SmPC provide management guidelines to reduce the potential for negative outcomes.

Impact on the benefit-risk balance of the product:

HLH is a rare, severe, and potentially fatal condition associated with impaired functioning of cytotoxic T lymphocytes and natural killer cells, as well as macrophages; therefore, the impact on the individual patient is potentially significant.

A patient card will be provided to reduce the severity of HLH by informing patients and physicians about this risk as well as relevant monitoring instructions and management

guidelines, to facilitate earlier diagnosis and timely intervention. This will reduce the impact of HLH on the benefit–risk balance of the product.

Public health impact:

Given the rarity of this event, the public health impact is expected to be minimal.

Table 69 Hemophagocytic Lymphohistiocytosis: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Haemophagocytic Lymphohistiocytosis

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	1 (<0.1%)	1 (<0.1%)	0	0	0
95% CI for % of patients with at least one AE	(0.00%, 0.13%)	(0.00%, 0.20%)	(0.00%, 0.37%)	(0.00%, 1.22%)	(0.00%, 1.48%)
Overall total number of events	2	2	0	0	0
No. of Patients with at least one AE by Worst Grade					
Grade 1	0	0	0	0	0
Grade 2	0	0	0	0	0
Grade 3	0	0	0	0	0
Grade 4	1 (<0.1%)	1 (<0.1%)	0	0	0
Grade 5	0	0	0	0	0
No. of Patients with at least one Serious AE	1 (<0.1%)	1 (<0.1%)	0	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	1 (100%)	1 (100%)	0	0	0
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	1 (100%)	1 (100%)	0	0	0
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.
Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out
24JUN2024 20:15. Adapted from t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out

Table 70 Hemophagocytic Lymphohistiocytosis: Frequency, Severity, Seriousness, and Outcomes – Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Haemophagocytic Lymphohistiocytosis

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	0	0	0	0
95% CI for % of patients with at least one AE	(0.00%, 0.15%)	(0.00%, 0.25%)	(0.00%, 0.75%)	(0.00%, 0.81%)

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/
t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out
02DEC2022 22:08
Adapted from t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out.

2. INFUSION-RELATED REACTIONS

Infusion-Related Reactions: Includes two MedDRA PTs: Infusion related reaction and Cytokine release syndrome.

Potential mechanisms:

Infusion-related reactions (IRRs) are thought to be due to release of cytokines and/or other chemical mediators. Anaphylactic or hypersensitivity reactions to the IV administration of protein (e.g., mAbs) may also play a part in some patients. Despite the different possible mechanisms underlying hypersensitivity and infusion reactions, the clinical signs and symptoms of these reactions overlap (Lenz 2007).

Evidence source(s) and strength of evidence:

Clinical trial data

Characterisation of the risk:

See Table 71 and Table 72. There were no IRRs observed in the IMscin001 (SC monotherapy) population. There are no clinically relevant differences in the frequency of this event among the monotherapy and combination therapy populations, with the exception of the HCC combination therapy population, where a numerically higher rate (8.7%) was observed. IRRs within the HCC combination therapy population were primarily non-serious Grade 1 or 2 in severity, with the exception of 8 patients (1.6%) who experienced IRR events which were Grade 3 in severity. Overall, the clinical impact of IRRs in the HCC combination therapy population was considered limited.

Risk factors and risk groups:

Treatment with monoclonal antibodies is associated with an increased risk for IRRs (Keating et al. 2014; Thompson et al. 2014). There are no known risk factors associated with the development of IRRs in atezolizumab-treated patients.

Preventability:

There are currently no reliable predictors of patients who may be susceptible to IRRs, hypersensitivity, or anaphylaxis to atezolizumab. Sections 4.2 and 4.4 of the E.U. SmPC provide guidelines to appropriately manage IRRs.

Impact on the benefit-risk balance of the product:

While patients may experience considerable discomfort during an IRR, most events were mild and self-limiting, and did not require discontinuation of therapy. Therefore, the impact on the individual patient is considered to be low.

A patient card will be provided to reduce the severity of IRRs by informing patients and physicians about this risk as well as relevant monitoring instructions and management guidelines, to facilitate earlier diagnosis and timely intervention. This will reduce the impact of IRRs to the benefit–risk balance of the product.

Public health impact:

Given most patients have only experienced mild to moderate events that fully resolved and the fact that monitoring and treatment of IRRs is a routine part of oncology care, the impact on public health is considered minimal.

Table 71 Infusion-Related Reactions: Frequency, Severity, Seriousness, and Outcomes – Monotherapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

Infusion-Related Reactions

	All Patients IV (N=4156)	All Lung IV (N=2717)	All Bladder IV (N=983)	IPSOS Atezo (N=300)	IMscin001 Atezo SC (N=247)
Number of patients with at least one AE	41 (1.0%)	30 (1.1%)	11 (1.1%)	2 (0.7%)	0
95% CI for % of patients with at least one AE	(0.71%, 1.34%)	(0.75%, 1.57%)	(0.56%, 1.99%)	(0.08%, 2.39%)	(0.00%, 1.48%)
Overall total number of events	50	38	12	2	0
No. of Patients with at least one AE by Worst Grade					
Grade 1	11 (0.3%)	9 (0.3%)	2 (0.2%)	0	0
Grade 2	26 (0.6%)	17 (0.6%)	9 (0.9%)	2 (0.7%)	0
Grade 3	4 (<0.1%)	4 (0.1%)	0	0	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
No. of Patients with at least one Serious AE	6 (0.1%)	5 (0.2%)	1 (0.1%)	0	0
Number of patients with at least one AE by outcome					
Fatal outcome	0	0	0	0	0
Unresolved	0	0	0	0	0
Recovering/Resolving	1 (2.4%)	0	1 (9.1%)	0	0
Recovered/Resolved	40 (97.6%)	30 (100%)	10 (90.9%)	2 (100%)	0
Resolved with sequelae	1 (2.4%)	1 (3.3%)	0	0	0
Unknown outcome	0	0	0	0	0

Atezo = Atezolizumab, SC = Subcutaneous. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
Investigator text for AEs encoded using MedDRA v26.1.
CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. Death due to progressive disease is excluded from this summary. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.
Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/
t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out
24JUN2024 20:15
Adapted from t_ae_rmp_byrisk_RMPALL_AAG6x15_30APR2022_29872P.out

Table 72 Infusion-Related Reactions: Frequency, Severity, Seriousness, and Outcomes - Combination Therapy (Pooled)

Seriousness, Outcomes, Severity, Frequency with 95% Confidence Interval for Adverse Events of Important Identified or Potential Risks
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

Infusion-Related Reactions

	All Patients (N=2409)	Lung (N=1464)	HCC (N=493)	Breast (N=452)
Number of patients with at least one AE(n)	98 (4.1%)	50 (3.4%)	43 (8.7%)	5 (1.1%)
95% CI for % of patients with at least one AE	(3.31%, 4.94%)	(2.55%, 4.48%)	(6.38%, 11.57%)	(0.36%, 2.56%)
Overall total number of events	125	60	59	6
No. of Patients with at least one AE by Worst Grade				
Grade 1	24 (1.0%)	5 (0.3%)	18 (3.7%)	1 (0.2%)
Grade 2	55 (2.3%)	34 (2.3%)	17 (3.4%)	4 (0.9%)
Grade 3	18 (0.7%)	10 (0.7%)	8 (1.6%)	0
Grade 4	1 (<0.1%)	1 (<0.1%)	0	0
Grade 5	0	0	0	0
No. of Patients with at least one Serious AE	12 (0.5%)	8 (0.5%)	4 (0.8%)	0
Number of patients with at least one AE by outcome				
Fatal outcome	0	0	0	0
Unresolved	0	0	0	0
Recovering/Resolving	0	0	0	0
Recovered/Resolved	98 (100%)	50 (100%)	43 (100%)	5 (100%)
Resolved with sequelae	0	0	0	0
Unknown outcome	0	0	0	0

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
Investigator text for AEs encoded using MedDRA v25.0.
CI = Confidence Interval; 95% CI where computed using Clopper-Pearson method. Grades are based on NCI-CTCAE. Multiple occurences of qualifying events in a patient are counted only once at the patient's worst grade. Percentages for Number of patients with at least one AE by outcome are relative to n. All other percentages are relative to N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_rmp_byrisk.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/
t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out
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Adapted from t_ae_rmp_byrisk_RMPALL_p14659_MedDRA25x0.out.

INFORMATION ON IMPORTANT POTENTIAL RISKS

3. ATTENUATED EFFICACY OR REDUCED TOLERABILITY IN PATIENTS WITH ANTI-DRUG ANTIBODIES

Attenuated efficacy or reduced tolerability in patients with anti-drug antibodies (ADA): Data on the incidence of ADAs and their potential effect on safety were presented for the main pooled monotherapy populations for safety evaluable patients who had a post-treatment ADA status available: All IV patients, all IV Lung, and all IV Bladder in Table 74 and Table 76, and IMscin001 in Table 75 and Table 77. Data are also provided for patients in combination pool from studies (GO29537 [IMpower130], GO29436 [IMpower150], GO30081 [IMpower133], WO29522 [IMpassion130], YO40245 [IMbrave150], and GO30140) in Table 78, Table 79, and Table 80.

Potential mechanisms:

All therapeutic proteins have the potential to elicit unwanted immune responses, which may affect pharmacokinetics, pharmacodynamics, safety, and/or efficacy of the molecule to various degrees (FDA Guidance for Industry 2014; EMA Guideline 2017).

Evidence source(s) and strength of evidence:

Clinical trial data

Characterisation of the risk:

ADAs against Atezolizumab

Within the atezolizumab development program, the incidence of treatment-emergent ADAs observed across studies was variable. There was no clear pattern to explain this variability; a mix of high and low incidences was observed among patients with different tumour types and those treated with atezolizumab monotherapy, as well as in combination therapy. Immunogenicity assay results are highly dependent on several factors, including assay sensitivity and specificity, assay methodology, timing of sample collection, concomitant medications, and underlying disease.

The post-baseline incidence of treatment-emergent ADAs in the IV and SC monotherapy and combination therapy populations is presented in Table 73. No ADAs were assessed in IPSOS as pharmacokinetic sample collection was not done.

