European Union Risk Management Plan	
Drug Substance	Durvalumab
Version Number	11
Succession Number	2
Data lock point	15 January 2024
Date	See e-signature page

EUROPEAN UNION (EU) RISK MANAGEMENT PLAN (RMP)

FOR

IMFINZI™ (DURVALUMAB)

The content of this EU RMP has been reviewed and approved by the Marketing Authorisation Holder's Deputy Qualified Person for Pharmacovigilance (QPPV), as delegated by the QPPV. The electronic signature is available at the end of the document.

ADMINISTRATIVE INFORMATION

Rationale for submitting an updated RMP

This EU RMP (Version 11) has been updated to:

- Add a new indication (*IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy as adjuvant treatment, for the treatment of adults with resectable NSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements*; see Part I:).

Summary of significant changes in this RMP

Part I:	Updated to include an additional indication and dosage regimen.
Part II SI:	Epidemiology data relevant to the new indication added.
Part II SIII:	Exposure data in support of the new indication added.
Part II SIV:	Exposure data in support of the new indication added.
Part IV:	AEGEAN study added as a post-authorisation efficacy study
Part VI:	Updated with the changes outlined above.
Part VII:	Annex 5: Updated to reference the AEGEAN study protocol

Other RMP versions under evaluation

Not applicable.

Details of currently approved RMP

Version number:	Version 11
Approved with procedure:	EMEA/H/C/004771/II/0064
Date of approval:	27 February 2025

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
ALK	anaplastic lymphoma kinase
AST	aspartate aminotransferase
BCG	Bacillus Calmette-Guérin
BIL	bilirubin
BRAF	activating serine threonine-protein kinase-B-raf kinase
BTC	biliary tract cancer
BMI	body mass index
CCRT	concurrent chemoradiation therapy
CD	cluster of differentiation
CNS	central nervous system
CrCL	creatinine clearance
CRT	chemoradiation therapy
CTLA-4	cytotoxic t-lymphocyte-associated antigen 4
CTx	platinum based doublet chemotherapy
D	durvalumab
DCO	data cut-off
dMMR	mismatch repair deficient
DNA	deoxyribonucleic acid
EEA	European Economic Area
EGFR	epidermal growth factor receptor
EP	etoposide with either carboplatin or cisplatin
EPAR	European Public Assessment Report
ePPND	Enhanced prenatal and postnatal development
ESMO	European Society for Medical Oncology
ES-SCLC	Extensive-stage small cell lung cancer
EU	European Union
FDA	Food and Drug Administration
GBC	gallbladder cancer
GBD	Global Burden of Disease
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HRQoL	health-related quality of life

Abbreviation/ Special term	Definition/Explanation
IARC	International Agency for Research on Cancer
ICH	International Council for Harmonisation
IgG1κ	immunoglobulin G1 kappa
IHCC	intrahepatic cholangiocarcinoma
imAE	immune-mediated adverse event
iv	intravenous
LS-SCLC	limited-stage small cell lung cancer
mAb	monoclonal antibody
MOA	mechanism of action
NCCN	National Comprehensive Cancer Network
NPCR	National Program of Cancer Registries
NSCLC	non-small cell lung cancer
NTRK	neurotrophic receptor tyrosine kinase
O	olaparib
OS	overall survival
PCI	prophylactic cranial irradiation
PD-1	programmed cell death protein 1
PD-L(1/2)	programmed cell death ligand (1/2)
PL	patient leaflet
pMMR	mismatch repair proficient
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
QPPV	Qualified Person for Pharmacovigilance
RECIST	Response Evaluation Criteria in Solid Tumours
RMP	Risk Management Plan
SCLC	Small cell lung cancer
SEER	Surveillance, Epidemiology, and End Results
SoC	standard-of-care (chemotherapy)
SmPC	Summary of Product Characteristics
UC	urothelial carcinoma
ULN	upper limit of normal
UK	United Kingdom
US	United States

I: PART I: PRODUCT OVERVIEW

Table I-1 Product Overview

Active substance(s) (INN or common name)	Durvalumab
Pharmacotherapeutic group(s) (ATC Code)	L01FF03
Marketing Authorisation Holder	AstraZeneca AB, 15185 Södertälje, Sweden
Medicinal products to which this RMP refers	One
Invented name(s) in the EEA	IMFINZI
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class**: IMFINZI is a fully human, high affinity, IgG1κ mAb.
	Summary of mode of action: IMFINZI is an immunomodulatory therapy within the pharmacotherapeutic group of the antineoplastic agents, which selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1) while leaving PD-1/PD-L2 interaction intact.
	Important information about its composition: IMFINZI is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. IMFINZI contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma receptors involved in triggering effector function.
Hyperlink to the Product Information	[Summary of Product Characteristics]
Indication(s) in the EEA	**Current**: • IMFINZI as monotherapy is indicated for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. • IMFINZI in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with ES-SCLC. • IMFINZI in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic BTC. • IMFINZI in combination with tremelimumab 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. • IMFINZI in combination with tremelimumab is indicated for the first-line treatment of adults with advanced or unresectable HCC. • IMFINZI as monotherapy is indicated for the first-line treatment of adults with advanced or unresectable HCC.

