European Union Risk Management Plan	
Drug Substance	Tremelimumab
Version Number	2
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EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR IMJUDO™ / TREMELIMUMAB ASTRAZENECA™ (TREMELIMUMAB)

The content of this EU RMP has been reviewed and endorsed by the Marketing Authorisation Holder's Qualified Person for Pharmacovigilance. The electronic signature is available at the end of the document.

ADMINISTRATIVE INFORMATION

Rationale for submitting an updated RMP

Not applicable – this is the first approved EU RMP.

Summary of significant changes in this RMP

Not applicable – this is the first approved EU RMP.

Other RMP versions under evaluation

Not applicable.

Details of currently approved RMP

Not applicable.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
ADR	adverse drug reaction
ALK	anaplastic lymphoma kinase
ALT	alanine transaminase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BIL	bilirubin
CrCL	creatinine clearance
CNS	central nervous system
CTLA-4	cytotoxic T lymphocyte associated antigen 4
D	durvalumab
DCO	data cut-off
DNA	deoxyribonucleic acid
EEA	European Economic Area
EGFR	epidermal growth factor receptor
ESMO	European Society for Medical Oncology
EU	European Union
GBD	Global Burden of Disease
GI	gastrointestinal
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
IARC	International Agency for Research on Cancer
ICH	International Council for Harmonisation
IgG2a	immunoglobulin G2
INN	International Nonproprietary Name
iv	intravenous
NCCN	National Comprehensive Cancer Network
NSCLC	non-small cell lung cancer
PD-1 / PD-L1	programmed death-1 / programmed death ligand-1
PL	Package Leaflet
PT	Preferred Term
Q3W	every 3 weeks
Q4W	every 4 weeks
RMP	Risk Management Plan
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SoC	standard of care
T(300)	tremelimumab (300mg)

Abbreviation/ Special term	Definition/Explanation
ULN	upper limit of normal
UK	United Kingdom
US	United States (of America)

I. PART I: PRODUCT OVERVIEW

Table I-1 Product Overview

Active substance(s) (INN or common name)	Tremelimumab
Pharmacotherapeutic group(s) (ATC Code)	L01FX20
Marketing Authorisation Applicant	AstraZeneca AB, 15185 Södertälje, Sweden
Medicinal products to which this RMP refers	One
Invented name(s) in the EEA	IMJUDO and TREMELIMUMAB ASTRAZENECA
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class**: Tremelimumab is a human anti-CTLA-4-IgG2a monoclonal antibody.
	Summary of mode of action: CTLA-4 is primarily expressed on the surface of T lymphocytes. Interaction of CTLA-4 with its ligands, CD80 and CD86, limits effector T-cell activation, through a number of potential mechanisms, but primarily by limiting co-stimulatory signalling through CD28. Tremelimumab blocks CTLA-4 interaction with CD80 and CD86, thus enhancing T-cell activation and proliferation, resulting in increased T-cell diversity and enhanced antitumour immune activity.
	Important information about its composition: Tremelimumab is expressed in a NS0 (murine myeloma) cell line. It is purified using 3 chromatography steps, a virus inactivation step, and a virus reduction filtration step.
Hyperlink to the Product Information	Summary of Product Characteristics
Indication(s) in the EEA	**Current:** • TREMELIMUMAB ASTRAZENECA in combination with durvalumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations. • IMJUDO in combination with durvalumab is indicated for the first-line treatment of adults with advanced or unresectable HCC.

Table I-1 Product Overview

Dosage in the EEA	**Current:** • Metastatic NSCLC: – *During platinum chemotherapy*: 75 mg in combination with durvalumab 1500 mg and platinum-based chemotherapy Q3W (21 days) for 4 cycles (12 weeks). – *Post-platinum chemotherapy*: Durvalumab 1500 mg Q4W and histology-based pemetrexed maintenance therapy Q4W. A fifth dose of TREMELIMUMAB ASTRAZENECA 75 mg should be given at Week 16 alongside durvalumab dose 6. *Note: Up to a maximum of 5 doses of TREMELIMUMAB ASTRAZENECA can be administered. Patients may receive less than 5 doses of TREMELIMUMAB ASTRAZENECA in combination with durvalumab 1500 mg and platinum-based chemotherapy if there is disease progression or unacceptable toxicity. Patients with a body weight of ≤ 30 kg must receive weight-based dosing, equivalent to 1 mg/kg of TREMELIMUMAB ASTRAZENECA and 20 mg/kg of durvalumab until weight improves to > 30 kg.* • Advanced or unresectable HCC: – IMJUDO 300 mg as a single dose administered in combination with durvalumab 1500 mg at Cycle 1/Day 1, followed by durvalumab monotherapy Q4W, until disease progression or unacceptable toxicity. *Note: Patients with a body weight of ≤ 30 kg must receive weight-based dosing, equivalent to IMJUDO 4 mg/kg and durvalumab 20 mg/kg until weight is > 30 kg.*
Pharmaceutical form(s) and strengths in the EEA	**Current:** Sterile, preservative-free, clear to slightly opalescent, colourless to slightly yellow solution, free from or practically free from visible particles. Concentrate for solution for infusion; 20 mg/mL in a single-dose vial for iv administration. Each mL contains 20 mg of tremelimumab. Each vial of 1.25 mL contains 25 mg of tremelimumab. Each vial of 15 mL contains 300 mg of tremelimumab.
Will the product be subject to additional monitoring in the EU?	Yes

II. PART II: SAFETY SPECIFICATION

II.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

II.1.1 Hepatocellular Carcinoma

Incidence

Primary liver cancer is a major global health problem accounting for approximately 906,000 new cases per year globally (American Cancer Society 2021). In Europe, approximately 87,000 new cases a year are reported (WHO 2020), whereas the US reports approximately 42,000 new cases a year (American Cancer Society 2021). As of 2020, liver cancer was the seventh most common cancer worldwide (Sung et al 2021).

Hepatocellular carcinoma is the most common histologic type of primary liver cancer, accounting for around 90% of these malignancies (EASL 2018). The incidence of HCC varies globally due to the difference in the prevalence of risk factors across geographic regions (Sung et al 2021). The highest incidence rates are seen in East Asia and Sub-Saharan Africa, while lower rates are seen in Europe and North America (WHO 2019).

Table II-1 presents an estimated incidence of liver cancer and HCC worldwide, by region and gender.

Table II-1 Estimated Number of Incidence Cases of Liver Cancer and HCC, by Gender and Region, 2018

	Liver Cancer				HCC			
	Incident cases		Crude incidence rate (per 100,000)		Incident cases		Crude incidence rate (per 100,000)	
Population	Male	Female	Male	Female	Male	Female	Male	Female
World	596574	244506	15.5	6.5	536917	220055	14.0	5.9
Asia	443744	165852	19.1	7.5	399370	149267	17.2	6.8
Europe	55825	26641	15.5	6.9	50243	23977	14.0	6.2
Africa	43530	21249	6.8	3.3	39177	19124	6.1	3.0
North America	29900	11951	16.6	6.5	26910	10756	14.9	5.9
Latin America and the Caribbean	20784	17616	6.5	5.3	18706	15854	5.9	4.8
Oceania	2791	1197	13.5	5.8	2512	1077	12.2	5.2

Although IARC estimates for HCC prevalence are not readily available, they are calculated based on evidence from the literature that indicates HCC accounts for approximately 90% of all cases of primary liver cancer (Llovet et al 2016).
Source: Bray et al 2018

Prevalence

Using 2017 data from the GBD project, the estimated crude 1-year prevalence rate of liver cancer was 3.99 per 100,000 individuals in Europe (Institute for Health Metrics and Evaluation 2017).

A north-south gradient was seen in the estimated age-standardised prevalence rate for HCC within Europe. According to the GBD 2016 project, the prevalence rate in Italy was greater than 12 per 100,000, while the rates were slightly lower for Austria, Germany, Luxembourg, and Switzerland (range: 6 to 11.99 per 100,000). In the same year, countries such as Poland and Hungary had prevalence rates of HCC below 5 per 100,000 (Institute for Health Metrics and Evaluation 2016).