Table 73 Incidence of Treatment-Emergent ADAs in Atezolizumab Monotherapy and Combination Therapy Populations

Population	Post-Baseline incidence of ADAs
Lung monotherapy IV	34.5% (789/2290)
Bladder monotherapy IV	39.5% (355/898)
All Patients monotherapy IV	35.2% (1219/3460)
IMscin001 monotherapy SC	19.5% (43/221)
Lung combination therapy IV	30.0% (413/1377)
Breast combination therapy IV	13.1% (57/434)
HCC combination therapy IV	28.3% (134/474)
All Patients combination therapy IV	26.4% (604/2285)

ADA = anti-drug antibody; HCC = hepatocellular carcinoma; IV = intravenous; SC = subcutaneous.

Sources: Table 74, Table 75, Table 78, Table 79.

In the All Patients IV monotherapy population, the incidence of all Grade AEs, Grade 5 AEs, AEs leading to atezolizumab treatment withdrawal, AEs leading to atezolizumab dose interruption and AESIs were similar irrespective of post-baseline ADA status (negative or positive); see Table 74 and Table 76. The incidence of SAEs and Grade 3–4 AEs increased in ADA-positive patients compared with ADA-negative patients. However, no pattern or focus of events driven by any specific System Organ Class (SOC) or individual AE PT was identified. In addition, the incidence of hypersensitivity events and IRRs was low and consistent between ADA-positive and ADA-negative patients. In the IMscin001 (SC monotherapy) population, the incidence of treatment-emergent related AEs, Grade 3–4 AEs, Grade 5 AEs, SAEs, and AEs leading to atezolizumab dose modification or interruption were similar irrespective of post-baseline ADA status (negative or positive) (Table 75). The incidence of treatment-emergent related AESI decreased in ADA-positive patients compared with ADA-negative patients (Table 77).

In both Lung and Breast combination therapy populations, the incidence of all Grade AEs, Grade 3-4 AEs, Grade 5 AEs, AEs leading to treatment withdrawal, AEs leading to dose modification/interruption and AESIs was similar irrespective of post-baseline ADAs status (negative or positive); see Table 79, and Table 80. A numerically higher proportion of ADA-positive (28.1%) compared to ADA-negative (21.5%) patients experienced SAEs in the Breast combination therapy population. However, the types of SAEs were those that are commonly reported in cancer patients and were not driven by any specific SOC or individual AE preferred term. In addition, for both combination therapy populations, the incidences of IRRs and hypersensitivity were low and balanced between ADA-negative and ADA-positive patients.

In HCC combination therapy populations, there was a higher incidence of safety events in ADA-positive vs. ADA-negative patients; however, analysis of events relevant to immunogenicity (IRRs) revealed limited clinical impact on patients. Additionally, based on case review of Grade 3-4 AEs, SAEs and assessment of biological plausibility, it is unlikely that there is a relationship between ADA status and these events. The poorer baseline disease characteristics in ADA-positive patients may have attributed to the higher incidence of these events in ADA-positive compared to ADA-negative patients.

For the combination therapy (Table 80 and Table 80), IV monotherapy (Table 74 and Table 76) and IMscin001 (SC monotherapy, Table 75 and Table 77) populations, ADA status appeared to have no clinically relevant impact on safety.

ADAs against the recombinant human hyaluronidase enzyme PH20 (rHuPH20)

The SC formulation of atezolizumab contains the recombinant human hyaluronidase enzyme PH20 (rHuPH20), which is used to facilitate the dispersion and absorption of atezolizumab. In the IMscin001 (SC monotherapy) study population, the incidence of treatment-emergent anti-rHuPH20 ADAs was 5.4% and is within the range of treatment-emergent ADA incidence rates observed across other clinical trials containing rHuPH20 SC formulations (2 – 18%) (Rosengren et al. 2015, Printz et al. 2022).

Risk factors and risk groups:

Risk factors for the development of ADAs against atezolizumab and rHuPH20 (SC formulation) are currently unknown.

Preventability:

The extent to which patients may develop ADAs to atezolizumab or rHuPH20 (SC formulation) cannot be predicted or prevented. However, the detection of ADAs has not been observed to be associated with any clinically relevant impact on safety or efficacy.

Impact on the benefit-risk balance of the product:

The impact is considered minimal because the detection of ADAs has not been associated with any clinically relevant impact on safety or efficacy.

Public health impact

The impact is considered minimal because the detection of ADAs has not been associated with any clinically relevant impact on safety or efficacy.

Table 74 Overview of Safety by ADA Status (Safety-Evaluable Patients with Available Post-Treatment ADA Status) – Monotherapy IV (Pooled)

Overview of Adverse Events, by ADA Status
Safety Evaluable Patients
Protocols: GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

	All Patients IV (N=3460)		All Lung IV (N=2290)		All Bladder IV (N=898)	
	ADA- (N=2241)	ADA+ (N=1219)	ADA- (N=1501)	ADA+ (N=789)	ADA- (N=543)	ADA+ (N=355)
Total number of patients with at least one AE	2145 (95.7%)	1174 (96.3%)	1421 (94.7%)	752 (95.3%)	531 (97.8%)	347 (97.7%)
Total number of events	22231	12375	13493	6994	6001	4043
Total number of patients with at least one						
Treatment-related AE	1587 (70.8%)	857 (70.3%)	1039 (69.2%)	534 (67.7%)	397 (73.1%)	261 (73.5%)
Grade 3-4 AE	884 (39.4%)	563 (46.2%)	498 (33.2%)	314 (39.8%)	286 (52.7%)	204 (57.5%)
Treatment-related Grade 3-4 AE	327 (14.6%)	192 (15.8%)	188 (12.5%)	114 (14.4%)	114 (21.0%)	58 (16.3%)
Grade 5 AE	61 (2.7%)	36 (3.0%)	38 (2.5%)	22 (2.8%)	20 (3.7%)	13 (3.7%)
Treatment-related Grade 5 AE	4 (0.2%)	5 (0.4%)	2 (0.1%)	3 (0.4%)	2 (0.4%)	2 (0.6%)
Serious AE	747 (33.3%)	483 (39.6%)	435 (29.0%)	284 (36.0%)	236 (43.5%)	169 (47.6%)
Treatment-related serious AE	217 (9.7%)	138 (11.3%)	129 (8.6%)	84 (10.6%)	73 (13.4%)	44 (12.4%)
AE leading to any Study Treatment discontinuation	174 (7.8%)	104 (8.5%)	128 (8.5%)	77 (9.8%)	36 (6.6%)	23 (6.5%)
AE leading to any Dose modification or Study Treatment interruption	626 (27.9%)	380 (31.2%)	419 (27.9%)	236 (29.9%)	165 (30.4%)	120 (33.8%)

Atezo = Atezolizumab. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
ADA=Anti-Drug Antibodies, -=Negative, +=Positive. MO29872(IPSOS) did not collect ADA data.
Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v26.1. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. All treatment emergent AEs are included. For the counts in the rows by grade, the patients are counted once at the highest grade.

Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_sum.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/t_ae_sum_RMP1_A_byada_30APR2022_29872P.out
24JUN2024 19:58 Page 1 of 1

Table 75 Overview of Safety by ADA Status (Safety-Evaluable Patients with Available Post-Treatment ADA Status) – Monotherapy

Overview of Adverse Events, by ADA Status
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

	All Patients IV (N=3460)		IMSCIN001 Atezo SC (N=221)	
	ADA- (N=2241)	ADA+ (N=1219)	ADA- (N=178)	ADA+ (N=43)
Total number of patients with at least one AE	2145 (95.7%)	1174 (96.3%)	159 (89.3%)	40 (93.0%)
Total number of events	22231	12375	898	203
Total number of patients with at least one				
Treatment-related AE	1587 (70.8%)	857 (70.3%)	84 (47.2%)	18 (41.9%)
Grade 3-4 AE	884 (39.4%)	563 (46.2%)	38 (21.3%)	9 (20.9%)
Treatment-related Grade 3-4 AE	327 (14.6%)	192 (15.8%)	10 (5.6%)	1 (2.3%)
Grade 5 AE	61 (2.7%)	36 (3.0%)	7 (3.9%)	2 (4.7%)
Treatment-related Grade 5 AE	4 (0.2%)	5 (0.4%)	1 (0.6%)	0
Serious AE	747 (33.3%)	483 (39.6%)	33 (18.5%)	8 (18.6%)
Treatment-related serious AE	217 (9.7%)	138 (11.3%)	4 (2.2%)	0
AE leading to any Study Treatment discontinuation	174 (7.8%)	104 (8.5%)	3 (1.7%)	0
AE leading to any Dose modification or Study Treatment interruption	626 (27.9%)	380 (31.2%)	66 (37.1%)	11 (25.6%)

Atezo = Atezolizumab, SC = Subcutaneous. All Patients IV: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS).
ADA=Anti-Drug Antibodies, -=Negative, +=Positive. MO29872(IPSOS) did not collect ADA data.
Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v26.1. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. All treatment emergent AEs are included. For the counts in the rows by grade, the patients are counted once at the highest grade.

Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_sum.sas
Output: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/output/t_ae_sum_RMP2_A_byada_30APR2022_29872P.out
24JUN2024 20:02 Page 1 of 1

Table 76 Overview of Safety by ADA Status (Safety-Evaluable Patients with Available Post-Treatment ADA Status) for Monotherapy IV – Adverse Events of Special Interest (Pooled)

Overview of Adverse Events of Special Interest for Atezolizumab, by ADA Status
Safety Evaluable Patients
Protocols: GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

	All Patients IV (N=3460)		All Lung IV (N=2290)		All Bladder IV (N=898)	
	ADA- (N=2241)	ADA+ (N=1219)	ADA- (N=1501)	ADA+ (N=789)	ADA- (N=543)	ADA+ (N=355)
Total number of patients with at least one AE of Special Interest	886 (39.5%)	487 (40.0%)	614 (40.9%)	321 (40.7%)	186 (34.3%)	127 (35.8%)
Total number of events	1734	984	1174	642	381	264
Total number of patients with at least one						
Treatment-related AE of Special Interest	670 (29.9%)	360 (29.5%)	469 (31.2%)	239 (30.3%)	139 (25.6%)	95 (26.8%)
Grade 3-4 AE of Special Interest	176 (7.9%)	112 (9.2%)	108 (7.2%)	73 (9.3%)	48 (8.8%)	29 (8.2%)
Treatment-related Grade 3-4 AE of Special Interest	124 (5.5%)	77 (6.3%)	78 (5.2%)	50 (6.3%)	37 (6.8%)	19 (5.4%)
Grade 5 AE of Special Interest	3 (0.1%)	3 (0.2%)	3 (0.2%)	2 (0.3%)	0	1 (0.3%)
Treatment-related Grade 5 AE of Special Interest	1 (<0.1%)	3 (0.2%)	1 (<0.1%)	2 (0.3%)	0	1 (0.3%)
Serious AE of Special Interest	121 (5.4%)	67 (5.5%)	83 (5.5%)	48 (6.1%)	31 (5.7%)	16 (4.5%)
Treatment-related Serious AE of Special Interest	99 (4.4%)	52 (4.3%)	66 (4.4%)	37 (4.7%)	27 (5.0%)	13 (3.7%)
AE of Special Interest leading to any Study Treatment discontinuation	71 (3.2%)	40 (3.3%)	60 (4.0%)	31 (3.9%)	9 (1.7%)	6 (1.7%)

Atezo = Atezolizumab. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
ADA=Anti-Drug Antibodies, -=Negative, +=Positive. MO29872(IPSOS) did not collect ADA data.
Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v26.1. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. All treatment emergent AEs are included. For the counts in the rows by grade, the patients are counted once at the highest grade.

Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_si_sum.sas
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Table 76 Overview of Safety by ADA Status (Safety-Evaluable Patients with Available Post-Treatment ADA Status) for Monotherapy IV– Adverse Events of Special Interest (Pooled) (cont.)

Overview of Adverse Events of Special Interest for Atezolizumab, by ADA Status
Safety Evaluable Patients
Protocols: GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

	All Patients IV (N=3460)		All Lung IV (N=2290)		All Bladder IV (N=898)	
	ADA- (N=2241)	ADA+ (N=1219)	ADA- (N=1501)	ADA+ (N=789)	ADA- (N=543)	ADA+ (N=355)
Total number of patients with at least one AE of Special Interest leading to any Dose modification or Study Treatment interruption	177 (7.9%)	109 (8.9%)	127 (8.5%)	78 (9.9%)	41 (7.6%)	25 (7.0%)
AE of Special Interest Requiring the Use of Systemic Corticosteroids	190 (8.5%)	118 (9.7%)	135 (9.0%)	76 (9.6%)	42 (7.7%)	33 (9.3%)

Atezo = Atezolizumab. All Lung IV: GO27831(PCD4989g NSCLC Cohort) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS); All Bladder IV: GO27831(PCD4989g UC Cohort) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211); All Patients IV: Lung IV + Bladder IV + GO27831(non-UC/non-NSCLC cohort).
ADA=Anti-Drug Antibodies, -=Negative, +=Positive. MO29872(IPSOS) did not collect ADA data.
Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v26.1. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. All treatment emergent AEs are included. For the counts in the rows by grade, the patients are counted once at the highest grade.

Clinical cut-off dates: GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_si_sum.sas
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Adapted from t_ae_si_sum_RMP1_A_byada_AAG6x15_30APR2022_29872P.out

Table 77 Overview of Safety by ADA Status (Safety-Evaluable Patients with Available Post-Treatment ADA Status) for Monotherapy – Adverse Events of Special Interest

Overview of Adverse Events of Special Interest for Atezolizumab, by ADA Status
Safety Evaluable Patients
Protocols: BP40657, GO27831, GO28625, GO28753, GO28754, GO28915, GO29293, GO29294, GO29431, GO29527, MO29872

	All Patients IV (N=3460)		IMSCIN001 Atezo SC (N=221)	
	ADA- (N=2241)	ADA+ (N=1219)	ADA- (N=178)	ADA+ (N=43)
Total number of patients with at least one AE of Special Interest	886 (39.5%)	487 (40.0%)	64 (36.0%)	9 (20.9%)
Total number of events	1734	984	127	24
Total number of patients with at least one				
Treatment-related AE of Special Interest	670 (29.9%)	360 (29.5%)	50 (28.1%)	6 (14.0%)
Grade 3-4 AE of Special Interest	176 (7.9%)	112 (9.2%)	9 (5.1%)	1 (2.3%)
Treatment-related Grade 3-4 AE of Special Interest	124 (5.5%)	77 (6.3%)	6 (3.4%)	0
Grade 5 AE of Special Interest	3 (0.1%)	3 (0.2%)	1 (0.6%)	0
Treatment-related Grade 5 AE of Special Interest	1 (<0.1%)	3 (0.2%)	1 (0.6%)	0
Serious AE of Special Interest	121 (5.4%)	67 (5.5%)	4 (2.2%)	0
Treatment-related Serious AE of Special Interest	99 (4.4%)	52 (4.3%)	3 (1.7%)	0
AE of Special Interest leading to any Study Treatment discontinuation	71 (3.2%)	40 (3.3%)	1 (0.6%)	0
AE of Special Interest leading to any Dose modification or Study Treatment interruption	177 (7.9%)	109 (8.9%)	14 (7.9%)	1 (2.3%)
AE of Special Interest Requiring the Use of Systemic Corticosteroids	190 (8.5%)	118 (9.7%)	14 (7.9%)	1 (2.3%)

Atezo = Atezolizumab, SC = Subcutaneous. All Patients IV: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + GO29431(IMPOWER110) + GO29527(IMPOWER010) + MO29872(IPSOS).
ADA=Anti-Drug Antibodies, -=Negative, +=Positive. MO29872(IPSOS) did not collect ADA data.
Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v26.1. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. All treatment emergent AEs are included. For the counts in the rows by grade, the patients are counted once at the highest grade.

Clinical cut-off dates: BP40657:16JAN2023, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, MO29872:30APR2022.

Program: root/clinical_studies/RO5541267/CDT80009/MO29872/data_analysis/ICSD_RMP/prod/program/t_ae_si_sum.sas
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Table 78 Overview of Safety by ADA Status (Safety-Evaluable Patients with Available Post-Treatment ADA Status) - Combination therapy (Pooled)

Overview of Adverse Events, by ADA Status
ADA Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

	All Patients (N=2285)	
	ADA- (N=1681)	ADA+ (N=604)
Total number of patients with at least one AE	1663 (98.9%)	598 (99.0%)
Total number of events	25472	8129
Total number of patients with at least one		
Treatment-related AE	1580 (94.0%)	567 (93.9%)
Atezo-related AE	1266 (75.3%)	448 (74.2%)
Grade 3-4 AE	1023 (60.9%)	386 (63.9%)
Treatment-related Grade 3-4 AE	846 (50.3%)	313 (51.8%)
Atezo-related Grade 3-4 AE	424 (25.2%)	162 (26.8%)
Grade 5 AE	45 (2.7%)	21 (3.5%)
Treatment-related Grade 5 AE	16 (1.0%)	8 (1.3%)
Atezo-related Grade 5 AE	11 (0.7%)	6 (1.0%)
Serious AE	598 (35.6%)	265 (43.9%)
Treatment-related serious AE	302 (18.0%)	145 (24.0%)
Atezo-related serious AE	200 (11.9%)	94 (15.6%)
AE leading to any Study Treatment withdrawal	309 (18.4%)	138 (22.8%)
AE leading to Atezo withdrawal	141 (8.4%)	74 (12.3%)
AE leading to any Dose modification or Study Treatment interruption	999 (59.4%)	389 (64.4%)
AE leading to Atezo interruption	744 (44.3%)	299 (49.0%)

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
ADA=Anti-Drug Antibodies, -=Negative, +=Positive.
Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v25.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. All treatment emergent AEs are included. For the counts in the rows by grade,the patients are counted once at the highest grade.
Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_sum.sas
Output: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/output/
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Adapted from t_ae_sum_RMPALL_A_byada_p14659_MedDRA25x0.out.

Table 79 Overview of Safety by ADA Status (Safety-Evaluable Patients with Available Post-Treatment ADA Status) - Combination Therapy (Stratified by Indications)

Overview of Adverse Events, by ADA Status
ADA Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

	Lung (N=1377)		Breast (N=434)		HCC (N=474)	
	ADA- (N=964)	ADA+ (N=413)	ADA- (N=377)	ADA+ (N=57)	ADA- (N=340)	ADA+ (N=134)
Total number of patients with at least one AE	958 (99.4%)	410 (99.3%)	374 (99.2%)	57 (100%)	331 (97.4%)	131 (97.8%)
Total number of events	15725	6005	6500	830	3247	1294
Total number of patients with at least one						
Treatment-related AE	931 (96.6%)	400 (96.9%)	369 (97.9%)	53 (93.0%)	280 (82.4%)	114 (85.1%)
Atezo-related AE	702 (72.8%)	301 (72.9%)	314 (83.3%)	42 (73.7%)	250 (73.5%)	105 (78.4%)
Grade 3-4 AE	672 (69.7%)	279 (67.6%)	181 (48.0%)	28 (49.1%)	170 (50.0%)	79 (59.0%)
Treatment-related Grade 3-4 AE	583 (60.5%)	240 (58.1%)	152 (40.3%)	23 (40.4%)	111 (32.6%)	50 (37.3%)
Atezo-related Grade 3-4 AE	263 (27.3%)	113 (27.4%)	88 (23.3%)	14 (24.6%)	73 (21.5%)	35 (26.1%)
Grade 5 AE	30 (3.1%)	11 (2.7%)	4 (1.1%)	1 (1.8%)	11 (3.2%)	9 (6.7%)
Treatment-related Grade 5 AE	11 (1.1%)	4 (1.0%)	1 (0.3%)	0	4 (1.2%)	4 (3.0%)
Atezo-related Grade 5 AE	7 (0.7%)	3 (0.7%)	1 (0.3%)	0	3 (0.9%)	3 (2.2%)
Serious AE	410 (42.5%)	182 (44.1%)	81 (21.5%)	16 (28.1%)	107 (31.5%)	67 (50.0%)
Treatment-related serious AE	210 (21.8%)	100 (24.2%)	45 (11.9%)	9 (15.8%)	47 (13.8%)	36 (26.9%)
Atezo-related serious AE	131 (13.6%)	62 (15.0%)	32 (8.5%)	9 (15.8%)	37 (10.9%)	23 (17.2%)
AE leading to any Study Treatment withdrawal	202 (21.0%)	104 (25.2%)	60 (15.9%)	10 (17.5%)	47 (13.8%)	24 (17.9%)
AE leading to Atezo withdrawal	95 (9.9%)	54 (13.1%)	22 (5.8%)	6 (10.5%)	24 (7.1%)	14 (10.4%)
AE leading to any Dose modification or Study Treatment interruption	677 (70.2%)	287 (69.5%)	179 (47.5%)	29 (50.9%)	143 (42.1%)	73 (54.5%)
AE leading to Atezo interruption	523 (54.3%)	219 (53.0%)	115 (30.5%)	22 (38.6%)	106 (31.2%)	55 (41.0%)

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
ADA=Anti-Drug Antibodies, -=Negative, +=Positive.
Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v25.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. All treatment emergent AEs are included. For the counts in the rows by grade,the patients are counted once at the highest grade.
Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_sum.sas
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13DEC2022 7:49 Adapted from t_ae_sum_RMPALL_A_byada_p14659_MedDRA25x0.out.