Table I-1 Product Overview

	• IMFINZI in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with: – IMFINZI as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR) – IMFINZI in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR) • IMFINZI as monotherapy is indicated for the treatment of adults LS-SCLC whose disease has not progressed following platinum-based CRT. • IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy as adjuvant treatment, is indicated for the treatment of adults with resectable NSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements.
Dosage in the EEA	**Current**: • For locally advanced NSCLC: 10 mg/kg Q2W or 1500 mg Q4W[a] until disease progression, or unacceptable toxicity, or a maximum duration of 12 months[b]. • For ES-SCLC: 1500 mg[c] in combination with chemotherapy Q3W (21 days) for 4 cycles, followed by 1500 mg Q4W as monotherapy, until disease progression or unacceptable toxicity. • For BTC: 1500 mg[g] in combination with chemotherapy Q3W (21 days), followed by 1500 mg Q4W as monotherapy, until disease progression or unacceptable toxicity. • For metastatic NSCLC: – *During platinum chemotherapy*: 1500 mg[d] in combination with tremelimumab 75 mg and platinum-based chemotherapy Q3W (21 days) for 4 cycles (12 weeks). – *Post-platinum chemotherapy*: 1500 mg Q4W as monotherapy and histology-based pemetrexed maintenance therapy Q4W. A fifth dose of tremelimumab 75 mg alongside IMFINZI dose 6 should be given at Week 16. Treatment should be continued until disease progression or unacceptable toxicity. • For HCC: – IMFINZI 1500 mg[e] administered in combination with 300 mg[e] tremelimumab as a single dose, followed by IMFINZI 1500 mg as monotherapy Q4W, until disease progression or unacceptable toxicity. – IMFINZI 1500 mg Q4W[f], as long as clinical benefit is observed or until unacceptable toxicity. • For endometrial cancer: IMFINZI 1120 mg in combination with carboplatin and paclitaxel Q3W (21 days) for a minimum of 4 and up to 6 cycles, followed by maintenance with IMFINZI 1500 mg[h] Q4W as monotherapy (dMMR patients) or in combination with olaparib 300 mg twice daily (pMMR patients), until disease progression or unacceptable toxicity. • For LS-SCLC: IMFINZI 1500 mg[a] Q4W, until disease progression, unacceptable toxicity, or a maximum of 24 months. • For resectable NSCLC: IMFINZI 1500 mg[i] in combination with platinum-based chemotherapy Q3W for up to 4 cycles prior to surgery,

Table I-1 Product Overview

	followed by 1500 mg monotherapy Q4W for up to 12 cycles after surgery, until disease progression that precludes definitive surgery or unacceptable toxicity (neoadjuvant phase) or recurrence, unacceptable toxicity, or a maximum of 12 cycles after surgery (adjuvant phase).
Pharmaceutical form(s) and strengths	Concentrate for solution for infusion (sterile concentrate). Clear to opalescent, colourless to slightly yellow solution, free from visible particles. Each mL of concentrate for solution contains 50 mg of durvalumab. Each 2.4 mL vial contains 120 mg of durvalumab. Each 10 mL vial contains 500 mg of durvalumab.
Is the product subject to additional monitoring in the EU?	Yes

[a] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 10 mg/kg Q2W or 20 mg/kg Q4W as monotherapy until weight increases to greater than 30 kg.

[b] It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

[c] ES-SCLC patients with a body weight of 30 kg or less must receive weight-based dosing of IMFINZI 20 mg/kg in combination with chemotherapy Q3W (21 days), followed by 20 mg/kg Q4W as monotherapy until weight increases to greater than 30 kg.

[d] Metastatic NSCLC patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg until weight increases to greater than 30 kg. Patients with a body weight of 34 kg or less must receive weight-based dosing equivalent to tremelimumab 1 mg/kg until the weight increases to greater than 34 kg.

[e] HCC patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg until weight increases to greater than 30 kg. Patients with a body weight of 40 kg or less must receive weight-based dosing, equivalent to tremelimumab 4 mg/kg until weight increases to greater than 40 kg.

[f] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg Q4W as monotherapy until weight increases to greater than 30 kg.

[g] BTC patients with a body weight of 36 kg or less must receive weight-based dosing of IMFINZI at 20 mg/kg in combination with chemotherapy Q3W (21 days), followed by 20 mg/kg Q4W as monotherapy until weight increases to greater than 36 kg.

[h] Endometrial cancer patients with a body weight of 30 kg or less during maintenance phase must receive weight-based dosing equivalent to IMFINZI at 20 mg/kg, until weight is greater than 30 kg.

[i] Resectable NSCLC patients with a body weight of 30 kg or less must receive weight-based dosing of IMFINZI at 20 mg/kg. In combination with platinum-based chemotherapy dose at 20 mg/kg Q3W (21 days) prior to surgery, followed by monotherapy at 20 mg/kg Q4W after surgery until weight increases to greater than 30 kg.

II: PART II: SAFETY SPECIFICATION

II: 1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

II: 1.1 Lung Cancer

There are 2 distinct histological subtypes of lung cancer: NSCLC and SCLC representing approximately 85% and 10 to 15% of all lung cancers, respectively (American Cancer Society 2019).

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).

NSCLC

The incidence rates of NSCLC are highly variable and depend largely on local smoking prevalence. An overview of incident cases of Stage III unresectable and Stage IV NSCLC, by region, are presented in Table II-1.

In the US from 2010 to 2017, incidence rates of Stage II, IIIA, and IIIB NSCLC remained stable, and in 2017 ranged from 3.0 for Stage II disease, to 4.7 for stage IIIA disease (Ganti et al 2021).