Table II-2 presents the estimated 5-year prevalence of liver cancer and HCC worldwide and by region extracted from IARC.

Table II-2 Estimated 5-Year Prevalence of HCC Worldwide and by Region, 2018

Region	Liver Cancer		HCC	
	Five-year prevalence [a]	Proportion/ 100,000 [b]	Five-year prevalence	Proportion/ 100,000
Worldwide	675210	8.8	607689	7.9
Asia	494783	10.9	445305	9.8
Europe	58477	7.9	52629	7.1
Africa	56736	4.4	51062	4.0
North America	34107	9.4	30696	8.5
Latin America and the Caribbean	27795	4.3	25016	3.9
Oceania	3312	8.0	2981	7.2

[a] 5-year prevalence: defined as sum of region-specific prevalence cases over 5 years.
[b] Proportion/100000: defined as proportion of population per 100000 persons.
Although IARC estimates for HCC prevalence are not readily available, they are calculated based on evidence from the literature that indicates HCC accounts for approximately 90% of all cases of primary liver cancer (Llovet et al 2016).
Source: Bray et al 2018

Demographics of the population in the proposed indication (age, gender, racial and/or ethnic origin) and risk factors for the disease

The incidence of HCC increases progressively with advancing age in all populations, reaching a peak at 70 years (El Serag 2012, White et al 2017). While HCC is more common in men than women (2- to 3-fold higher), it is believed this is most likely due to differences in the behaviours associated with relevant risk factors rather than underlying risk (Llovet et al 2016, Sung et al 2021).

Cirrhosis and chronic liver disease are the most important risk factors for HCC (Balogh et al 2016, Asrani et al 2019, Janevska et al 2015). Viral hepatitis infections, alcohol abuse, and

metabolic diseases including obesity and diabetes mellitus are all conditions that may result in cirrhosis and the chronic liver damage that is associated with increased risk for HCC (Balogh et al 2016, Asrani et al 2019, Massarweh and El-Serag 2017, Reeves et al 2016).

Globally, chronic infections with hepatitis B or C virus are the most commonly occurring risk factors for HCC (Caldwell and Park 2009). Approximately 80% of HCC cases worldwide can be attributed to either hepatitis B or C virus (Caldwell and Park 2009). Other HCC risk factors include exposure to aflatoxin (Janevska et al 2015), tobacco use, and certain genetic conditions including Wilson disease (Balogh et al 2016).

The main existing treatment options

The ESMO and the European Association for the Study of the Liver 2018 guidelines recommend systemic therapies for the management of unresectable HCC. Since 2020, the NCCN, ESMO, and Japanese Society of Hepatology guidelines have recommended atezolizumab (a PD-L1 inhibitor) in combination with bevacizumab (an angiogenesis inhibitor targeting vascular endothelial growth factor A) as the preferred option to treat first-line HCC (NCCN 2021a, JSH 2021, Vogel and Martinelli 2021 [ie, ESMO Guidelines 2021]).

Lenvatinib (a multiple kinase inhibitor against vascular endothelial growth factor receptor-1, -2, and -3 and fibroblast growth factor receptor-1, -2, -3, and -4) is also approved as first-line treatment for advanced HCC in patients without main portal vein invasion and a Performance Status of 0 to 1.

Selective internal radiation therapy may be considered as an alternative therapy, following multidisciplinary board discussion, in exceptional circumstances and in a subset of patients for whom systemic therapy is not possible (EASL 2018, Vogel et al 2018).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

The 5-year survival rate for HCC is less than 20% (Sarveazad et al 2019, Villanueva 2019), with a median survival following diagnosis ranging from 6 to 20 months (McGlynn et al 2015).

HCC is often associated with non-specific complaints. Patients typically manifest symptoms related to underlying cirrhosis, a condition present in 80% to 90% of patients with HCC (Tinkle and Haas-Kogan 2012). Rarely, patients may present with acute onset of severe symptoms (Rossetto et al 2010). HCC is also associated with a number of paraneoplastic syndromes. Extrahepatic spread at presentation is relatively uncommon, ranging between 10% and 30%. The most common sites of metastasis include lung, adrenal gland, regional lymph node and bone (El-Serag and Rudolph 2007, Tinkle and Haas-Kogan 2012).

HCC carries a substantial mortality and morbidity burden (Tinkle and Haas-Kogan 2012), with HCC mortality rates increasing over recent decades in most countries. As of 2020, liver cancer was the third most common cause of cancer-related death (Sung et al 2021). Global variation in mortality estimates for liver cancer, of which approximately 90% of cases are HCC (Mak et al 2018) can be assessed through data extracted from the GLOBOCAN series (Table II-3).

Table II-3 Estimated Number of Deaths due to Liver Cancer, by Gender and Region, 2018

Population	Number of Deaths		Crude Mortality Rate (per 100,000)	
	Male	Female	Male	Female
World	548375	233256	14.2	6.2
Asia	410223	156046	17.6	7
Europe	50365	27010	14	7
Africa	42786	20776	6.7	3.2
North America	22889	11450	12.7	6.2
Latin America and the Caribbean	19650	16786	6.1	5.1
Oceania	2462	1188	11.9	5.8

Source: Bray et al 2018

Untreated patients with advanced HCC, those who have macrovascular invasion or extrahepatic spread (lymph node involvement or metastases), have a median survival of 6 months (Llovet et al 2008) and a 25% survival at 1-year (Cabibbo et al 2010). Patients with end-stage disease have a median survival of 3 to 4 months (Llovet et al 1999) and an 11% survival at 1- year (Cabibbo et al 2010).

Important comorbidities

The most common liver-related comorbidities in patients with advanced HCC include cirrhosis, hepatitis B, hepatitis C, non-alcoholic steatohepatitis and/or non-alcoholic fatty liver disease, alcohol dependence, and portal vein thromboembolism (Bonafede et al 2020, Mallick et al 2013).

In general, elderly patients with advanced HCC also have high incidence of comorbidities such as cardiovascular disease, diabetes mellitus, and chronic renal disease (Nishikawa et al 2013). Hypertension, diabetes, anxiety, cardiovascular disease, chronic obstructive pulmonary disease, depression, osteoarthritis, osteoporosis, and chronic kidney disease are also reported among patients with advanced HCC (Bonafede et al 2020, Lee et al 2018, Arora et al 2016).

II.1.2 Non-Small Cell Lung Cancer

Incidence

Worldwide data from the IARC show that lung cancer is the most common type of cancer diagnosed, with 2.1 million new lung cancer cases predicted in 2018 (Bray et al 2018). The age-adjusted incidence rate of lung cancer worldwide was 22.5 per 100000 with lower rates in women (14.6 per 100000) compared to men (31.5 per 100000), which may be partly attributed to the gender difference in tobacco use. Incidence rates (per 100000) vary geographically, with the highest age-adjusted incidence rate reported in the US (35 in both sexes; 40.1 in males; 30.8 in females), followed by Western Europe (33.9 in both sexes; 43.3 in males; 25.7 in females).

The incidence rates of NSCLC are highly variable and depend largely on local smoking prevalence. A summary of NSCLC incidence, by country, is presented in Table II-4.