Table 80 Overview of Safety by ADA Status (Safety-Evaluable Patients with Available Post-Treatment ADA Status) for Combination Therapy – Adverse Events of Special Interest

Overview of Adverse Events of Special Interest, by ADA Status
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

	All Patients (N=2285)		Lung (N=1377)		HCC (N=474)		Breast (N=434)	
	ADA- (N=1681)	ADA+ (N=604)	ADA- (N=964)	ADA+ (N=413)	ADA- (N=340)	ADA+ (N=134)	ADA- (N=377)	ADA+ (N=57)
Total number of patients with at least one AESI	904 (53.8%)	327 (54.1%)	462 (47.9%)	210 (50.8%)	218 (64.1%)	87 (64.9%)	224 (59.4%)	30 (52.6%)
Total number of events	1876	696	895	428	522	199	459	69
Total number of patients with at least one								
Treatment-related AESI	722 (43.0%)	265 (43.9%)	377 (39.1%)	172 (41.6%)	161 (47.4%)	67 (50.0%)	184 (48.8%)	26 (45.6%)
Atezo-related AESI	663 (39.4%)	246 (40.7%)	347 (36.0%)	158 (38.3%)	155 (45.6%)	62 (46.3%)	161 (42.7%)	26 (45.6%)
Grade 3-4 AESI	178 (10.6%)	96 (15.9%)	83 (8.6%)	52 (12.6%)	64 (18.8%)	40 (29.9%)	31 (8.2%)	4 (7.0%)
Treatment-related Grade 3-4 AESI	131 (7.8%)	61 (10.1%)	69 (7.2%)	37 (9.0%)	35 (10.3%)	22 (16.4%)	27 (7.2%)	2 (3.5%)
Atezo-related Grade 3-4 AESI	119 (7.1%)	58 (9.6%)	64 (6.6%)	35 (8.5%)	31 (9.1%)	21 (15.7%)	24 (6.4%)	2 (3.5%)
Grade 5 AESI	7 (0.4%)	3 (0.5%)	2 (0.2%)	1 (0.2%)	4 (1.2%)	2 (1.5%)	1 (0.3%)	0
Treatment-related Grade 5 AESI	5 (0.3%)	3 (0.5%)	2 (0.2%)	1 (0.2%)	2 (0.6%)	2 (1.5%)	1 (0.3%)	0
Atezo-related Grade 5 AESI	5 (0.3%)	3 (0.5%)	2 (0.2%)	1 (0.2%)	2 (0.6%)	2 (1.5%)	1 (0.3%)	0
Serious AESI	114 (6.8%)	60 (9.9%)	57 (5.9%)	37 (9.0%)	41 (12.1%)	20 (14.9%)	16 (4.2%)	3 (5.3%)

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
ADA=Anti-Drug Antibodies, -=Negative, +=Positive.
AESI=Adverse Events of Special Interest. Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v25.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. All treatment emergent AEs are included. For the counts in the rows by grade,the patients are counted once at the highest grade.
Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

Program: root/clinical_studies/RO5541267/CDPT7692/GO27831/data_analysis/ICSD_MedDRA250/prod/program/t_ae_si_sum.sas
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Adapted from t_ae_si_sum_RMPALL_A_byada_p14659_AAG6x12_MedDRA25x0.out.

Table 80 Overview of Safety by ADA Status (Safety-Evaluable Patients with Available Post-Treatment ADA Status) for Combination Therapy – Adverse Events of Special Interest (contd.)

Overview of Adverse Events of Special Interest, by ADA Status
Safety Evaluable Patients
Protocols: GO29436, GO29537, GO30081, GO30140, WO29522, YO40245

	All Patients (N=2285)		Lung (N=1377)		HCC (N=474)		Breast (N=434)	
	ADA- (N=1681)	ADA+ (N=604)	ADA- (N=964)	ADA+ (N=413)	ADA- (N=340)	ADA+ (N=134)	ADA- (N=377)	ADA+ (N=57)
Total number of patients with at least one								
Treatment-related Serious AESI	84 (5.0%)	42 (7.0%)	50 (5.2%)	28 (6.8%)	20 (5.9%)	11 (8.2%)	14 (3.7%)	3 (5.3%)
Atezo-related Serious AESI	78 (4.6%)	41 (6.8%)	48 (5.0%)	28 (6.8%)	17 (5.0%)	10 (7.5%)	13 (3.4%)	3 (5.3%)
AESI leading to any Study Treatment withdrawal	68 (4.0%)	29 (4.8%)	37 (3.8%)	21 (5.1%)	21 (6.2%)	7 (5.2%)	10 (2.7%)	1 (1.8%)
AESI leading to Atezo withdrawal	55 (3.3%)	26 (4.3%)	34 (3.5%)	18 (4.4%)	14 (4.1%)	7 (5.2%)	7 (1.9%)	1 (1.8%)
AESI leading to any Dose modification or Study Treatment interruption	215 (12.8%)	89 (14.7%)	115 (11.9%)	57 (13.8%)	53 (15.6%)	26 (19.4%)	47 (12.5%)	6 (10.5%)
AESI leading to Atezo interruption	0	0	0	0	0	0	0	0
AESI Requiring the Use of Systemic Corticosteroids	212 (12.6%)	92 (15.2%)	127 (13.2%)	68 (16.5%)	35 (10.3%)	17 (12.7%)	50 (13.3%)	7 (12.3%)

Lung: GO29436(IMPOWER150 Arm A+B) + GO29537(IMPOWER130 Arm A) + GO30081(IMPOWER133 ARM A). HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Breast: WO29522(IMPASSION130 Arm A). All Patients = Lung + HCC + Breast.
ADA=Anti-Drug Antibodies, -=Negative, +=Positive.
AESI=Adverse Events of Special Interest. Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v25.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. All treatment emergent AEs are included. For the counts in the rows by grade,the patients are counted once at the highest grade.
Clinical cut-off dates: GO29436:22JAN2018, GO29537:15MAR2018, GO30081:24APR2018, GO30140:14JUN2019, WO29522:17APR2018, YO40245:29AUG2019.

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4. EMBRYO-FETAL TOXICITY

Embryo-fetal Toxicity: Pregnancy and neonatal topics (SMQ)

Potential Mechanisms:

Several nonclinical studies have demonstrated that the PD-L1/ PD-1 signalling pathway is critical in establishing and maintaining maternal/fetal tolerance, which is essential for embryo-fetal survival during gestation (Guleria et al. 2005; Habicht et al. 2007; D'Addio et al. 2011). Inhibition of the PD-L1/PD 1 pathway has not been reported to result in teratogenic effects and syngeneic homozygous knockout foetuses (PD-L1 or PD-1 knockouts) develop normally and have not shown skeletal or visceral defects. Administration of atezolizumab is expected to have an adverse effect on pregnancy via modulation of maternal/fetal tolerance, and poses a risk to the human foetus, including embryo-lethality via an increased risk of immune mediated rejection.

Evidence source(s) and strength of evidence:

Literature and nonclinical studies (see PART II: MODULE SII).

Characterisation of the risk:

Three pregnancies, including one case from IMpower130, have been reported from across the clinical development program in female patients exposed to atezolizumab. None of these pregnancies were carried to term.

Risk factors and risk groups:

The at-risk group for experiencing atezolizumab-related embryo-fetal toxicity includes female patients of child-bearing potential and developing foetuses who are exposed to atezolizumab during gestation.

Preventability:

The E.U. SmPC recommends the use of effective contraception in female patients of childbearing potential during treatment with atezolizumab, and up to 5 months after the last dose.

Impact on the benefit-risk balance of the product:

The need to avoid pregnancy during and for at least 5 months following atezolizumab treatment may have an impact on the individual patient's quality of life. However, most cancer therapies are associated with significant risks on the developing foetus and pregnancy can easily be avoided via the use of appropriate contraception. As described in Section SI (Part II), lung and bladder cancer mainly occur in older adults with the mean age at diagnosis of >70 years. Patients in the proposed indications will not be subjected to any effects of this potential risk and the impact on the individual patient is considered low.

Public health impact

The public health impact associated with this safety concern is considered to be low. Pregnancies are usually contraindicated in patients with advanced malignancy due to the risks of chemotherapy, targeted agents, and other immunotherapy drugs.