Table II-1 Incident Cases of NSCLC, 2018

	Stage III unresectable	Stage IV	Total NSCLC all stages	Stage III unresectable as % of total NSCLC	Stage IV as % of total NSCLC
United States	39731	75643	181788	21.9	41.6
France	5984	16300	34059	17.6	47.9
Germany	7182	19601	43754	16.4	44.8
Italy	5673	17561	37433	15.2	46.9
Spain	3798	10613	21083	18.0	50.3
United Kingdom	7102	18000	39870	17.8	45.1

Table II-1 Incident Cases of NSCLC, 2018

	Stage III unresectable	Stage IV	Total NSCLC all stages	Stage III unresectable as % of total NSCLC	Stage IV as % of total NSCLC
Japan	15871	24509	93276	17.0	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

SCLC

Approximately 250000 new cases of SCLC are reported globally each year, which results in approximately 200000 patient deaths (Rudin et al 2021).

A summary of incident cases of SCLC (by geographic region) in 2018 is provided in Table II-2; however, the relative incidence of SCLC has decreased over the last 4 decades reflecting decreases in smoking prevalence and reduced occupational hazards (Basumallik and Agarwal 2023).

Table II-2 Incident Cases of SCLC, 2018

Geography	Incident cases
United States	27083
France	4217
Germany	8945
Italy	4459
Spain	3988
United Kingdom	5340
Japan	7860

Note: The Decision Resources Group utilised different data sources for different countries. SCLC is defined according to the International Classification of Diseases, Tenth Revision utilising diagnosis code C34 and histology codes 8041-8045.
Source: Decision Resources Group 2018

Prevalence

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-3).

Table II-3 Five-year Prevalence Rate for Lung Cancer (per 100000), 2018

Region/country	Males	Females	Total
World	34.1	21.6	27.9
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 in GLOBOCAN based on the International Classification of Diseases, Tenth Revision as a diagnosis with the code C33-34 (including trachea).
Source: Bray et al 2018

NSCLC

The number of prevalent (restaged, to allow for movement by stage over time, over 5 years) cases of Stages IIIB and IV NSCLC in 2018 is presented in Table II-4.

Table II-4 Prevalent Cases of Stages IIIB and IV NSCLC, 2018

Country	Stage IIIB NSCLC	Stage IV
United States	17388	202933
France	3662	44095
Germany	4692	56689
Italy	4084	50029
United Kingdom	3849	50446
Spain	2343	27980
Japan	15014	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

SCLC

Small-cell lung cancer accounts for between 10% and 15% of all lung cancer cases (American Cancer Society 2024). Amongst patients presenting with SCLC, approximately 30% will be diagnosed with LS-SCLC and approximately 70% will be diagnosed with ES-SCLC (Faivre-Finn et al 2017).

Demographics of the population in the authorised 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-5.

Table II-5 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
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
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

NSCLC

Across the US, Japan and EU 5, the estimated numbers of Stage III unresectable NSCLC cases diagnosed among persons aged ≥ 65 years was more than double the number in adults aged 20 to 64 years (72.4% of cases of Stage III unresectable) (Decision Resources Group 2018). In the US, the majority of cases of resectable NSCLC are diagnosed in patients aged 65 to 75 (ASCO CancerLinQ 2014-2019).

Males are more likely to be diagnosed with NSCLC; 56% of incident resectable Stage II to III NSCLC case, 62% of incident unresectable Stage III NSCLC cases, and 60% of incident Stage IV NSCLC cases occur in males (Decision Resources Group 2018, ASCO CancerLinQ 2014-2019). 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.

SCLC

Overall, SCLC has a strong association with current or former tobacco smoking (Peifer et al 2012); however, incidence rates have decreased over time, likely reflecting the decreasing prevalence of tobacco use (Stinchcombe and Gore 2010), and there remains a consistently small percentage of never smokers who are diagnosed with SCLC (approximately 2% to 8% based on published studies; Rudin et al 2021, Paz-Ares et al 2019, Rudin et al 2020).

Small-cell lung cancer is more prevalent in men, although worldwide incidence is increasing in women. In the US, SCLC is less prevalent in African-Americans than White Americans (Rudin et al 2021). In the US during 2016 to 2020, 66% of cases of SCLC were reported in patients ≥ 65 years of age (SEER*Explorer 2023).

Important risk factors for SCLC include tobacco use, gender, age, family history of lung cancer, and environmental factors such as air pollution and exposure to asbestos (Alberg et al 2007, Straif et al 2009, Gray et al 2009, Katanoda et al 2011, Cao et al 2011, Hales et al 2012, Lissowska et al 2010).

The main existing treatment options

NSCLC

The recommended treatment for patients with resectable NSCLC is surgical resection, with or without neoadjuvant/adjuvant chemotherapy. Anti-PD-L1/PD-1 immunotherapy agents have recently become an important part of the therapeutic armamentarium in the treatment of patients with resectable NSCLC, demonstrating clinical benefit in combination with chemotherapy in the neoadjuvant setting (nivolumab) and as monotherapy in the adjuvant setting (atezolizumab and pembrolizumab). Adjuvant osimertinib is recommended in those patients with stage IB-IIIA disease with EGFR exon 19 deletions or L858R who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy (NCCN 2023b).

The standard-of-care for patients with Stage III unresectable NSCLC is definitive platinum based CCRT. IMFINZI may be given as consolidation therapy for patients with Performance Status 0 to 1 who do not experience disease progression after 2 or more cycles of CCRT (NCCN 2018).

Other options are a weekly paclitaxel/carboplatin regimen or pembrolizumab for the first-line treatment of patients with Stage III, unresectable NSCLC who are not candidates for CCRT.