Table II-4 Incident Cases of NSCLC, 2018

Country	Stage IV	Total NSCLC all stages	Stage IV as % of total NSCLC
United States	75643	181788	41.6
France	16300	34059	47.9
Germany	19601	43754	44.8
Italy	17561	37433	46.9
Spain	10613	21083	50.3
United Kingdom	18000	39870	45.1
Japan	24509	93276	26.3

Note: The Decision Resources Group utilised different data sources for different countries. NSCLC is defined according to the International Classification of Diseases, Tenth Revision with a diagnosis code C34 excluding cases with the histology codes 8041-8045 for small cell lung cancer.
Source: Decision Resources Group 2018

Prevalence

The IARC estimates that there will be 2129964 prevalent cases of lung cancer worldwide in 2018. In many regions, the pattern of lung cancer prevalence rates (over 5 years) generally follows that of incidence rates, except for Northern Europe, North America, and the US, where prevalence rates for males and females are converging (Bray et al 2018). Across Europe, the highest prevalence was reported for Western and Northern European countries; 84.1 and 76.0 per 100000, respectively. The prevalence of lung cancer in the US and Asia in the same year was 78.3 and 26.6 per 100000, respectively (Table II-5).

Table II-5 Five-year Prevalence Rate for Lung Cancer (per 100000), 2018

Region/country	Males	Females	Total
World	34.1	21.6	27.9

Table II-5 Five-year Prevalence Rate for Lung Cancer (per 100000), 2018

Region/country	Males	Females	Total
North America	77.4	78.7	78.1
United States	78.4	78.3	78.3
Europe	86.3	48.7	66.9
Central and Eastern Europe	77.5	28.7	51.7
Northern Europe	75.4	76.6	76.0
Southern Europe	94.4	42.1	67.6
Western Europe	98.4	70.2	84.1
Asia	33.6	19.1	26.6

Note: Age standardised to the world population. Lung cancer is defined based on the International Classification of Diseases, Tenth Revision as a diagnosis with the code C33-34 (including trachea).
Source: Bray et al 2018

The number of prevalent (re-staged, to allow for movement by stage over time, over 5 years) cases of Stage IV NSCLC was estimated at 541691 in the US, Japan and EU-5 (France, Germany, Italy, Spain, and the UK) in 2018 (Kantar Health 2018) (Table II-6).

Table II-6 Prevalent Cases of Stage IV NSCLC, 2018

Country	Stage IV
United States	202933
France	44095
Germany	56689
Italy	50029
UK	50446
Spain	27980
Japan	109519

Note: Standard prevalence assumes all those diagnosed at a given stage remain in that stage. Restaged prevalence corrects for this and estimates the number of patients currently in a specific stage during a given time frame.
Source: Kantar Health 2018.

Demographics of the population in the proposed indication (age, gender, racial and/or ethnic origin) and risk factors for the disease

The age-adjusted incidence and death rates for all lung and bronchus cancers by race-ethnicity groups in the US for 2011 to 2015 are presented in Table II-7.

Table II-7 Age-adjusted Incidence and Death Rates of Lung and Bronchus Cancer by Race/Ethnicity in the US

	Incidence rates (2009-2013)		Death rates (2010-2014)	
Race/ethnicity	Male	Female	Male	Female
All races	63.8	47.8	53.8	35.4
Non-Hispanic White	68.6	54.8	56.3	39.0
Non-Hispanic Black	81.2	47.9	65.1	33.5

Table II-7 Age-adjusted Incidence and Death Rates of Lung and Bronchus Cancer by Race/Ethnicity in the US

Race/ethnicity	Incidence rates (2009-2013)		Death rates (2010-2014)	
	Male	Female	Male	Female
Asian/Pacific Islander	45.9	28.0	31.2	17.8
American Indian/Alaska Native	45.4	31.2	35.3	23.7
Hispanic	34.1	23.2	26.5	13.3

Note: Data are based on the US SEER registries. Rates are per 100000 population and age adjusted to the 2000 US standard population. Non-Hispanic White and Non-Hispanic Black are not mutually exclusive of Hispanic origin.
Source: Siegel et al 2017.

Males are more likely to be diagnosed with NSCLC; 60% of incident Stage IV NSCLC cases occur in males (Decision Resources Group 2018). Risk factors for NSCLC include tobacco, environmental tobacco smoke, family history of lung cancer, genetic factors, occupational factors and radiation risk, air pollution, and inflammation and infection.

The main existing treatment options

In Stage IV NSCLC, preferred first-line systemic treatments are based on the presence of specific molecular characteristics including activating EGFR mutations (osimertinib, afatinib, erlotinib, gefitinib, and dacomitinib), ALK rearrangements (alectinib, brigatinib, lorlatinib, ceritinib, and crizotinib), ROS1 rearrangement (entrectinib, ceritinib and crizotinib), BRAF V600E mutation (dabrafenib plus trametinib, and vemurafenib), NTRK gene fusion (larotrectinib and entrectinib), MET exon 14 skipping (capmatinib and tepotinib), and RET rearrangements (selpercatinib and pralsetinib) (NCCN 2021b).

Platinum-based systemic therapy in combination with anti PD-1/PD-L1 agents (eg, pembrolizumab and atezolizumab) is the SoC for patients who do not have mutation positive tumours. Regimens containing pembrolizumab are preferred for those with tumours that express PD-L1. These include pembrolizumab + cisplatin/carboplatin + pemetrexed for adenocarcinoma and large cell subtypes, and pembrolizumab + carboplatin + paclitaxel (or albumin-bound paclitaxel) for squamous cell carcinoma. For patients with tumours expressing high levels of PD-L1 (> 50%), pembrolizumab monotherapy is an option (NCCN 2021b).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Patients with NSCLC commonly experience multiple symptoms, both lung-specific (eg, cough, shortness of breath, chest pain, hoarseness, and haemoptysis) and systemic (loss of weight or appetite, feeling tired or weak).

There are limited inter-regional statistics on mortality for the worldwide target population. The highest age-adjusted mortality rate (per 100000) for lung cancer in 2018 was reported from Western Europe (24.6), followed by Central and Eastern Europe (23.6), and Southern Europe (22.7). According to data collected from SEER cancer registries in 2008 to 2014, the

5-year survival for patients diagnosed with lung cancer that has spread to distant sites is below 5% (Siegel et al 2017).

Important co-morbidities

Common co-morbidities in patients with NSCLC include chronic obstructive pulmonary disease, diabetes, cerebrovascular disease, peripheral vascular disease, myocardial infarction, congestive heart failure, renal disease, and non-lung malignancy (Nilsson et al 2017, Wang et al 2012, Edwards et al 2014).

Common sequelae associated with systemic chemotherapy specifically in Stage IV NSCLC are reported to include dyspnoea (30% of treated patients), anaemia (26%), hypertension (15%), atypical pneumonia (15%), and fatigue (14%) (Bittoni et al 2018).

II.2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

II.2.1 Summary of Key Findings from Non-Clinical Data

Key safety findings from non-clinical studies and their relevance to human usage are described below.

Toxicity

- **Key issues identified from acute or repeat-dose toxicity studies:**

  Gastrointestinal toxicity: In both single- and repeat-dose toxicity studies in cynomolgus monkeys, iv administration of tremelimumab was associated with increased incidence and frequency of diarrhoea or loose stools, consistent with the primary pharmacodynamics of tremelimumab. Histopathology changes included inflammation of the cecum and colon; these changes correlated with the diarrhoea and loose stools and were considered consistent with immune activation and, therefore, consistent with the mode of action of tremelimumab. All treatment related histopathology findings generally reversed or showed a trend towards reversibility. In conclusion, treatment of cynomolgus monkeys with tremelimumab in repeat dose toxicity studies resulted in the identification of the gastrointestinal tract as a potential target organ.

  Relevance to human use: Immune-mediated colitis (in addition to diarrhoea and intestinal perforation as a consequence of immune-mediated colitis) are included as ADRs in the tremelimumab SmPC and are categorised as important identified risks in this EU RMP (under the topic of immune-mediated adverse reactions; see Section II.7.3.1).