SVII.3.2. Presentation of the Missing Information

Not applicable.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 81 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Immune-mediated adverse reactions Infusion-related reactions
Important potential risks	Attenuated efficacy or reduced tolerability in patients with anti-drug antibodies Embryo-fetal toxicity
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

There are no ongoing routine pharmacovigilance activities beyond adverse reactions reporting and signal detection for atezolizumab.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities are considered by the MAH to be sufficient to obtain and analyse relevant post-marketing safety data for all safety concerns with the aim to fully assess the safety of atezolizumab.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 82 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
There are no Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
There are no Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Category 3 - Required additional pharmacovigilance activities				
There are no Required additional pharmacovigilance activities.				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table 83 Planned and ongoing post-authorisation imposed efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1 ROUTINE RISK MINIMISATION MEASURES

Table 84 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Immune-mediated adverse reactions	**Proposed measures are described in the E.U. SmPC under the following sections:** Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Immune-mediated adverse reaction monitoring guidelines in SmPC Section 4.4 Relevant information for patients provided in PIL **Other risk minimisation measures beyond the Product Information:** None
Infusion-related reactions	**Proposed measures are described in the E.U. SmPC under the following sections:** Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Infusion-related reactions monitoring guidelines in SmPC Section 4.4 Relevant information for patients provided in PIL **Other risk minimisation measures beyond the Product Information:** None

Safety concern	Routine risk minimisation activities
Attenuated efficacy or reduced tolerability in patients with anti-drug antibodies	**Proposed measures are described in the E.U. SmPC under the following sections:** Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** None
Embryo-fetal toxicity	**Proposed measures are described in the E.U. SmPC under the following sections:** Section 4.6 Fertility, pregnancy and lactation Section 5.3 Preclinical safety data **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Relevant information for patients provided in PIL **Other risk minimisation measures beyond the Product Information:** None

E.U.=European Union; PIL=patient information leaflet; SmPC=Summary of Product Characteristics.

V.2. ADDITIONAL RISK MINIMISATION MEASURES

Table 85 Additional Risk Minimisation Measures

Additional Risk Minimisation Measures	Patient Card
Objectives	Patient cards will promote awareness among patients and are intended to help minimise the risk in the following important identified immune-mediated risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, myelitis, meningoencephalitis, myocarditis, nephritis, myositis, pericardial disorders, and HLH in clinical practice; the same applies to infusion-related reactions.
Rationale for the additional risk minimisation activity	Patient cards will enable patient awareness of side effects and early recognition of immune-mediated events supporting risk minimisation. These materials are specific to the European Union.
Target audience and planned distribution path	Patients will receive a Patient Card to educate the patient about the signs and symptoms of important identified immune-mediated adverse reactions and the need to report them immediately to their health care provider. Additional instructions will be provided to the patient on the importance of carrying the Patient Card with them at all times and show it to any healthcare professional who may treat them.
Plans for evaluating the effectiveness of the interventions and criteria for success	Process indicators: Distribution metrics of the Patient Cards through the internal RMP implementation process. Outcome indicators: Review of reporting rates for serious instances of the important identified immune-mediated risks (pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, myelitis, meningoencephalitis, myocarditis, nephritis, myositis, pericardial disorders, and HLH); and of infusion-related reactions over the PBRER reporting period.
Immune-mediated SCARs	
Additional Risk Minimisation Measures	Direct Healthcare Professional Communication (DHPC)
Objectives	To communicate the identified risk of immune-mediated Severe Cutaneous Adverse Reactions with Tecentriq (atezolizumab).
Rationale for the additional risk minimisation activity	A one-off DHPC was disseminated in March 2021 to inform healthcare professionals that, following a review of the totality of evidence, immune-mediated SCARs which were previously known to be potentially associated with the use of Tecentriq (atezolizumab), are now considered to be an identified risk.

Target audience and planned distribution path	Prescribing Physicians, for example, Oncologists, Nurses and Pharmacists as per country-specific distribution channels, wholesalers, hospitals, and Oncology clinics, according to local regulations.
Plans for evaluating the effectiveness of the interventions and criteria for success	Metrics on the distribution and receipt of the DHPC were taken to assess the effectiveness of this risk minimisation activity

DHPC = Direct Healthcare Professional Communication; HLH = hemophagocytic lymphohistiocytosis; PBRER = Periodic Benefit Risk Evaluation Report; RMP = Risk Management Plan; SCAR = severe cutaneous adverse reaction.

V.3 SUMMARY OF RISK MINIMISATION MEASURES

Table 86 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Immune-mediated adverse reactions	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimisation measures:** • Patient cards (all immune-mediated adverse reactions excluding SCARs) • SCARs**:** A one-off DHPC was disseminated in March 2021 to inform healthcare professionals that immune-mediated SCARs, which were previously known to be potentially associated with use of Tecentriq (atezolizumab), are now considered to be an identified risk.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** SCARs: Metrics on the distribution and receipt of the DHPC were taken to assess the effectiveness of this risk minimisation activity.
Infusion-related reactions	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections:	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimisation measures:** Patient cards	**Additional pharmacovigilance activities:** None
Attenuated efficacy or reduced tolerability in patients with anti-drug antibodies	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.8 Undesirable effects **No additional risk minimisation measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Embryo-fetal toxicity	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.6 Fertility, pregnancy and lactation Section 5.3 Preclinical safety data Relevant information for patient in PIL **No additional risk minimisation measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

DHPC = Direct Healthcare Professional Communication; E.U. = European Union; PIL = patient information leaflet; SCAR = severe cutaneous adverse reaction; SmPC = Summary of Product Characteristics.

BIBLIOGRAPHY

Aarts MJ, Aerts JG, van den Borne BE, et al. Comorbidity in Patients with Small-Cell Lung Cancer: Trends and Prognostic Impact. Clin Lung Cancer. 2015 Jul;16(4):282-91.

Abdel-Rahman O. Changing epidemiology of elderly small cell lung cancer patients over the last 40 years; a SEER database analysis. Clin Respir J. 2018 Mar;12(3):1093-1099.

Akada K, Koyama N, Taniguchi S, et al. Database analysis of patients with hepatocellular carcinoma and treatment flow in early and advanced stages. Pharmacol Res Perspect. 2019 Jun 20;7(4):e00486.

American Cancer Society. Cancer Facts and Figures 2014. Atlanta: American Cancer Society; 2014.

American Cancer Society; Breast Cancer Facts and Figures 2017-2018. Atlanta: American Cancer Society; 2017

American Cancer Society; Cancer Facts and Figures 2018. Atlanta: American Cancer Society; 2018.

American Cancer Society, Cancer Facts and Figures 2019. From https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf. Accessed on 8 November 2019.

American Cancer Society 2021:American Cancer Society. Lung Cancer Overview. Available from:https://www.cancer.org/cancer/lung-cancer/about/what-is.html. Accessed on 10 April 2021.

Anders CK and Carey LA. Biology, metastatic patterns, and treatment of patients with triple-negative breast cancer. Clin Breast Cancer. 2009 Jun;9 Suppl 2:S73-81.

Barber DL, Mayer-Barber KD, Feng CG, et al. CD4 T cells promote rather than control tuberculosis in the absence of PD-1–mediated inhibition. J Immunol 2011;186:1 – 10.

Bauer KR, Brown M, Cress RD, et al. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer. 2007 May 1;109(9):1721-8

Beach JE, Blair AMJN, Pirani CL, et al. An unusual form of proliferative arteriopathy in macaque monkeys (Macacca sps). Exp Molec Pathol. 1974;21:322 – 38.

Bellmunt J, Orsola A, Leow JJ, et al. Bladder cancer: ESMO practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(3):iii40-iii48.

Bellmunt J, Thedore 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(27):4454 – 61.

Belot A, Fowler H, Njagi EN, et al. Association between age, deprivation and specific comorbid conditions and the receipt of major surgery in patients with non-small cell lung cancer in England: A population-based study. Thorax. 2019 Jan;74(1):51-59.

Benson AB, D'Angelica MI, Abbott DE, et al. Guidelines Insights: Hepatobiliary Cancers, Version 2.2019. J Natl Compr Canc Netw. 2019 Apr 1;17(4):302-310.

Boyle P. Triple-negative breast cancer: epidemiological considerations and recommendations. Ann Oncol. 2012 Aug;23 Suppl 6:vi7-12

Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424.

Bray F, Ren JS, Masuyer E, e al. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer 2013; 132(5):1133 – 45.

Brewster AM, Chavez-MacGregor M, Brown P. Epidemiology, biology, and treatment of triple-negative breast cancer in women of African ancestry. Lancet Oncol. 2014 Dec;15(13):e625-34

Bruno G, Runzo C, Cavallo-Perin P, et al. Incidence of type 1 and type 2 diabetes in adults aged 30-49 years. Diabetes Care 2005;28(11):2613 – 19.

Burazor I, Imazio M, Markel G, et al. Malignant pericardial effusion. Cardiology. 2013;124:224-32.

Burger RA, Brady MF, Rhee J, et al. Independent radiologic review of the gynecologic oncology group study 0218, a phase III trial of bevacizumab in the primary treatment of advanced epithelial ovarian, primary peritoneal, or fallopian tube cancer. Gynecol Oncol. 2013;131:21 – 26.

Cancer Facts and Figures 2020. American Cancer Society. Available From https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.

Chamanza R, Parry NMA, Rogerson P, et al. Spontaneous lesions of the cardiovascular system in purpose-bred laboratory nonhuman primates. Toxicol Pathol. 2006;34:357 – 63.

Chavan S, Bray F, Lortet-Tieulent J, et al. International Variations in Bladder Cancer Incidence and Mortality. European Urology 2014;66:59 – 73.

Cortet M, Bertaut A, Molinié F, et al. Trends in molecular subtypes of breast cancer: description of incidence rates between 2007 and 2012 from three French registries. BMC Cancer. 2018 Feb 7;18(1):161

D'Addio F, Riella LV, Mfarrej BG, et al. The link between the PDL1 costimulatory pathway and Th17 in fetomaternal tolerance. J Immunol. 2011;187:4530 – 41.

de Jong WK, Schaapveld M, Blaauwgeers JL, Groen HJ. Pulmonary tumours in the Netherlands: focus on temporal trends in histology and stage and on rare tumours. Thorax. 2008 Dec;63(12):1096-102.

Dent R, Trudeau M, Pritchard KI et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007 Aug 1;13(15 Pt 1):4429-34

DeSantis CE, Fedewa SA, Goding Sauer A, et al. Breast cancer statistics, 2015: Convergence of incidence rates between black and white women. CA Cancer J Clin. 2016 Jan-Feb;66(1):31-42

Dobruch J, Daneshmand S, Fisch M, et al. Gender and Bladder Cancer: A Collaborative Review of Etiology, Biology, and Outcomes. European Urology 2016;69:300 – 10.

Dores GM, Qubaiah O, Mody A, Ghabach B, Devesa SS. A population-based study of incidence and patient survival of small cell carcinoma in the United States, 1992-2010. BMC Cancer. 2015 Mar 27;15:185.

EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. European Association of Urology. 2017: 1-76.

Edwards BK, Noone AM, Mariotto AB, et al. Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. Cancer. 2014;120(9):1290–314.

Eskandar A, Ahmed A, Daughtey M, et al. Racial and sex differences in presentation and outcomes of small cell lung cancer in the United States: 1973 to 2010. Chest. 2015 Apr;147(4):e164-e165.

Ettinger DS, Wood DE, Aisner DL, et al. Non–Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2022;20(5):497–530.

European Cancer Information System-ECIS 2020. European Commission. From https://ecis.jrc.ec.europa.eu. Accessed on 12 March 2021.

European Commission; ECIS - European Cancer Information System. From https://ecis.jrc.ec.europa.eu. Accessed on 27 June 2018.European Commission; ECIS - European Cancer Information System. From https://ecis.jrc.ec.europa.eu. Accessed on 7 November 2019.

European Medicines Agency. Guideline on Immunogenicity assessment of therapeutic proteins 2017. EMEA/CHMP/BMWP/14327/2006 Rev.1.

Fam SR, Hughes M, Argent-Katwala M, et al. Niche Markets and Rare Disease: Bladder Cancer 2011:1 –176.

Ferlay J, Soerjomataram I, Dikshit R et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136(5):E359-86.

Ferlay J, Steliarova FE, Lortet TJ, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. Eur J Cancer 2013;49(6):1374-403.

Fitzmaurice C, Allen C, Barber RM, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol. 2017 Apr 1;3(4):524-48.

Früh M, De Ruysscher D, Popat S, et al. ESMO Guidelines Working Group. Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013 Oct;24 Suppl 6:vi99-105.

GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017 Sep 16;390(10100):1211-1259

Gerstl B, Sullivan E, Ives A, et al. Pregnancy Outcomes After a Breast Cancer Diagnosis: A Systematic Review and Meta-analysis. Clin Breast Cancer. 2018 Feb;18(1):e79-e88.

Goossens-Laan CA, Leliveld AM, Verhoeven RH, et al. Effects of age and comorbidity on treatment and survival of patients with muscle-invasive bladder cancer. Int J Cancer 2014;135(4):905 – 12.

Guidance for Industry (FDA). Immunogenicity Assessment for Therapeutic Protein Products. August 2014. Avilable from: https://www.fda.gov/media/85017/download

Guleria I, Khosroshahi A, Ansari MJ, et al. A critical role for the programmed death ligand 1 in fetomaternal tolerance. J Exp Med 2005;202(2):231-237.

Habicht A, Dada S, Jurewicz M, et al. A link between PDL1 and T regulatory cells in fetomaternal tolerance. J Immunol 2007;179:5211 – 19.

Hinotsu S, Akaza H, Miki T, et al. Bladder cancer develops 6 years earlier in current smokers: Analysis of bladder cancer registry data collected by the cancerregistration committee of the Japanese Urological Association. International Journal of Urology 2009;16:64 – 9.

Howe HL, Wu X, Ries LA, et al. Annual Report to the Nation on the Status of Cancer, 1975–2003, Featuring Cancer Among U.S. Hispanic/Latino Populations. Cancer 2006;107(8):1711 – 42.

Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst. 2014 Apr 28;106(5). pii: dju055

Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site, 2015.

ICH Harmonised Tripartite Guideline. Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. S6(R1). Current Step 4 version (2011). Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S6_R1/Step4/S6_R1_Guideline.pdf.

Janssen-Heijnen ML, Karim-Kos HE, van der Drift MA, et al. Modest improvements of survival for patients with small cell lung cancer aged 45 to 59 years only, diagnosed in the Netherlands, 1989 to 2008. J Thorac Oncol. 2012 Jan;7(1):227-32.

Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. CA Cancer J Clin 2005;55(1):10 – 30. Erratum in: CA Cancer J Clin. 2005 Jul-Aug;55(4):259.

Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010 Sep-Oct;60(5):277-300. Erratum in: CA Cancer J Clin. 2011 Mar-Apr;61(2):133 – 4.

Jimenez J, Gwillim EC, Kosche C, et al. Bullous disorders associated with PD-1 and PD-L1 inhibitors: Pharmacovigilance analysis of the United States Food and Drug Administration Adverse Event Reporting System from the Research on Adverse Drug Events And Reports Program. J Am Acad Dermatol. 2020 Sep;83(3):955-957.

Kanwal F, Kramer JR, Mapakshi S, et al. Risk of Hepatocellular Cancer in Patients with Non-Alcoholic Fatty Liver Disease. Gastroenterology. 2018 Dec;155(6):1828-1837.

Keating K, Walko C, Stephenson B, et al. Incidence of cetuximab-related infusion reactions in oncology patients treated at the University of North Carolina Cancer Hospital. J Oncol Pharm Practice 2014;20(6):409 – 16.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–4.

Kim NG, Nguyen PP, Dang H, et al. Temporal trends in disease presentation and survival of patients with hepatocellular carcinoma: A real-world experience from 1998 to 2015. Cancer. 2018 Jun 15;124(12):2588-2598.

Lambertini M, Blondeaux E, Bruzzone M, et al. Pregnancy After Breast Cancer: A Systematic Review and Meta-Analysis. J Clin Oncol. 2021 Oct 10;39(29):3293-305.

Lau WY, Leung WT, Ho S, et al. Hepatocellular carcinoma during pregnancy and its comparison with other pregnancy-associated malignancies. Cancer. 1995 Jun 1;75(11):2669-76.

Lembicz M, Gabryel P, Brajer-Luftmann B, et al. Comorbidities with non-small cell lung cancer: Is there an interdisciplinary consensus needed to qualify patients for surgical treatment? Ann Thorac Med. 2018 Apr-Jun;13(2):101-107.

Lenz HJ. Management and Preparedness for Infusion and Hypersensitivity Reactions. The Oncologist 2007;12: 601 – 9.

Li L, Zhong Y, Zhang H, et al. Association between oral contraceptive use as a risk factor and triple-negative breast cancer: A systematic review and meta-analysis. Mol Clin Oncol. 2017 Jul;7(1):76-80.

Lou Y, Dholaria B, Soyano A, et al. Survival trends among non-small-cell lung cancer patients over a decade: impact of initial therapy at academic centers. Cancer Med. 2018 Oct;7(10):4932-4942.

Lund MJ, Butler EN, Bumpers HL, et al. High prevalence of triple-negative tumors in an urban cancer center. Cancer. 2008 Aug 1;113(3):608-15.

Malats N and Real FX. Epidemiology of Bladder Cancer. Hematol Oncol Clin N Am 2015;29:177 – 89.

Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018 Aug;68(2):723-750.

Matsushita K, Cha EK, Matsumoto K, et al. Immunohistochemical biomarkers for bladder cancer prognosis. Int J Urol 2011;18:616–29.

Mikkelsen AP, Egerup P, Ebert JFM, et al. Pregnancy Loss and Cancer Risk: A Nationwide Observational Study. EClinicalMedicine. 2019 Oct 9;15:80-8.

Mitrou S, Petrakis D, Fotopoulos G, et al. Lung cancer during pregnancy: A narrative review. J Adv Res. 2016 Jul;7(4):571-4.

Muriithi AK, Leung N, Valeri AM, et al. Biopsy-proven acute interstitial nephritis, 1993-2011: a case series. Am J Kidney Dis 2014;64(4):558 – 66.

Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol. 2015;26(12):2375 – 91.

National Cancer Institute 2017. Surveillance, Epidemiology, and End Result Program. From https://seer.cancer.gov/statfacts. Accessed on 26 June 2018

NCCN Clinical practice guidelines in oncology. Bladder Cancer. Version 5; 25 May 2017; 1-94.

NCCN Clinical practice guidelines in oncology; Small Cell Lung Cancer. Version 2; 17 January 2018; 1-61.

National Cancer Institute 2017. Surveillance, Epidemiology, and End Result Program. From https://seer.cancer.gov/statfacts. Accessed on 8 August 2018.

Nitsche C, Maertin S, Scheiber J, et al. Drug-induced pancreatitis. Curr Gastroenterol Rep. 2012;14:131 – 8.

Oberli LS, Valeri F, Korol D, et al. 31 years of lung cancer in the canton of Zurich, Switzerland: incidence trends by sex, histology and laterality. Swiss Med Wkly. 2016 Jul 11;146: w14327.

Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol 2007;19:813–24.

Periodic Benefit-Risk Evaluation Report for Atezolizumab/Tecentriq Reporting Interval 18 May 2022 to 17 May 2023. Report No. 1122480. 20 July 2023.

Pierobon M, Frankenfeld CL. Obesity as a risk factor for triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat. 2013 Jan;137(1):307-14.

Planchard D, Popat S, Kerr K, et al. ESMO Guidelines Committee. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018 Oct 1;29(Supplement_4):iv192-iv237.

Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al; ESMO Guidelines Committee. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Updated version 15 September 2020. Ann Oncol. 2018 Oct;29 Suppl 4:iv192-iv237.

Ploeg M, Aben KK, Kiemeney LA. The present and future burden of urinary bladder cancer in the world. World J Urol 2009;27(3):289 – 93.

Postmus P, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(4):v11–21.

Powles T, Park SH, Voog E et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med. 2020;383:1218-30.

Printz MA, Sugarman BJ, Paladini RD, et al. Risk factors, hyaluronidase expression, and clinical immunogenicity of recombinant human hyaluronidase PH20, an enzyme enabling subcutaneous drug administration. AAPS J. 2022; 24(110): 1-15.

Prout GR, Wesley MN, Yancik R, et al. Age and Comorbidity Impact Surgical Therapy in Older Bladder Carcinoma Patients. Cancer 2005;104(8):1638 – 47.

Raschi E, Antonazzo IC, La Placa M, et al. Serious Cutaneous Toxicities with Immune Checkpoint Inhibitors in the U.S. Food and Drug Administration Adverse Event Reporting System. Oncologist. 2019 Nov; 24(11): e1228–e1231.

Ray M and Polite BN. Triple-Negative Breast Cancers: A View From 10,000 Feet. The Cancer Journal 2010;16:17-22

Riaz SP, Lüchtenborg M, Coupland VH, et al. Trends in incidence of small cell lung cancer and all lung cancer. Lung Cancer. 2012 Mar;75(3):280-4.