Sequential chemotherapy/radiation therapy or radiation therapy alone is appropriate for frail patients unable to tolerate CCRT.

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 standard-of-care 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).

SCLC

The SoC for the majority of patients diagnosed with LS-SCLC is curative intent concurrent CRT, comprising 4 cycles of platinum-based chemotherapy typically administered every 21 to 28 days concurrently with radiation therapy (NCCN 2024, Dingemans et al 2021 [ESMO Guideline]). The preferred chemotherapy regimen is cisplatin and etoposide; however, for patients who are not candidates for cisplatin or who opt not to receive cisplatin, carboplatin and etoposide is widely accepted as an alternative regimen (Skarlos et al 2001, NCCN 2024, Dingemans et al 2021). For radiation therapy, commonly used regimens include thoracic radiation delivered either over a 3- or 6-week period (Faivre-Finn et al 2017, Bogart et al 2022, Bogart et al 2023, NCCN 2024). Patients diagnosed with very early Stage I-IIA (T1-2, N0, M0) disease are also potential candidates for surgical resection followed by adjuvant platinum-based chemotherapy with or without adjuvant radiation therapy (Rudin et al 2021).

In ES-SCLC, platinum-based chemotherapy (cisplatin or carboplatin in combination with etoposide, irinotecan), are common first-line options (NCCN 2019). Atezolizumab in combination with etoposide and carboplatin was recently approved by the FDA for the first line treatment of ES-SCLC (FDA 2019).

Consolidative thoracic radiotherapy is beneficial for selected patients with extensive-stage disease and good response to systemic therapy (NCCN 2019). Extensive stage patients who also respond to systemic therapy may also receive PCI. If the patient has extensive disease with localised symptomatic sites, palliative radiotherapy should be administered directly to the symptomatic sites (NCCN 2019). Brain metastases should be treated with whole brain radiation therapy.

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

There are very 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).

Morbidity:

NSCLC

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) (American Cancer Society 2019, Walter et al 2015).

SCLC

Patients with SCLC experience a short duration of symptoms prior to diagnosis, with lesions usually inducing cough, wheezing, deep chest pain, and dyspnoea caused by airway obstruction (American Cancer Society 2019).

Mortality:

NSCLC

Median survival data from international randomised controlled trials of nonresectable locally advanced NSCLC following chemoradiation ranges from 12 to 26 months (Spina et al 2013).

For early-stage NSCLC, the 5-year survival rate remains low at approximately 60% for patients with Stage II disease (Goldstraw et al 2016). According to the National Cancer Institute's SEER data, the median survival for Stage III NSCLC patients who did not have surgery (during the initial 6-month period) diagnosed in 2010 to 2014 was 11 months for males and 13 months for females (Spina et al 2013). Furthermore, SEER reported a 5-year survival rate of 14% for Stage IIIA lung cancer patients. 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 just under 5% (Siegel et al 2017).

SCLC

The prognosis of SCLC is poor, with a median OS of 25 to 30 months reported for patients with LS-SCLC after curative intent treatment (Bogart et al 2022), and a median OS of < 10 months reported for patients with ES-SCLC (Wang et al 2017, Alvarado-Luna and Morales-Espinosa 2016).

Important comorbidities

NSCLC

Common comorbidities in patients with NSCLC include: chronic 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).

Comorbidities associated with sequelae from concurrent chemoradiation and Stage III unresectable NSCLC include oesophagitis, radiation pneumonitis, pneumonitis, pulmonary fibrosis, anaemia and neutropenia (Rodrigues et al 2004, Mazeron et al 2010, Rowell and O'Rourke 2004).

SCLC

Common comorbidities in all patients with SCLC (regardless of stage) include hypertension, cardiovascular and cerebrovascular diseases, diabetes (Aarts et al 2015), and chronic obstructive pulmonary disease (Lee et al 2018a, Maxwell et al 2016).

Common side effects associated with chemotherapy include neutropenia, nausea and vomiting, fatigue, anaemia, thrombocytopaenia and risk of infections (Crvenkova 2018).

Toxicities associated with radiation therapy include radiation pneumonitis, radiation pneumonopathy, and acute oesophagitis (Yavas and Yavas 2017). PCI-related acute side effects include fatigue, alopecia, headaches and low-grade nausea while long-term toxicities include memory loss, intellectual impairment or even dementia, and seizures (Yavas and Yavas 2017).

II: 1.2 Biliary Tract Cancer

Incidence

Biliary tract cancers are a group of rare and highly aggressive gastrointestinal cancers with wide geographical diversity (Turkes et al 2019). Biliary tract cancer is comprised of three primary subtypes: GBC, ampullary cancer, and cholangiocarcinomas (IHCC and extrahepatic cholangiocarcinoma [both perihilar and distal]) (Bridgewater et al 2016, Valle et al 2017, Oneda et al 2020).

Globally the incidence of BTC is low, accounting for approximately 3% of all adult cancers (Bridgewater et al 2016); however, incidence varies dependent on geographic region. The incidence rate of cholangiocarcinoma in Western countries is < 3 per 100000 person-years annually, whereas in Southern China and Northern Thailand, it can be up to 40 times higher. The incidence rate of GBC is uniform for most of the Western world, whereas disease clusters are found in India, Japan, and South America (SEER Program [Data Period 2008 to 2018], Valle et al 2021).