  Skin effects: In the 6-month chronic toxicity study in cynomolgus monkeys, development of adverse skin reactions (open sores along swollen eyelids; dry, cracked, scaly, or crusty skin; rash or reddened skin; scabbed areas and yellowish skin) were observed, with earlier onset and highest incidence and severity at the 50 mg/kg high dose. At the low and intermediate doses, clinical signs of skin reactions generally occurred with lower incidence and reduced severity and resolved despite continued dosing. Histopathology findings included mononuclear cell inflammation in the skin that correlated with the observed clinical signs. These treatment-related histopathology findings were typically related to immune activation, and, therefore, generally consistent with the primary mode of action of tremelimumab. No skin effects were noted in the single dose or 4-week repeat-dose toxicity studies. As a result of the findings in the 6-month chronic toxicity study, the skin was identified a potential target organ of tremelimumab toxicity.

  Relevance to human use: Immune-mediated rash and dermatitis are included as ADRs in the tremelimumab SmPC, and are categorised as important identified risks in this EU RMP (under the topic of immune-mediated adverse reactions; see Section II.7.3.1).

Liver toxicity: In the 4-week Good Laboratory Practice repeat-dose toxicity study, histopathology findings included non-adverse and pharmacodynamic-mediated, slight-to-mild, focal-to-multifocal periportal infiltration of mixed mononuclear cells in the liver. At the end of the treatment-free phase, these liver changes reversed in females but not in males. As a result, treatment of cynomolgus monkeys with tremelimumab in repeat-dose toxicity studies resulted in the identification of the liver as a potential target organ.

Relevance to human use: Immune-mediated hepatitis is included as an ADR in the tremelimumab SmPC, and is categorised as an important identified risk in this EU RMP (under the topic of immune-mediated adverse reactions; see Section II.7.3.1).

Mononuclear cell infiltration: In the 6-month chronic toxicity study, mononuclear cell infiltration was observed in the skin and hyperplasia in lymphoid tissues. A dose-dependent increase in the incidence and severity of mononuclear cell infiltration with or without mononuclear cell inflammation was observed in the salivary gland, pancreas (acinar), thyroid, parathyroid, adrenal, heart, oesophagus, tongue, periportal liver area, skeletal muscle, prostate, uterus, pituitary, eye (conjunctiva, extra ocular muscles), and choroid plexus of the brain.

Relevance to human use: The presence of mononuclear infiltration across different organs and systems is indicative of pro-inflammatory effects, and is consistent with the mode of action of tremelimumab. No specific safety concerns relevant to human use have been identified.

- **Reproductive/developmental toxicity:**

  In an embryofoetal toxicity study, iv administration of tremelimumab from confirmation of pregnancy and throughout the period of organogenesis (Gestational Days 20 to 50) was not associated with any effects on pregnant females or foetal weights; external, visceral, or skeletal abnormalities; or weights of selected organs post-caesarean section. Therefore, tremelimumab did not elicit maternal toxicity, developmental toxicity, or teratogenicity.

  Relevance to human use: No safety concerns relevant to human usage have been identified.

- **Genotoxicity:**

  Tremelimumab is a large protein molecule. Genotoxicity is not applicable for large protein molecules that are not expected to cross the nuclear or mitochondrial membranes and interact directly with DNA or other chromosomal constituents.

  Relevance to human use: No safety concerns relevant to human usage have been identified.

- **Carcinogenicity:**

  In accordance with the ICH S6(R1) and S9 guidelines, studies evaluating carcinogenicity of tremelimumab have not been conducted and are not planned given the characteristics of this product and the intended clinical use in patients with advanced cancer.

  Relevance to human use: No safety concerns relevant to human usage have been identified.

Safety pharmacology

No standalone studies were conducted. Safety pharmacology endpoints were included in repeat-dose toxicity studies, and no treatment-related findings were observed.

II.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

A summary of exposure to IMJUDO and durvalumab treatment in patients with HCC is provided in Section II.3.1, and a summary of exposure to TREMELIMUMAB ASTRAZENECA and durvalumab (plus SoC chemotherapy) in patients with metastatic NSCLC is provided in Section II.3.2.

II.3.1 Exposure to IMJUDO + Durvalumab for HCC

The pivotal safety dataset in support of the use of IMJUDO in combination with durvalumab in patients with unresectable HCC was derived from pooled data from patients who received a single priming dose of IMJUDO 300 mg in combination with durvalumab 1500 mg via iv infusion on Day 1 (Week 0) in the T300 + D arms of the HIMALAYA study (D419CC00002; NCT03298451) (n = 388) and Study 22 (D4190C00022; NCT02519348) (n = 74). After initial combination dosing, patients in both studies subsequently received durvalumab 1500 mg monotherapy Q4W starting 4 weeks after the first and final infusion of the combination therapy until confirmed disease progression, unacceptable toxicity, or any discontinuation criterion was met.

Exposure to IMJUDO and durvalumab in the HCC tumour pool (T300 + D) by weeks, age group and sex, and race is presented in Table II-8, Table II-9, and Table II-10, respectively.

Table II-8 Duration of Exposure to IMJUDO and Durvalumab (HCC tumour pool [T300 + D]) (N = 462)

Duration of exposure (weeks)	Durvalumab (N=462)		IMJUDO (N=462)	
	n	Patient-years exposure	n	Patient-years exposure
≥ 0	462	370.5	462	42.7
≥ 4	455	370.1	455	42.3
≥ 8	378	362.9	36	10.2
≥ 12	327	354.4	6	5.6
≥ 16	286	343.7	6	5.6
≥ 20	242	329.6	6	5.6

Total treatment duration = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date +1/7, where X is defined as the planned frequency in dosing (in days) -1. For Q4W, X = 27.

Table II-9 Exposure to IMJUDO and Durvalumab by Age Group and Sex (HCC tumour pool [T300 + D]) (N = 462)

Age group (years)	Durvalumab (N=462)				IMJUDO (N=462)			
	Male		Female		Male		Female	
	n	Patient-years exposure	n	Patient-years exposure	n	Patient-years exposure	n	Patient-years exposure
< 65	193	153.1	33	19.3	193	16.5	33	3.0
≥ 65	194	160.3	42	37.8	194	20.0	42	3.3
Total	387	313.4	75	57.1	387	36.4	75	6.3

Total treatment duration = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date +1/7, where X is defined as the planned frequency in dosing (in days) -1. For Q4W, X = 27.

Table II-10 Exposure to IMJUDO and Durvalumab by Race (HCC tumour pool [T300 + D]) (N = 462)

Race	Durvalumab (N=462)		IMJUDO (N=462)	
	n	Patient-years exposure	n	Patient-years exposure
Asian	238	185.6	238	21.4
White	204	165.0	204	19.8
Black or African American	11	6.7	11	0.8
Other [a]	8	13.0	8	0.6
Missing	1	0.3	1	0.1
Total	462	370.5	462	42.7

[a] Other includes Multiple, American Indian or Alaska native and Native Hawaiian or other Pacific islander.
Total treatment duration = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date +1/7, where X is defined as the planned frequency in dosing (in days) -1. For Q4W, X = 27.

II.3.2 Exposure to TREMELIMUMAB ASTRAZENECA + Durvalumab + SoC Chemotherapy for NSCLC

The pivotal dataset in support of the use of TREMELIMUMAB ASTRAZENECA in combination with durvalumab and platinum-based chemotherapy (SoC) for the first-line treatment of metastatic NSCLC was derived from the T + D + SoC chemotherapy arm of the POSEIDON study (D419MC00004; NCT03164616), in which durvalumab 1500 mg plus TREMELIMUMAB ASTRAZENECA 75 mg was administered via iv infusion concurrently with platinum-based doublet chemotherapy (either abraxane or gemcitabine or pemetrexed [dependent on NSCLC histology] plus cisplatin or carboplatin) Q3W for 4 cycles (1 cycle = 3 weeks). Post-chemotherapy, durvalumab monotherapy (plus pemetrexed maintenance treatment unless contraindicated, based on investigator discretion] for participants with non-squamous tumours who had previously received chemotherapy with pemetrexed plus carboplatin/cisplatin) was continued Q4W until disease progression or

unacceptable toxicity. In addition, 1 further dose of TREMELIMUMAB ASTRAZENECA was administered alongside durvalumab dose 6 at Week 16.