Rojas PA, González C, Mendez GP, et al. San Francisco IF. Bladder squamous cell carcinoma in a pregnant woman: case report and review of the literature. BMC Urol. 2021 Jan 6;21(1):4.

Rosengren S, Dychter SS, Printz MA, et al. Clinical immunogenicity of rHuPH20, a hyaluronidase enabling subcutaneous drug administration. AAPS J. 2015;17:114456.

Schwaiblmair M, Behr W, Haeckel T et al. Drug Induced Interstitial Lung Disease. Open Respir Med J. 2012;6:63 – 74.

SEER Explorer: Surveillance Research Program, National Cancer Institute 2020. Available from https://seer.cancer.gov/explorer/. Accessed on 10 March 2021.

Somali I, Ustaoglu BY, Tarhan MO, et al. Clinicopathologic and demographic evaluation of triple- negative breast cancer patients among a turkish patient population: a single center experience. Asian Pac J Cancer Prev. 2013;14(10):6013-7.

Sun M, Trinh QD. Diagnosis and Staging of Bladder Cancer. Hematol Oncol Clin North Am 2015;29:205 – 18.

Surveillance, Epidemiology and End Result Program (SEER) Explorer Application. National Cancer Institute. Updated on April 15, 2019. Accessed from https://seer.cancer.gov/explorer/application.php. Accessed on 8 November 2019.

Surveillance, Epidemiology, and End Result Program. National Cancer Institute 2020. From https://seer.cancer.gov/statfacts. Accessed on 8 March 2021.

Svensson J, Arkema EV, Lundberg IE, et al. Incidence and prevalence of idiopathic inflammatory myopathies in Sweden: a nationwide population-based study. Rheumatology (Oxford). 2017;56(5):802-810.

Swede H, Sarwar A, Magge A, et al. Mortality risk from comorbidities independent of triple-negative breast cancer status: NCI-SEER-based cohort analysis. Cancer Causes Control. 2016 May;27(5):627-36.

Tang A, Hallouch O, Chernyak V, et al. Epidemiology of hepatocellular carcinoma: target population for surveillance and diagnosis. Abdom Radiol (NY). 2018 Jan;43(1):13-25.

Thompson LM, Eckmann K, Boster BL, et al. Incidence, risk factors, and management of infusion-related reactions in breast cancer patients receiving trastuzumab. Oncologist. 2014;19(3):228 – 34.

U.S. Food and Drug Administration: FDA approves olaparib for germline BRCA-mutated metastatic breast cancer. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-germline-brca-mutated-metastatic-breast-cancer. Accessed on 29 June 2018.

Villanueva A. Hepatocellular Carcinoma. N Engl J Med. 2019 Apr 11;380(15):1450-1462.

Vinklerova I, Prochazka M, Prochazka V, et al. Incidence, severity, and etiology of drug-induced acute pancreatitis. Dig Dis Sci. 2010;55:2977 – 81.

Vogel A, Cervantes A, Chau I, et al. ESMO Guidelines Committee. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018 Oct 1;29(Suppl 4):iv238-iv255.

Wafula PO, Teles A, Schumacher A, et al. PD-1 but not CTLA-4 blockage abrogates the protective effect of regulatory T cells in a pregnancy murine model. Am J Reprod Immunol 2009;62:283 – 292.

Wahba HA, El-Hadaad HA. Current approaches in treatment of triple-negative breast cancer. Cancer Biol Med. 2015 Jun;12(2):106-16

Wang S, Tang J, Sun T, et al. Survival changes in patients with small cell lung cancer and disparities between different sexes, socioeconomic statuses and ages. Sci Rep. 2017a May 2;7(1):1339.

Wang S, Sun T, Sun H, et al. Survival improvement in patients with non-small cell lung cancer between 1983 and 2012: Analysis of the Surveillance, Epidemiology, and End Results database. Tumour Biol. 2017b May;39(5):1010428317691677.

White DL, Thrift AP, Kanwal F, et al. Incidence of Hepatocellular Carcinoma in All 50 United States, From 2000 Through 2012. Gastroenterology. 2017 Mar;152(4):812-820.

World Health Organization; Cancer Today by International Agency for Research in Cancer; Powered By Global Cancer Observatory (GLOBOCAN) 2020. Available From http://gco.iarc.fr/today/online-analysis. Accessed on 8 March 2021.

World Health Organization; Cancer Today by International Agency for Research in Cancer; Powered By Global Cancer Observatory (GLOBOCAN) 2018. From http://gco.iarc.fr/today/online-analysis. Accessed on 7 November 2019.

World Health Organization; GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. From http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed on 8 August 2018.

Wu YL, Masahiro T, et al. Osimertinib in Resected EGFR-Mutated Non–Small-Cell Lung Cancer. Journal of Medicine 2020; 383:1711-1723.

Yoshida T, Jiang F, Honjo T, et al. 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 2008;105(9):3533 – 38.

Zhao CY, Hwang SJ, Consuegra G, et al. Anti-programmed cell death-1 therapy-associated bullous disorders: a systematic review of the literature. Melanoma Research. 2018 Dec 1;28(6):491-501.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR TECENTRIQ (ATEZOLIZUMAB)

This is a summary of the risk management plan (RMP) for Tecentriq. The RMP details important risks of Tecentriq, how these risks can be minimised, and how more information will be obtained about Tecentriq's risks and uncertainties (missing information).

Tecentriq's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Tecentriq should be used.

This summary of the RMP for Tecentriq should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Tecentriq's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Tecentriq contains atezolizumab as the active substance and it is given by intravenous (IV) or subcutaneous (SC) routes of administration.

The recommended dosage for IV administration is either 840 mg every two weeks (q2w), 1200 mg every three weeks (q3w) or 1680 mg every four weeks (q4w). The recommended dosage for SC administration is 1875 mg q3w.

Monotherapy

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

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

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with epidermal growth factor receptor (EGFR) mutant or anaplastic lymphoma kinase (ALK)-positive NSCLC should also have received targeted therapies before receiving Tecentriq.

Tecentriq as monotherapy is indicated for the first-line (1L) treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥50% tumour cells (TC) or ≥10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC.

Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥50% of TC and who do not have EGFR mutant or ALK-positive NSCLC.

Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with advanced NSCLC who are ineligible for platinum-based therapy.

Combination Therapy

Tecentriq, in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC.

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

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

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

Tecentriq, in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

Further information about the evaluation of Tecentriq's benefits can be found in Tecentriq's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage (https://www.ema.europa.eu/en/medicines/human/EPAR/tecentriq).

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Tecentriq, together with measures to minimise such risks and the proposed studies for learning more about Tecentriq's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and the SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Tecentriq, these measures are supplemented with *additional risk-minimisation* measures mentioned under relevant risks below.

In addition to these measures, information about adverse events is collected continuously and regularly analysed: including Periodic Safety Updated Report assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Tecentriq is not yet available, it is listed under 'Missing Information' below.

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of Tecentriq are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tecentriq. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information about the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Immune-mediated adverse reactions Infusion-related reactions
Important potential risks	Attenuated efficacy or reduced tolerability in patients with anti-drug antibodies Embryo-fetal toxicity
Missing information	None