Age-standardised incidence rates, combining all main subtypes of BTC, based upon an analysis of data obtained from the IARC, are reported in Table II-6. Incidence rates are shown to vary widely, ranging from 14.35 in Chile, to 1.25 in Vietnam. Countries in the Asia Pacific region and South America have overall higher incidence rates per 100000 person years (Asia Pacific: 1.25 to 10.37, and South America: 3.07 to 14.35) compared with European and North American countries (Europe: 2.34 to 4.16, and North America: 2.67 and 2.70) (Wang et al 2020a).

Table II-6 Incidence Rates Reported As Age-Standardised Rates per 100000 person-years by Country between 2008 to 2012

Country	Incidence Rate	Country	Incidence Rate
Australia	2.76	Italy	4.16
China	3.87	Poland	3.38
Hong Kong	3.47	Spain	3.42
India	2.73	Switzerland	3.04
Japan	6.93	Turkey	2.5
Republic of Korea	10.37	UK	2.29
Thailand	4.72	Argentina	4.38
Vietnam	1.25	Brazil	3.07
Bulgaria	2.35	Chile	14.35
France	3.14	Canada	2.71
Germany	3.29	USA	2.67

Source: Wang et al 2020a

Prevalence

The global prevalence of BTC has risen by a factor of 22%, with 150000 patients being diagnosed with BTC in 2015 (GBD 2016).

Furthermore, the 10-year prevalence of BTC in the US in 2015 was 10.8 per 100000 patients, with Hispanic and Asian/Pacific Islander groups reporting a higher 10-year prevalence of BTC (16.6 and 13.8, respectively) than the other ethnic groups (Wang et al 2020b).

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

Analysis of data from the US NPCR and SEER databases between 2001 and 2015 indicated that age standardised rates for BTC per 100000 person-years in the US was slightly higher in males versus females (5.31 versus 4.85, respectively), although females had a higher incidence of GBC than males (1.92 versus 1.14, respectively) (Wang et al 2020b).

In Europe, most biliary tumours occur sporadically after the age of 50, with a slight predominance of male patients (Vogel et al 2021).

In a published analysis of data from the US NPCR and SEER databases from 2006 to 2015, Hispanic Americans have a higher rate of BTC compared to non Hispanic Americans. In addition, Blacks have a higher rate of BTC compared to Whites. Furthermore, these same data indicate that older age is a risk factor for BTC too (Centers for Disease Control and Prevention 2018).

Overall, the strongest risk factors for BTC are associated with chronic inflammation within the biliary system (Marcano-Bonilla et al 2016), however, there are differences in risk factors between the BTC subtypes. For example, risk factors for GBC include gallstones and gallbladder polyps. Risk factors for IHCC include, but are not limited to, primary sclerosing cholangitis, Caroli's disease, hepatolithiasis, cirrhosis, liver fluke infection, diabetes, hepatitis B and hepatitis C infections (Bridgewater et al 2016, Valle et al 2021). Additionally, the geographical variation in incidence may reflect exposure to different risk factors. For example, the incidence of cholangiocarcinoma in Thailand reflects the impact of chronic infection with liver fluke. In the West, cholangiocarcinoma is associated with chronic inflammation of the biliary tree and hepatic parenchyma (Bridgewater et al 2016).

The main existing treatment options

In patients who are diagnosed early (estimated to be less than 35% of patients globally, and approximately 10% of patients in the US), surgical resection is the only potentially curative treatment option (Ghidini et al 2019, Vogel et al 2021, Marcano-Bonilla et al 2016). However, over 75% of BTC patients present at a late unresectable stage; therefore, most patients are eligible for first-line systemic therapy (Lamarca et al 2014, Takahashi et al 2013).

Gemcitabine plus cisplatin is recommended by global clinical practice guidelines including NCCN, ESMO, and Japanese guidelines (Nagino et al 2021 [Japanese BTC Treatment Guidelines 2019], NCCN 2021a, Valle et al 2016). Other chemotherapy regimens are also actively used, and some are recommended by practice guidelines (eg, gemcitabine + S1 or gemcitabine/cisplatin + S1 in Japanese guidelines and multiple gemcitabine combination and platinum combinations in the NCCN guidelines) and have evidence to support their use in first-line advanced BTC (Nagino et al 2021 [Japanese BTC Treatment Guidelines 2019], NCCN 2021a, Sasaki et al 2021).

Following first-line chemotherapy, patients usually experience disease progression, and a variety of regimens may be required to provide customised care for each patient's needs.

Additional targeted treatment options with tumour agnostic indications include pembrolizumab, and entrectinib and larotrectinib; however, these therapies are limited to those who progressed following prior treatment and/or who have no satisfactory alternative treatment options (NCCN 2021c).

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

Biliary tract cancer is often difficult to diagnose due to its anatomical location and the non-specificity of symptoms. Consequently, approximately 75% of patients have locally advanced or metastatic disease at the time of diagnosis (Turkes et al 2019, Vogel et al 2021), at which time BTC has historically been associated with poor HRQoL (Heffernan et al 2002). Published qualitative research involving direct patient input, has identified significant

symptomatic, functional, and HRQoL burden experienced by patients with advanced BTC (Butt et al 2012, Darwisch et al 2013, Elberg Dengsø et al 2017).