Exposure to TREMELIMUMAB ASTRAZENECA and durvalumab in the T + D + SoC arm of the POSEIDON study by weeks, age group and sex, and race in the pivotal dataset is presented in Table II-11, Table II-12, and Table II-13, respectively.

Table II-11 Duration of Exposure to Durvalumab and TREMELIMUMAB ASTRAZENECA (T + D + SoC Chemotherapy Arm; POSEIDON Study) (N = 330)

Duration of exposure (weeks)	Durvalumab (N=330)		TREMELIMUMAB ASTRAZENECA (N=330)	
	n	Patient-years exposure	n	Patient-years exposure
≥ 0	330	308.8	330	112.4
≥ 8	280	304.6	280	108.3
≥ 16	250	298.1	228	96.3
≥ 24	198	278.2	38	20.6
≥ 32	153	254.1	7	4.8
≥ 40	125	234.7	0	0.0
≥ 48	107	219.6	0	0.0
≥ 50	100	213.1	0	0.0
≥ 52	97	210.2	0	0.0
Total	**330**	**308.8**	**330**	**112.4**

Total exposure = Minimum of (last infusion/dose date of the last cycle + 20 days (if last infusion/dose date was during combination)/last infusion/dose date of the last cycle + 27 days (if last infusion/dose date was in maintenance or TREMELIMUMAB ASTRAZENECA retreatment), date of death, date of DCO) – first infusion/dose date of first cycle + 1.

Table II-12 Exposure to Durvalumab and TREMELIMUMAB ASTRAZENECA by Age Group and Sex (T + D + Soc Chemotherapy Arm; POSEIDON Study) (N = 330)

Age group (years)	Durvalumab (N=330)				TREMELIMUMAB ASTRAZENECA (N=330)			
	Male		Female		Male		Female	
	n	Patient-years exposure	n	Patient-years exposure	n	Patient-years exposure	n	Patient-years exposure
< 65	151	145.6	36	36.0	151	51.6	36	12.4
≥ 65	113	101.8	30	25.5	113	38.1	30	10.3
Total	**264**	**247.4**	**66**	**61.4**	**264**	**89.7**	**66**	**22.7**

Total exposure = Minimum of (last infusion/dose date of the last cycle + 20 days (if last infusion/dose date was during combination)/last infusion/dose date of the last cycle + 27 days (if last infusion/dose date was in maintenance or TREMELIMUMAB ASTRAZENECA retreatment), date of death, date of DCO) – first infusion/dose date of first cycle + 1.

Table II-13 Exposure to Durvalumab and TREMELIMUMAB ASTRAZENECA by Race (T + D + SoC Chemotherapy Arm; POSEIDON Study) (N = 330)

Race	Durvalumab (N=330)		TREMELIMUMAB ASTRAZENECA (N=330)	
	n	Patient-years exposure	n	Patient-years exposure
White	201	189.7	201	69.2
Asian	97	84.3	97	31.8
American Indian or Alaska Native	11	9.5	11	3.7
Black or African American	8	11.4	8	3.9
Native Hawaiian or Other Pacific Islander	2	0.6	2	0.4
Other	11	13.2	11	3.4
Total	**330**	**308.8**	**330**	**112.4**

Total exposure = Minimum of (last infusion/dose date of the last cycle + 20 days (if last infusion/dose date was during combination)/last infusion/dose date of the last cycle + 27 days (if last infusion/dose date was in maintenance or TREMELIMUMAB ASTRAZENECA retreatment), date of death, date of DCO) – first infusion/dose date of first cycle + 1.

II.4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

II.4.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

- ***Current or prior use of immunosuppressive medications (with some specific exceptions) prior to starting study treatment***
  - Reason for exclusion: Systemic immunosuppressive medication pharmacologically impacts the different components of both the humoral and cell-mediated responses of the immune system. The impact on T-cells may interfere with the mechanism of action of tremelimumab.
  - Is it considered to be included as missing information: No
  - Rationale: Experience to date has indicated that treatment with tremelimumab has been well tolerated by patients receiving short-term physiological and high doses of systemic corticosteroids. Given the mechanism of action of immunotherapy agents, the continued, long-term use of other concomitant immunosuppressive medications for concurrent underlying medical conditions in the target population is not anticipated; therefore, this criterion is not relevant for inclusion as missing information.

- ***Patients with pre-existing autoimmune disease***
  - Reason for exclusion: Tremelimumab, by disrupting immune checkpoint function, can disturb mechanisms of immunologic tolerance that normally limit immune responses to healthy tissues, potentially leading to autoimmune-like/inflammatory side-effects or interference with down-regulation of immune responses to injury of normal tissue due to other causes (Naidoo et al 2015). Consequently, tremelimumab has the potential to exacerbate underlying autoimmune diseases in patients who already have a diminished mechanism of immunologic tolerance.
  - Is it considered to be included as missing information: No
  - Rationale: The possible risk to patients with pre-existing autoimmune disease is common to all immunotherapy agents (and as such is familiar to prescribers) and is sufficiently managed through the SmPC, which states that this population has not been studied. Further characterisation of this population is therefore neither feasible nor warranted, and as such, this criterion is not relevant for inclusion as missing information.

- ***Untreated CNS metastatic disease, leptomeningeal disease, or cord compression***
  - Reason for exclusion: Patients with these conditions have significantly worse prognoses and were excluded from the clinical development program to ensure the interpretability of efficacy. However, patients with stable CNS metastases were not excluded from tremelimumab clinical trials.
  - Is it considered to be included as missing information: No
  - Rationale: Based on the mechanism of action of tremelimumab, components of the immune system (eg, T cells) are capable of crossing the blood brain barrier and can possibly exert an antitumour response. Consequently, this population was excluded for concerns regarding efficacy, not safety. No evidence of a different safety profile in patients with stable CNS metastases has been evident in the clinical development programme to date, and the further investigation of tremelimumab in patients with untreated metastatic CNS disease, leptomeningeal disease, or cord compression is not feasible due to the poor prognosis in this patient population. Consequently, this criterion is not relevant for inclusion as missing information.

- ***Paediatric and adolescent patients < 18 years of age***
  - Reason for exclusion: This population was excluded from the tremelimumab clinical trial program based on the general principle that paediatric patients are not exposed to the investigational product where the benefit-risk profile for the intended adult population has not yet been established.
  - Is it considered to be included as missing information: No
  - Rationale: NSCLC is a disease of adults, with only exceptional occurrence in the paediatric population (Dishop and Kuruvilla 2008). Consequently, use in paediatric and adolescent patients is not anticipated for the proposed target indication, and therefore this population is not relevant for inclusion as missing information.

- ***Females who are pregnant or lactating***
  - Reason for exclusion: It is unknown whether tremelimumab is secreted in human milk, and pregnant and lactating females were therefore excluded from clinical studies to avoid potential harm to the unborn foetus or breastfeeding newborn.
  - Is it considered to be included as missing information: No
  - Rationale: The SmPC recommends tremelimumab not be used during pregnancy or lactation. Use in this population is therefore not anticipated and consequently not relevant for consideration as missing information.

- ***Patients with active primary immunodeficiency***
  - Reason for exclusion: Tremelimumab treatment may not be effective due to underlying immune deficiency.
  - Is it considered to be included as missing information: No
  - Rationale: The safety profile of tremelimumab in this population is not expected to be any different than in the general intended population, as immune checkpoint inhibitors can only alter existing immune mechanisms. Consequently, this criterion is not relevant for inclusion as missing information.