II.B SUMMARY OF IMPORTANT RISKS

Important identified risk: Immune-mediated adverse reactions	
Important identified risk: Hepatitis	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	There are no identified risk factors for the development of immune-mediated hepatitis in atezolizumab–treated patients.
Risk minimisation measures	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimisation measures:** Patient cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Pneumonitis	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	General factors that may be associated with an increased risk of drug-induced interstitial lung disease include: older age, male sex, pre-existing lung disease, smoking, prior radiation therapy, prior or concomitant treatment with medications with known pulmonary toxicity (e.g., some antimicrobial, anti-inflammatory and cardiovascular agents, biologics, and chemotherapeutics), inflammatory conditions (e.g., rheumatoid arthritis and inflammatory bowel disease). The underlying malignant disease itself may also increase the risk of pneumonitis and be a confounder of diagnosis (Barber et al. 2011; Schwaiblmair et al. 2012). There are currently no known risk factors that may predispose individual patients to develop immune-mediated pneumonitis following treatment with atezolizumab.
Risk minimisation measures	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimisation measures:** Patient cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Colitis	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	There are currently no known risk factors that may predispose individual patients to develop immune-mediated colitis following treatment with atezolizumab.
Risk minimisation measures	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimisation measures:** Patient cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Pancreatitis	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	Female sex, younger age, and pre-existing inflammatory bowel disease may be associated with an increased risk of drug-induced pancreatitis (Vinklerova et al. 2010; Nitsche et al. 2012). There are currently no known risk factors that may predispose individual patients to develop immune-mediated pancreatitis following treatment with atezolizumab.
Risk minimisation measures	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimisation measures:** Patient cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Endocrinopathies (Diabetes Mellitus, Hypothyroidism, Hyperthyroidism, Adrenal Insufficiency, and Hypophysitis)	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	An Italian study of adults between age 30 and 49 years found that the risk of type 1 diabetes was almost two times higher in males compared with females (rate ratio 1.70 [95% Confidence Interval 1.21, 2.38]) (Bruno et al. 2005). There are currently no known risk factors that may predispose individual patients to develop immune-mediated diabetes following treatment with atezolizumab. There are no known risk factors associated with the development of immune-mediated hypo- or hyperthyroidism, adrenal insufficiency, or hypophysitis in individual atezolizumab–treated patients.
Risk minimisation measures	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimisation measures:** Patient cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Neuropathies (Guillain-Barré Syndrome, Myasthenic Syndrome/Myasthenia Gravis, and Facial Paresis)	
Evidence for linking the risk to the medicine	**Guillain-Barré Syndrome and Myasthenic Syndrome/Myasthenia Gravis** Clinical trial data **Facial Paresis** Based on a comprehensive analysis of all the cases retrieved from the Roche global drug safety database reported with facial paresis in patients who received treatment with atezolizumab, as well as available data from the clinical database, FDA Adverse Event Reporting System (FAERS) and EudraVigilance (EV) databases, preclinical studies, published literature and considering the plausible mechanism of action and the known class effect of similar-in-class drugs, a causal association between atezolizumab and facial paresis has been established.
Risk factors and risk groups	There are no known risk factors associated with the development of immune-mediated neuropathies in atezolizumab-treated patients.
Risk minimisation measures	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimisation measures:** Patient cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Myelitis	
Evidence for linking the risk to the medicine	Based on a comprehensive analysis of all the cases retrieved from the Roche global drug safety database reported with myelitis and related events in patients who received treatment with atezolizumab, as well as available data from the clinical database, FAERS and EV databases, preclinical studies, published literature and considering the plausible mechanism of action and the known class effect of similar-in-class drugs, a causal association between atezolizumab and myelitis has been established.
Risk factors and risk groups	There are no identified risk factors for the development of immune-mediated myelitis in atezolizumab treated patients.
Risk minimisation measures	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimisation measures:** Patient cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk:	Meningoencephalitis
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	There are no known risk factors associated with the development of immune-mediated meningoencephalitis in atezolizumab-treated patients.
Risk minimisation measures	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimisation measures:** Patient cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Myocarditis	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	There are no known risk factors associated with the development of immune-mediated myocarditis in atezolizumab-treated patients
Risk minimisation measures	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimisation measures:** Patient cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Nephritis	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	Risk factors include certain infections, drugs (including antibiotics, non-steroidal anti-inflammatory drugs, proton pump inhibitors) and autoimmune diseases such as Sjögren's syndrome, and immunoglobulin G4 related disease (Muriithi et al. 2014). The risk factors that may predispose individual patients to developing immune-mediated nephritis following therapy with immune checkpoint inhibitors are unknown.
Risk minimisation measures	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimisation measures:** Patient cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Myositis	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	Like other autoimmune diseases, genes and environment/lifestyle factors are likely to contribute to susceptibility to myositis. Multiple independent associations within the human leukocyte antigen (HLA) 8.1 ancestral haplotype are the strongest genetic risk factors for idiopathic inflammatory myopathies. Epidemiological data support a role for infections, prior lung disease, physical exertion, collagen implants, exposure to ultraviolet radiation and smoking in the development of inflammatory myopathies. Females were found to be more prone to develop polymyositis and dermatomyositis, while males were more prone to develop inclusion body myositis. Drugs such as statins, D-penicillamine, interferon-α, and procainamide were found to be associated with myositis. The risk of developing myositis is found to increase with age and peaks in patients aged 50–79 years (Svensson et al. 2017).
Risk minimisation measures	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimisation measures:** Patient cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk:	Severe Cutaneous Adverse Reactions
Evidence for linking the risk to the medicine	Based on a comprehensive analysis of all the cases retrieved from the Roche global drug safety database reported under the Standardised MedDRA Query (SMQ) (narrow) 'severe cutaneous adverse reactions' in patients who received treatment with atezolizumab as well as available data from the clinical database, literature (Zhao et al. 2018; Raschi et al. 2019; Jimenez et al. 2020), and EV database with a cut-off date of 31 July 2020 and considering the plausible mechanism of action and background of Severe Cutaneous Adverse Reactions (SCARs) as a known class effect, a causal association between atezolizumab and SCARs has been established. As such, SCARs was updated from a potential risk to an important identified risk.
Risk factors and risk groups	There are no known risk factors associated with the development of SCARs in atezolizumab-treated patients.
Risk minimisation measures	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimisation measures:** Direct Healthcare Professional Communication (DHPC): A one-off DHPC was disseminated in March 2021 to inform healthcare professionals that immune-mediated SCARs which were previously known to be potentially associated with use of Tecentriq (atezolizumab), are now considered to be an identified risk.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Metrics on the distribution and receipt of the DHPC were taken to assess the effectiveness of this risk minimisation activity.

Important identified risk:	Pericardial Disorders
Evidence for linking the risk to the medicine	Based on a comprehensive analysis of all the cases retrieved from the Roche global drug safety database reported with the PTs autoimmune pericarditis, cardiac tamponade, pericarditis, pericarditis constrictive, pericardial disease and pericardial effusion in patients who received treatment with atezolizumab as well as available data from the clinical database, FAERS and EV databases, published literature with a cut-off date of 29 April 2022 and considering the plausible mechanism of action and the class effect of similar-in-class drugs, a causal association between atezolizumab and pericardial disorders has been established.
Risk factors and risk groups	The development of immune-mediated pericardial disorders may be higher in patients with lung, breast and oesophageal carcinoma due to direct local extension to the parietal pericardium and in patients treated with chest radiotherapy (Burazor et al. 2013).
Risk minimisation measures	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimisation measures:** Patient cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Hemophagocytic Lymphohistiocytosis	
Evidence for linking the risk to the medicine	Based on comprehensive review of the company global safety database including haemophagocytic lymphohistiocytosis (HLH) cases up to 17 October 2022, considering the potential mechanism of action, and known class effect of similar-in-class drugs, a causal association between atezolizumab and HLH has been established.
Risk factors and risk groups	There are no identified risk factors for the development of HLH in atezolizumab treated patients.
Risk minimisation measures	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimisation measures:** Patient cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Infusion-Related Reactions	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	Treatment with monoclonal antibodies is associated with an increased risk for infusion-related reactions (IRRs) (Keating et al. 2014; Thompson et al. 2014). There are no known risk factors associated with the development of IRRs in atezolizumab-treated patients.
Risk minimisation measures	**Routine risk minimisation measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimisation measures:** Patient cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important potential risk: Attenuated efficacy or reduced tolerability in patients with anti-drug antibodies	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	Risk factors for the development of anti-atezolizumab and anti-rHuPH20 ADAs are currently unknown.
Risk minimisation measures	**Routine risk minimisation measures**: Proposed measures are described in the E.U. SmPC under the following sections: Section 4.8 Undesirable effects **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important potential risk: Embryo-fetal toxicity	
Evidence for linking the risk to the medicine	Literature and nonclinical studies
Risk factors and risk groups	The at-risk group for experiencing atezolizumab-related embryo-fetal toxicity includes female patients of child-bearing potential and developing foetuses who are exposed to atezolizumab during gestation.
Risk minimisation measures	**Routine risk minimisation measures**: Proposed measures are described in the E.U. SmPC under the following sections: Section 4.6 Fertility, pregnancy and lactation Section 5.3 Preclinical safety data Relevant information for patient in PIL **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

ADA = anti-drug antibody; DHPC = Direct Healthcare Professional Communication; E.U. = European Union; EV = EudraVigilance; FAERS = FDA Adverse Event Reporting System; HLH = hemophagocytic lymphohistiocytosis; IRR=infusion-related reaction; PIL = Patient Information Leaflet; RMP = Risk Management Plan; SCAR = severe cutaneous adverse reaction; SmPC = Summary of Product Characteristics.

II.C POST-AUTHORISATION DEVELOPMENT PLAN

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of atezolizumab.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for atezolizumab.

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4:

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

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Specific adverse reactions follow-up forms/questionnaires

There are no specific adverse event follow-up forms in use for this product.

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

1. PATIENTS/CARERS

1.1 PATIENT CARD

The patient card contains a warning message that reminds the patient of actions to take for risk minimisation and aims to ensure that information regarding the patient's current treatment with atezolizumab and its risks including emergency care is held by the patient at all times and reaches the relevant healthcare professional when needed. The patient card also includes the patient's emergency contact and contact details of the atezolizumab prescriber.

The side effects associated with the important identified risks are included on this card as follows:

Serious side effects may include lung problems (pneumonitis), liver problems (hepatitis), intestinal problems (colitis), problems in hormone glands (e.g., hypothyroidism or diabetes), nervous problems (e.g., neuropathies or myelitis), pancreas problems (pancreatitis), heart problems (myocarditis, pericardial disorder), kidney problems (nephritis), and build-up of certain white blood cells (histiocytes and lymphocytes) in various organs (hemophagocytic lymphohistiocytosis).

These events may result in signs or symptoms such as:

Lungs: new or worsening cough, shortness of breath, chest pain.

Liver: yellowing of skin or the whites of eyes, severe nausea or vomiting, bleeding or bruising, dark urine, stomach pain.

Intestines: diarrhea (watery, loose, or soft stools), blood in stools, stomach pain.

Hormone glands: extreme tiredness, weight loss, weight gain, change in mood, hair loss, constipation, dizziness, feeling more hungry or thirsty than usual, need to urinate more often, increased sensitivity to cold or heat.

Brain: neck stiffness, headache, fever, chills, vomiting, eye sensitivity to light, confusion, sleepiness.

Musculoskeletal: inflammation or damage of the muscles, muscle pain and weakness.

Nerves: abnormal sensations such as numbness, coldness or burning, bladder and bowel problems, weakness in the arm and leg muscles, or face muscles, double vision, difficulties with speech and chewing, pain, stiffness, and tingling in your hands and feet.

Pancreas: abdominal pain, nausea, vomiting.

Heart: chest pain which could worsen with deep breathing, shortness of breath, irregular heartbeat, decreased exercise tolerance, swelling of the ankles, legs or abdomen, cough, fatigue, fainting.

Kidneys: changes in urine output and color, pain in pelvis, and swelling of the body that may lead to failure of the kidneys.

Reactions associated with infusion (during or within 1 day of infusion): fever, chills, shortness of breath, flushing.

2. HEALTH CARE PROFESSIONALS

2.1 DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION (DHPC)

The additional risk minimisation measure of a DHPC to communicate the Important Identified Risk of Severe Cutaneous Adverse Reactions (SCARs) with Tecentriq (atezolizumab), has been disseminated in all European Union (EU) countries in March 2021.

The key messages and recommendations in this DHPC were:

- SCARs, including cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients treated with Tecentriq (atezolizumab).
- Patients should be monitored for suspected severe skin reactions and other causes should be excluded. In case a SCAR is suspected, Tecentriq should be withheld and patients should be referred to a specialist in SCARs for diagnosis and treatment.
- In case SJS or TEN is confirmed, and for any Grade 4 rash/SCAR, treatment with Tecentriq should be permanently discontinued.
- Caution is recommended when considering the use of Tecentriq in patients with previous history of a severe or life-threatening SCAR with other immune-stimulatory cancer medicines.

The DHPC confirmed that the EU Product Information would be updated accordingly.