In patients diagnosed at an early stage and eligible for curative resection surgery, the relapse rate is high, with approximately 50% to 70% of patients with BTC who undergo resection surgery developing recurrence (Elberg Dengsø et al 2017, Ghidini et al 2019, Jung et al 2012, Tsilimigras et al 2020). For patients presenting at a late unresectable stage, treatment options are mainly palliative; advanced BTC patients who receive SoC chemotherapy have an extremely poor prognosis (median OS of approximately 1 year, and a 5-year overall survival of 7% to 20%) (Banales et al 2020, Eckel and Schmid 2007, Valle et al 2017, Yachimski and Pratt 2008).

For patients who are ineligible for treatment, approximately half die within 3 to 4 months of presentation from the indirect effects of local tumour progression, bile duct obstruction, liver failure, or sepsis from cholangitis and abscesses (Patel 2011).

Important comorbidities

Data describing comorbidities for patients with BTC is limited. Common comorbidities for BTC patients are hypertension, diabetes mellitus, chronic obstructive pulmonary disease, coronary heart disease, and cerebrovascular disease (Fernández-Ruiz et al 2009, Takahara et al 2020).

II: 1.3 Hepatocellular Carcinoma

Incidence

Primary liver cancer is a major global health problem accounting for approximately 906000 new cases per year globally (American Cancer Society 2021). In Europe, approximately 87000 new cases a year are reported (WHO 2020), whereas the US reports approximately 42000 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-7 presents an estimated incidence of liver cancer and HCC worldwide, by region and gender.

Table II-7 Estimated Number of Incidence Cases of Liver Cancer and HCC, by Gender and Region, 2018

Population	Liver Cancer				HCC			
	Incident cases		Crude incidence rate (per 100000)		Incident cases		Crude incidence rate (per 100000)	
	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 100000 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 100000, while the rates were slightly lower for Austria, Germany, Luxembourg, and Switzerland (range: 6 to 11.99 per 100000). In the same year, countries such as Poland and Hungary had prevalence rates of HCC below 5 per 100000 (Institute for Health Metrics and Evaluation 2016).

Table II-8 presents the estimated 5-year prevalence of liver cancer and HCC worldwide and by region extracted from IARC.

Table II-8 Estimated 5-Year Prevalence of HCC Worldwide and by Region, 2018

Region	Liver Cancer		HCC	
	Five-year prevalence [a]	Proportion/ 100000 [b]	Five-year prevalence	Proportion/ 100000
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

Table II-8 Estimated 5-Year Prevalence of HCC Worldwide and by Region, 2018

Region	Liver Cancer		HCC	
	Five-year prevalence [a]	Proportion/ 100000 [b]	Five-year prevalence	Proportion/ 100000
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 authorised 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]).

Prior to 2020, sorafenib (an oral tyrosine kinase inhibitor targeting multiple kinases) was considered the standard-of-care for advanced HCC in the first-line setting since its approval in 2007 (EASL 2018, Vogel et al 2018). 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).

Hepatocellular carcinoma 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). Hepatocellular carcinoma 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).

Hepatocellular carcinoma 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-9).

Table II-9 Estimated Number of Deaths due to Liver Cancer, by Gender and Region, 2018

Population	Number of Deaths		Crude Mortality Rate (per 100000)	
	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

Table II-9 Estimated Number of Deaths due to Liver Cancer, by Gender and Region, 2018

Population	Number of Deaths		Crude Mortality Rate (per 100000)	
	Male	Female	Male	Female
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 2016) 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 2018b, Arora et al 2016).

II: 1.4 Endometrial Cancer

Incidence

Endometrial cancer is the sixth most common cancer among women, with 417367 new cases being recorded worldwide in 2020, and an age-standardised incidence rate of 8.7 per 100000 women (Sung et al 2021). The highest age-standardised incidence rates of endometrial cancer have been recorded in Europe, North America, Australia/New Zealand, and Polynesia/Micronesia, while the lowest age-standardised incidence rates of endometrial cancer have been recorded in most regions of Africa and South Central Asia (Sung et al 2021).

In Europe, the age-standardised incidence rate per 100000 women for the year 2020 was 16.4 for Northern Europe, 14.2 for Southern Europe, 12.9 for Western Europe, and 20.2 for Eastern Europe (Sung et al 2021).

Prevalence

Endometrial cancer is the most prevalent gynaecologic cancer in high income countries (Ferlay et al 2015). In 2020, the 5-year prevalence rate for endometrial cancer in Europe was 124.74 per 100000 women (International Agency for Research on Cancer 2021).
In 2023, endometrial cancer was the fourth most prevalent cancer among women in the US (7% of cancer cases) (Siegel et al 2023).

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

Incidence of endometrial cancer increases with age. Across Europe, the incidence of endometrial cancer is at least 10 times greater among post-menopausal women compared to pre-menopausal women (Bray et al 2005).

Racial differences in endometrial cancer diagnosis have also been observed. For example, a large, prospective, cohort study conducted in the US demonstrated that the risk of endometrial cancer in women of White ethnicity far exceeded that of African Americans, Native Hawaiians, Japanese Americans, and Latinas; however, African Americans had the highest risk of developing advanced cancer, and African Americans and Latinas had the highest risk of developing tumours with aggressive histology (Setiawan et al 2007). Furthermore, a retrospective cohort study of women living in the UK found that women of South Asian ethnicity were diagnosed at a significantly younger age (mean age: 60.3 years) than women of White ethnicity (mean age: 66.9 years) (Mohammed et al 2021).

Results from meta-analyses have found highly suggestive evidence that BMI (per 5 kg/m2), height (per 10 cm), waist circumference (per 10 cm), weight gain (per 5 kg), type I and type II diabetes mellitus, sedentary behaviour, hypertension, and nulliparity are associated with increased risk of endometrial cancer (Raglan et al 2019).