- ***Patients with pre-existing active infection / co-infection including tuberculosis, hepatitis B, hepatitis C, or HIV***
  - Reason for exclusion: PD-L1 or CTLA-4 blockade could lead to an initial exacerbation of the underlying infectious disease or systemic inflammatory response.
  - Is it considered to be included as missing information: No
  - Rationale: The safety profile of this population may differ to that of the general target population as there is the potential for an increased risk of exacerbation of the underlying infectious disease or systemic inflammatory response; however, these are risks with all immunotherapy agents, and consequently prescribers are familiar with this concept. The possible risk to patients is consequently sufficiently managed through the SmPC, which states that this population has not been studied. Further characterisation is therefore neither feasible nor warranted, and as such, this criterion is not relevant for inclusion as missing information.

- ***Patients receiving live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving study treatment***
  - Reason for exclusion: This population is excluded due to concern of live attenuated vaccine complications. PD-1/PD-L1 or CTLA-4 blockade could lead to more vigorous inflammation. In analogy, immune reconstitution in HIV patients was associated with Bacillus Calmette-Guérin vaccine complications (Nuttall et al 2008).
  - Is it considered to be included as missing information: No
  - Rationale: The safety profile of this population may differ to that of the general target population as there is the potential for an increased risk of inflammation and/or vaccine complications; however, these are risks with all immunotherapy agents, and consequently prescribers are familiar with this concept. The possible risk to patients is consequently sufficiently managed through the SmPC, which states that this population has not been studied. Further characterisation is therefore neither feasible

nor warranted, and as such, this criterion is not relevant for inclusion as missing information.

II.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions or adverse reactions with a long latency.

II.4.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table II-14 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure	
	POSEIDON (T + D + SoC)	**HCC tumour pool (T300 + D)**
Pregnant women	Not included in the clinical development program.	
Breastfeeding women		
Patients with hepatic impairment:		
Moderate hepatic impairment [a]	1 participant	4 participants
Severe hepatic impairment [a]	0 participants	0 participants
Patients with severe renal impairment [b]	0 participants	1 participant
Patients with uncontrolled cardiovascular disorders (including congestive heart failure, hypertension, unstable angina, or cardiac arrhythmia)	Not included in the clinical development program.	
Patients with relevant different ethnic origin:		
White	201 participants	204 participants
Asian	97 participants	238 participants
Black or African American	8 participants	11 participants
Other [c]	24 participants	8 participants
Subpopulations carrying relevant genetic polymorphisms	No data available.	

[a] The definitions for hepatic impairment are as follows: normal hepatic function = BIL ≤ ULN and AST ≤ ULN; mild hepatic impairment = BIL ≤ ULN and AST > ULN or BIL > 1 to 1.5 × ULN and any AST; moderate hepatic impairment = BIL > 1.5 to 3 × ULN and any AST, where ULN of BIL is 1.9 IU/L and ULN of AST is 34 IU/L; and severe hepatic impairment = BIL > 3 x ULN and any AST.

[b] The definitions for renal impairment are as follows: normal renal function: CrCL ≥ 90 mL/min, mild renal impairment: CrCL = 60 to 89 mL/min, moderate renal impairment: CrCL = 30 to 59 mL/min, and severe renal impairment: CrCL = 15 to 29 mL/min.

[c] Other includes Multiple, American Indian or Alaska native and Native Hawaiian or other Pacific islander.

II.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

Not applicable.

II.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Based on the clinical setting of use, mode of action, physiological and pharmacological activity, and lack of stimulant and addictive properties, tremelimumab is unlikely to have any potential for abuse.

II.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

II.7.1 Identification of Safety Concerns in the Initial RMP Submission

II.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The reasons for not including an identified or potential risk in the list of safety concerns in the RMP (Version 1) are presented below:

- *Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised):*
  - Infusion-related reactions**.**
- *Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):*
  - Abdominal pain, Arthralgia, Cough/productive cough, Cystitis noninfective, Dysphonia, Dysuria, Myalgia, Night sweats, Peripheral oedema, Pruritus, and Pyrexia.
- *Known risks that do not impact the risk-benefit profile:*
  - Dental and oral soft tissue infections, Diabetes insipidus, Influenza, Oral candidiasis, Meningitis, Pneumonia, and Upper respiratory tract infections.
- *Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:*
  - Amylase increased, ALT increased, AST increased, Lipase increased, and Blood creatinine increased.

II.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

The following topic was classified as an important identified risk for tremelimumab at the time of initial EU RMP approval:

- **Immune-mediated adverse reactions**
  - *Risk benefit impact:* In tremelimumab clinical trials, double check-point inhibition with tremelimumab plus durvalumab (a PD-L1 inhibitor) exhibited a higher overall toxicity in relation to immune-mediated adverse reactions in the target patient population versus durvalumab alone. Although the incidence of severe immune-mediated adverse reactions was low, these events can be potentially serious

or life-threatening for the individual patient, and require careful monitoring, early recognition, timely intervention (by withholding/discontinuation of tremelimumab), and appropriate medical intervention, including systemic corticosteroids.

There were no important potential risks or areas of missing information.

II.7.2 New Safety Concerns and Reclassification with a Submission of an updated RMP

Not applicable.

II.7.3 Details of Important Identified Risks, Important Potential Risks and Missing Information

II.7.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Immune-mediated Adverse Reactions

Potential mechanisms

Tremelimumab specifically blocks CTLA-4 interaction with CD80 and CD86, thus enhancing T-cell activation and proliferation, resulting in increased T-cell diversity. Consequently, as tremelimumab significantly enhances cytotoxic T-cells throughout the body, autoimmune toxicity can arise due off-target effects of an excessively activated immune system.

The spectrum of organ systems affected by immune-mediated adverse reactions is very broad, and as such toxicities can affect almost any organ.

Evidence source(s) and strength of evidence

The development of immune-mediated adverse reactions is consistent with the anti-CTLA-4 drug class (Quirk et al 2015).

In tremelimumab clinical trials, double check-point inhibition with tremelimumab plus durvalumab (a PD-L1 inhibitor) exhibited a higher overall toxicity in relation to immune-mediated adverse reactions in the target patient population versus durvalumab alone.

Characterisation of the risk

This risk is characterised in Table II-15 (immune-mediated pneumonitis), Table II-16 (immune-mediated hepatic events), Table II-17 (immune-mediated GI events), Table II-18 (immune-mediated endocrinopathies), Table II-19 (immune-mediated renal events), Table II-20 (immune-mediated skin events), and Table II-21 (other immune-mediated events). Note: Data in these tables are derived from adverse events programmatically adjudicated as immune-mediated by a pre-specified algorithm.

Risk factors and risk groups

Risk factors for immune-mediated adverse reactions associated with CTLA-4 inhibition are unknown. It is conceivable that any pre-existing immune conditions in any organ system could be risk factors for tremelimumab immune-mediated adverse reactions.

Preventability

As described in the tremelimumab SmPC and PL, careful monitoring for signs and symptoms of immune-mediated adverse reactions, withholding/discontinuation of tremelimumab, and provision of appropriate medical intervention, including systemic corticosteroids, are performed to help prevent further complications.

Impact on the risk-benefit balance of the product

Severe immune-mediated adverse reactions, if not recognised or managed appropriately, can become life-threatening or fatal, which can impact the benefit-risk of tremelimumab.

Public health impact

There is no potential public health impact beyond that within the treated population.