Additionally, there is suggestive evidence that coffee intake (per one cup/day), physical activity, age at menarche (per 2-year delay), age at last birth (per 5 year increment), metformin use, oral contraceptive use, and smoking are associated with decreased risk of endometrial cancer (Raglan et al 2019).

The main existing treatment options

The current standard-of-care for the first-line treatment for patients with advanced or recurrent endometrial cancer comprises platinum-based chemotherapy, with the combination of carboplatin and paclitaxel the preferred regimen (NCCN 2023a, Oaknin et al 2022).

For patients who progress following prior platinum-based chemotherapy, pembrolizumab (as monotherapy or in combination with lenvatinib) and dostarlimab (as monotherapy) are approved and recommended in NCCN and ESMO guidelines as second-line treatment for

patients who have progressed following prior treatment and who have no satisfactory alternative treatment options, with the choice of treatment guided by a patient's deficient mismatch repair or proficient mismatch repair status (NCCN 2023a, Oaknin et al 2022).

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

Globally, the age-standardised mortality rate for cancer of the corpus uteri is 1.8 per 100000, with the highest rates in Eastern Europe (3.7 per 100,000), Micronesia/Polynesia (3.5 per 100000), and Northern America (3.0 per 100000) (Sung et al 2021). A total of 97370 deaths worldwide were recorded in 2020 (Sung et al 2021).

Endometrial cancer often presents as post-menopausal bleeding with a median age at diagnosis of 61 years (Crosbie et al 2022). The majority of patients are diagnosed at an early stage (Stage I or II) and these patients have a better prognosis with 5-year survival rates ranging from 74% to 91% (Creasman et al 2006). For patients diagnosed at a later stage or with advanced endometrial cancer the 5-year survival rates range from 50% to 66% for Stage III and 20% to 26% for Stage IV disease (Creasman et al 2006). The poor survival rate for advanced endometrial cancer is due, in part, to the limited treatment options available after first-line chemotherapy (Halla 2022).

Important comorbidities

In a retrospective study of 594 endometrial cancer or endometrial lesions cases in Romania, the most common comorbidities were hypertension (62.28%), obesity (35.01%), and diabetes (22.89%) (Furau et al 2021). Endometrial cancer has also been associated with comorbid hypertension in meta-analyses (Connaughton and Dabagh 2022) and database studies (Nicholas et al 2014), and compared to patients without endometrial cancer, patients with a diagnosis of endometrial cancer had a higher prevalence of cardiovascular disease at cancer index date and an increased risk for developing cardiovascular disease including ischaemic heart diseases, pulmonary heart disease, and diseases of the veins and lymphatics after endometrial cancer diagnosis (Anderson et al 2022).

Additionally, evidence suggests that metabolic syndrome may be a comorbidity in endometrial cancer. In a systematic literature review, the prevalence of metabolic syndrome in endometrial cancer patients compared to individuals without endometrial cancer varied based on metabolic syndrome definition, ranging from 6% versus 2% (International Diabetes Federation definition) to 62% versus 38% (Harmonised metabolic syndrome guidelines) (Adambekov et al 2019).

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

II: 2.1 Summary of Key Safety Findings from Non-Clinical Data

Key safety findings from the non-clinical toxicology and safety pharmacology studies with potential relevance to human usage are described in Table II-10.

Table II-10 IMFINZI: Key Findings from Non-clinical Data

Toxicity
Key issues identified from acute or repeat-dose toxicity studies
Administration of IMFINZI to cynomolgus monkeys was not associated with any treatment-related adverse effects considered relevant to humans. The only adverse findings in the repeat-dose toxicity studies were consistent with antidrug antibody-associated morbidity and mortality. Similar observations have been made in cynomolgus monkeys administered human mAbs unrelated to IMFINZI, and it is generally recognised that immunogenicity of human mAbs in non-clinical species and consequent adverse events are not predictive for humans. In the pivotal Good Laboratory Practice, 13-week, repeat-dose toxicity study in cynomolgus monkeys, treatment with IMFINZI was not associated with any adverse effects. No safety concerns relevant to human usage have been identified.
Reproductive/development toxicity
In the 3-month iv repeat-dose toxicity study in sexually mature cynomolgus monkeys, no treatment-related effects were observed on the male or female reproductive organs, the regulatory accepted surrogate endpoint for fertility in nonhuman primates. In an ePPND study, iv administration of IMFINZI from confirmation of pregnancy (gestation day 20) until parturition was associated with an apparent increase in mid- and late-stage pregnancy losses, stillbirths or infants found dead, and total pregnancy and infant losses compared to a concurrent control, without a clear trend in dose relationship. Pregnancy outcomes in the IMFINZI -treated groups were within the normal range when compared to historical control. Considering the findings in the ePPND study and scientific literature data indicating a role for PD-1/PD-L1 interactions on the maternal-foetal interface, with antibody-mediated PD-L1 blockade resulting in an increase in foetal resorption in mice (D'Addio et al 2011, Guleria et al 2005, Taglauer et al 2009), appropriate labelling and risk management procedures for women of childbearing potential are warranted.
Genotoxicity
In accordance ICH S6(R1) guidance, genotoxicity testing has not been conducted with IMFINZI and is not planned. Genotoxicity is not applicable to biotechnology-derived large protein products, as they are not expected to cross the nuclear or mitochondrial membrane and interact directly with DNA or other chromosomal material. No safety concerns relevant to human usage have been identified.
Carcinogenicity
In accordance with ICH S6(R1) and ICH S9 guidance, carcinogenicity studies have not been conducted with IMFINZI and are not planned given the characteristics of the product and the intended clinical use in patients with advanced cancer. No safety concerns relevant to human usage have been identified.
Safety pharmacology
In accordance with ICH S6(R1) and ICH S7A, no stand-alone safety pharmacology studies were conducted with IMFINZI, and safety pharmacology endpoints (including neurological [assessed by clinical observations], cardiovascular [electrocardiogram and blood pressure] parameters, and respiration rate) were included in repeat-dose toxicity studies. No IMFINZI-related effects on any of the parameters evaluated were observed.