Table II-15 Important Identified Risk: Immune-mediated Adverse Reactions - Immune-mediated Pneumonitis

Indication	Treatment group	Number of patients (%)						
		Frequency and severity			Event outcome			Discontinuation of study treatment
		Any AE	CTCAE Grade 3-4	Serious	Resolved	Not resolved	Resulted in death	
Pneumonitis (Grouped term)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	12 (3.6)	3 (0.9)	5 (1.5)	9 (2.7)	2 (0.6)	1 (0.3)	3 (0.9)
	D + SoC (N=334)	10 (3.0)	4 (1.2)	5 (1.5)	6 (1.8)	4 (1.2)	0	2 (0.6)
HCC (HCC-tumour pool)	T300 + D (N=462)	6 (1.3)	1 (0.2)	4 (0.9)	3 (0.6)	2 (0.4)	1 (0.2)	2 (0.4)

Table II-16 Important Identified Risk: Immune-mediated Adverse Reactions - Immune-mediated Hepatic Events

Indication	Treatment group	Number of patients (%)						
		Frequency and severity			Event outcome			Discontinuation of study treatment
		Any AE	CTCAE Grade 3-4	Serious	Resolved	Not resolved	Resulted in death	
Hepatic Events (Grouped term)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	12 (3.6)	7 (2.1)	6 (1.8)	7 (2.1)	4 (1.2)	1 (0.3)	3 (0.9)
	D + SoC (N=334)	11 (3.3)	8 (2.4)	5 (1.5)	10 (3.0)	1 (0.3)	0	5 (1.5)
HCC (HCC-tumour pool)	T300 + D (N=462)	34 (7.4)	21 (4.5)	11 (2.4)	13 (2.8)	18 (3.9)	3 (0.6)	10 (2.2)

Table II-17 Important Identified Risk: Immune-mediated Adverse Reactions - Immune-mediated GI Events

Indication	Treatment group	Number of patients (%)						
		Frequency and severity			Event outcome			Discontinuation of study treatment
		Any AE	CTCAE Grade 3-4	Serious	Resolved	Not resolved	Resulted in death	
Diarrhoea / Colitis (Grouped term)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	17 (5.2)	6 (1.8)	6 (1.8)	15 (4.5)	2 (0.6)	0	4 (1.2)
	D + SoC (N=334)	6 (1.8)	2 (0.6)	4 (1.2)	4 (1.2)	2 (0.6)	0	3 (0.9)
HCC (HCC-tumour pool)	T300 + D (N=462)	31 (6.7)	17 (3.7)	17 (3.7)	29 (6.3)	2 (0.4)	0	5 (1.1)
Intestinal Perforation (Grouped term)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	0	0	0	0	0	0	0
	D + SoC (N=334)	0	0	0	0	0	0	0
HCC (HCC-tumour pool)	T300 + D (N=462)	0	0	0	0	0	0	0
Pancreatic Events (Grouped term)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	6 (1.8)	4 (1.2)	4 (1.2)	4 (1.2)	1 (0.3)	1 (0.3)	1 (0.3)
	D + SoC (N=334)	3 (0.9)	2 (0.6)	0	3 (0.9)	0	0	1 (0.3)
HCC (HCC-tumour pool)	T300 + D (N=462)	9 (1.9)	7 (1.5)	1 (0.2)	6 (1.3)	3 (0.6)	0	0

Table II-18 Important Identified Risk: Immune-mediated Adverse Reactions - Immune-mediated Endocrinopathies

Indication	Treatment group	Number of patients (%)						
		Frequency and severity			Event outcome			Discontinuation of study treatment
		Any AE	CTCAE Grade 3-4	Serious	Resolved	Not resolved	Resulted in death	
Adrenal Insufficiency (Grouped term)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	8 (2.4)	2 (0.6)	3 (0.9)	1 (0.3)	7 (2.1)	0	0
	D + SoC (N=334)	4 (1.2)	1 (0.3)	2 (0.6)	0	4 (1.2)	0	0
HCC (HCC-tumour pool)	T300 + D (N=462)	6 (1.3)	1 (0.2)	1 (0.2)	2 (0.4)	4 (0.9)	0	0
Type I Diabetes Mellitus (Grouped term)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	1 (0.3)	1 (0.3)	1 (0.3)	0	1 (0.3)	0	0
	D + SoC (N=334)	1 (0.3)	1 (0.3)	1 (0.3)	0	1 (0.3)	0	1 (0.3)
HCC (HCC-tumour pool)	T300 + D (N=462)	0	0	0	0	0	0	0
Hyperthyroid Events (Grouped term)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	9 (2.7)	0	0	7 (2.1)	2 (0.6)	0	0
	D + SoC (N=334)	4 (1.2)	1 (0.3)	0	0	4 (1.2)	0	0
HCC (HCC-tumour pool)	T300 + D (N=462)	21 (4.5)	1 (0.2)	2 (0.4)	17 (3.7)	4 (0.9)	0	1 (0.2)
Hypophysitis (Grouped term)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	5 (1.5)	2 (0.6)	3 (0.9)	0	5 (1.5)	0	0
	D + SoC (N=334)	1 (0.3)	1 (0.3)	1 (0.3)	0	1 (0.3)	0	0
HCC (HCC-tumour pool)	T300 + D (N=462)	5 (1.1)	0	1 (0.2)	2 (0.4)	3 (0.6)	0	0
Hypothyroid Events (Grouped term)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	27 (8.2)	0	0	5 (1.5)	22 (6.7)	0	0
	D + SoC (N=334)	20 (6.0)	0	0	8 (2.4)	12 (3.6)	0	0

Table II-18 Important Identified Risk: Immune-mediated Adverse Reactions - Immune-mediated Endocrinopathies

Indication	Treatment group	Number of patients (%)						
		Frequency and severity			Event outcome			Discontinuation of study treatment
		Any AE	CTCAE Grade 3-4	Serious	Resolved	Not resolved	Resulted in death	
HCC (HCC-tumour pool)	T300 + D (N=462)	46 (10.0)	0	0	6 (1.3)	40 (8.7)	0	0
Thyroiditis (Grouped term)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	4 (1.2)	0	0	2 (0.6)	2 (0.6)	0	1 (0.3)
	D + SoC (N=334)	3 (0.9)	0	0	2 (0.6)	1 (0.3)	0	0
HCC (HCC-tumour pool)	T300 + D (N=462)	6 (1.3)	0	0	2 (0.4)	4 (0.9)	0	0

Table II-19 Important Identified Risk: Immune-mediated Adverse Reactions - Immune-mediated Renal Events

Indication	Treatment group	Number of patients (%)						
		Frequency and severity			Event outcome			Discontinuation of study treatment
		Any AE	CTCAE Grade 3-4	Serious	Resolved	Not resolved	Resulted in death	
Renal Events (Grouped term)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	4 (1.2)	1 (0.3)	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)	3 (0.9)
	D + SoC (N=334)	2 (0.6)	2 (0.6)	2 (0.6)	0	2 (0.6)	0	1 (0.3)
HCC (HCC-tumour pool)	T300 + D (N=462)	4 (0.9)	2 (0.4)	2 (0.4)	3 (0.6)	1 (0.2)	0	2 (0.4)

Table II-20 Important Identified Risk: Immune-mediated Adverse Reactions - Immune-mediated Skin Events

Indication	Treatment group	Number of patients (%)						
		Frequency and severity			Event outcome			Discontinuation of study treatment
		Any AE	CTCAE Grade 3-4	Serious	Resolved	Not resolved	Resulted in death	
Dermatitis / Rash (Grouped term)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	24 (7.3)	4 (1.2)	3 (0.9)	16 (4.8)	8 (2.4)	0	1 (0.3)
	D + SoC (N=334)	9 (2.7)	3 (0.9)	2 (0.6)	5 (1.5)	4 (1.2)	0	2 (0.6)
HCC (HCC-tumour pool)	T300 + D (N=462)	26 (5.6)	10 (2.2)	7 (1.5)	19 (4.1)	7 (1.5)	0	3 (0.6)

Table II-21 Important Identified Risk: Immune-mediated Adverse Reactions – Other Immune-mediated Events

Indication	Treatment group	Number of patients (%)						
		Frequency and severity			Event outcome			Discontinuation of study treatment
		Any AE	CTCAE Grade 3-4	Serious	Resolved	Not resolved	Resulted in death	
Myocarditis (Grouped term)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	1 (0.3)	0	1 (0.3)	0	0	1 (0.3)	1 (0.3)
	D + SoC (N=334)	1 (0.3)	0	1 (0.3)	0	0	1 (0.3)	0
HCC (HCC-tumour pool)	T300 + D (N=462)	2 (0.4)	0	1 (0.2)	0	1 (0.2)	1 (0.2)	1 (0.2)
Myositis (Grouped term)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	2 (0.6)	2 (0.6)	2 (0.6)	1 (0.3)	1 (0.3)	0	1 (0.3)
	D + SoC (N=334)	0	0	0	0	0	0	0
HCC (HCC-tumour pool)	T300 + D (N=462)	3 (0.6)	2 (0.4)	2 (0.4)	1 (0.2)	2 (0.4)	0	2 (0.4)

Table II-21 Important Identified Risk: Immune-mediated Adverse Reactions – Other Immune-mediated Events

Indication	Treatment group	Number of patients (%)						
		Frequency and severity			Event outcome			Discontinuation of study treatment
		Any AE	CTCAE Grade 3-4	Serious	Resolved	Not resolved	Resulted in death	
Myasthenia Gravis (Grouped term)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	0	0	0	0	0	0	0
	D + SoC (N=334)	0	0	0	0	0	0	0
HCC (HCC-tumour pool)	T300 + D (N=462)	2 (0.4)	0	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Guillain-Barre Syndrome (PT)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	0	0	0	0	0	0	0
	D + SoC (N=334)	0	0	0	0	0	0	0
HCC (HCC-tumour pool)	T300 + D (N=462)	0	0	0	0	0	0	0
Immune Thrombocytopenia (PT)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	1 (0.3)	0	0	0	1 (0.3)	0	0
	D + SoC (N=334)	0	0	0	0	0	0	0
HCC (HCC-tumour pool)	T300 + D (N=462)	0	0	0	0	0	0	0
Encephalitis Autoimmune (PT)								
NSCLC (POSEIDON study)	T + D + SoC (N=330)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0	0	1 (0.3)
	D + SoC (N=334)	0	0	0	0	0	0	0
HCC (HCC-tumour pool)	T300 + D (N=462)	0	0	0	0	0	0	0

II.7.3.2 Presentation of Missing Information

There is no missing information for tremelimumab.

II.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

II.8.1 Summary of the Safety Concerns

Safety concerns for tremelimumab are summarised in Table II-22.

Table II-22 Summary of Safety Concerns

Important identified risks	• Immune-mediated adverse reactions
Important potential risks	None
Missing information	None

III. PART III: PHARMACOVIGILANCE PLAN

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Not applicable - no routine pharmacovigilance activities are proposed beyond adverse reaction reporting and signal detection.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable - no additional pharmacovigilance activities are proposed.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable.

IV. PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

V. PART V: RISK MINIMISATION MEASURES

V.1 ROUTINE RISK MINIMISATION MEASURES

A summary of routine risk minimisation measures per safety concern are provided in Table V-1.

Table V-1 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Immune-mediated adverse reactions	**Routine risk communication:** • SmPC Section 4.8 • PL Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC Sections 4.2 and 4.4: – Monitoring for signs and symptoms – Withholding dose or stopping treatment – Treating with corticosteroids • PL Section 2: – How to detect early signs and symptoms **Other routine risk minimisation measures beyond the Product Information:** • Prescription-only medicine

V.2 ADDITIONAL RISK MINIMISATION MEASURES

V.2.1 Patient Card

Objectives

To ensure patients and carers are aware of the symptoms of immune-mediated adverse reactions and understand the importance of early detection and prompt action.

Rationale for the additional risk minimisation activity

Appropriate recognition and management of immune-mediated adverse reactions can avoid worsening to life-threatening or fatal complications. Raising awareness of potential symptoms of immune-mediated adverse reactions will promote early detection and facilitate prompt management; this will reduce the clinical impact of immune-mediated adverse reactions.

Target audience and planned distribution path

Information will be made available to patients and carers in a manner appropriate to each market in which AstraZeneca launches tremelimumab and in accordance with local regulatory requirements.

Plans to evaluate the effectiveness of the interventions and criteria for success

Routine pharmacovigilance is in place to evaluate effectiveness of risk minimisation measures.

V.3 SUMMARY OF RISK MINIMISATION MEASURES

Table V-2 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Immune-mediated adverse reactions	**Routine risk minimisation measures:** • SmPC Sections 4.2, 4.2, and 4.8 • PL Sections 2 and 4 • Prescription-only medicine **Additional risk minimisation measures:** • Patient card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None. **Additional pharmacovigilance activities:** • None.

VI. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR IMJUDO™ / TREMELIMUMAB ASTRAZENECA™ (TREMELIMUMAB)

Summary of risk management plan for IMJUDO™ / TREMELIMUMAB ASTRAZENECA (tremelimumab)

This is a summary of the risk management plan (RMP) for IMJUDO / TREMELIMUMAB ASTRAZENECA (tremelimumab). The RMP details important risks of IMJUDO / TREMELIMUMAB ASTRAZENECA, how these risks can be minimised, and how more information will be obtained about IMJUDO / TREMELIMUMAB ASTRAZENECA's risks and uncertainties (missing information).

IMJUDO / TREMELIMUMAB ASTRAZENECA's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how IMJUDO / TREMELIMUMAB ASTRAZENECA should be used.

This summary of the RMP for IMJUDO / TREMELIMUMAB ASTRAZENECA 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 the IMJUDO / TREMELIMUMAB ASTRAZENECA RMP.

VI.1 The medicine and what it is used for

IMJUDO / TREMELIMUMAB ASTRAZENECA is authorised:

- In combination with durvalumab and platinum-based chemotherapy for the first-line treatment of adults with metastatic non-small cell lung cancer (NSCLC) with no sensitising epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) positive mutations (under the tradename TREMELIMUMAB ASTRAZENECA); and
- In combination with durvalumab for the first-line treatment of adults with advanced or unresectable hepatocellular carcinoma (under the tradename IMJUDO).

It contains tremelimumab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of IMJUDO / TREMELIMUMAB ASTRAZENECA's benefits can be found in IMJUDO / TREMELIMUMAB ASTRAZENECA's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage**.**

VI.2 Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of IMJUDO / TREMELIMUMAB ASTRAZENECA, together with measures to minimise such risks and the proposed studies for learning more about IMJUDO / TREMELIMUMAB ASTRAZENECA'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 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 (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of IMJUDO / TREMELIMUMAB ASTRAZENECA, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

VI.2.1 List of important risks and missing information

Important risks of IMJUDO / TREMELIMUMAB ASTRAZENECA 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 IMJUDO / TREMELIMUMAB ASTRAZENECA. 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 on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table VI-1 List of Important Risks and Missing Information

Important identified risks	• Immune-mediated adverse reactions
Important potential risks	None
Missing Information	None

VI.2.2 Summary of important risks

A summary of the important identified risk of immune-mediated adverse reactions is provided in Table VI-2.

Table VI-2 Important Identified Risk: Immune-mediated Adverse Reactions

Evidence for linking the risk to the medicine	The development of immune-mediated adverse reactions is consistent with the anti-CTLA-4 drug class. In IMJUDO / TREMELIMUMAB ASTRAZENECA clinical trials, double check-point inhibition with IMJUDO / TREMELIMUMAB ASTRAZENECA plus durvalumab (a PD-L1 inhibitor) exhibited a higher overall toxicity in relation to immune-mediated adverse reactions in the target patient population versus durvalumab alone.
Risk factors and risk groups	Risk factors specific for immune-mediated adverse reactions associated with CTLA-4 inhibition are unknown. It is conceivable that any pre-existing immune conditions in any organ system could be risk factors for IMJUDO / TREMELIMUMAB ASTRAZENECA immune-mediated adverse reactions.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections 4.2, 4.2, and 4.8 • PL Sections 2 and 4 • Prescription-only medicine **Additional risk minimisation measures:** • Patient card

VI.2.3 Post-authorisation development plan

VI.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of IMJUDO / TREMELIMUMAB ASTRAZENECA.

VI.2.3.2 Other studies in post-authorisation development plan

There are no studies required for IMJUDO / TREMELIMUMAB ASTRAZENECA.

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