II: 3 MODULE SIII: CLINICAL TRIAL EXPOSURE

IMFINZI is indicated for use as monotherapy and in combination with other anticancer agents. The key features of all studies included in this RMP are summarised in Table II-11.

In order to evaluate the safety and tolerability of IMFINZI monotherapy, data from a number of key studies have been pooled to create a pan-tumour dataset. This population (N = 3006) consists of patients who have received at least 1 dose of IMFINZI monotherapy given at a dose of either 10 mg/kg Q2W iv or 20 mg/kg Q4W iv for any line of therapy (across tumour types) in the studies listed in Table II-11. A summary of exposure data pertaining to the IMFINZI monotherapy pool is provided in Section II: 3.8.

Data from IMFINZI monotherapy studies and monotherapy treatment arms of combination studies with DCO dates after 2018 have not been incorporated into this pool, as this is deemed of sufficient size to characterise the safety profile of IMFINZI across tumour types. Monotherapy data from these studies/treatment arms are presented separately in the following sections: Section II: 3.1 (IMFINZI as monotherapy in patients with LS-SCLC), and Section II: 3.6 (IMFINZI as monotherapy in patients with unresectable HCC).

Data from IMFINZI in combination with other anticancer agents are described separately by treatment regimen (where relevant) in the following sections: Section II: 3.2 (IMFINZI in combination with neoadjuvant platinum-based chemotherapy in patients with resectable NSCLC), Section II: 3.3 (IMFINZI in combination with SoC chemotherapy [paclitaxel and carboplatin] followed by IMFINZI with or without olaparib as maintenance treatment in patients with endometrial cancer), Section II: 3.4 (IMFINZI in combination with chemotherapy [gemcitabine and cisplatin] in patients with BTC), Section II: 3.5 (IMFINZI in combination with tremelimumab [plus SoC chemotherapy] in patients with metastatic NSCLC), Section II: 3.6 (IMFINZI in combination with tremelimumab in patients with advanced or unresectable HCC), and Section II: 3.7 (IMFINZI in combination with etoposide plus platinum-based chemotherapy [carboplatin or cisplatin] in patients with ES-SCLC).

Table II-11 Summary of Studies Included in the RMP

Study name (number) Data cut-off	Study design	Treatment arms	Patient population
CASPIAN (D419QC00001 [NCT03043872]) 26 April 2019	Phase III Randomised, open-label, comparative, multicentre	• D + EP • D + T + EP • EP	Patients with ES-SCLC

Table II-11 Summary of Studies Included in the RMP

Study name (number) Data cut-off	Study design	Treatment arms	Patient population
POSEIDON (D419MC00004 [NCT03164616]) 12 Mar 2021	Phase III Randomised, open-label, comparative, multicentre	• D • D + T • D + T + SoC	Patients with metastatic (Stage IV) NSCLC, with tumours that lack activating EGFR mutations and ALK fusions. Patients must have had no prior chemotherapy or any other systemic therapy for metastatic NSCLC
HIMALAYA (D419CC00002 [NCT03298451]) 27 Aug 2021	Phase III Randomised, open-label, multicentre	• D • D + T75 • D + T300 • Sorafenib	Patients with unresectable HCC not eligible for locoregional therapy who have not received prior systemic therapy for HCC (first-line setting)
Study 22 (D4190C00022 [NCT02519348]) 06 Nov 2020	Phase II Randomised, open-label, multicentre	• D • D + T75 • D + T300 • T	Patients with unresectable HCC who were immunotherapy-naïve and had either progressed on, were intolerant to, or refused treatment with sorafenib or other approved VEGFR
TOPAZ-1 (D933AC00001 [NCT03875235]) 11 Aug 2021	Phase III Randomised, double-blind, placebo-controlled, multicentre	• D + Gem/Cis • Placebo + Gem/Cis	Patients with previously untreated, unresectable locally advanced or metastatic BTC
DUO-E (D9311C00001 [NCT04269200]) 12 April 2023	Phase III Randomised, double-blind, placebo-controlled, multicentre	• SoC + D • SoC + D + O • SoC	Patients with advanced or recurrent endometrial cancer who were eligible for treatment with first-line SoC chemotherapy (carboplatin and paclitaxel)
ADRIATIC (D933QC00001 [NCT03703297]) 15 Jan 2024	Phase III Randomized, double-blind, placebo-controlled, multicentre	• D • D + T • Placebo	Patients with LS-SCLC whose disease had not progressed following definitive, platinum-based concurrent CRT
AEGEAN (D9106C00001 [NCT03800134]) 10 Nov 2022	Phase III Randomized, double-blind, placebo-controlled, multicentre	• D + CTx • Placebo + CTx	Patients with resectable Stage II-IIIB[N2] NSCLC. Patients were not to have received prior treatment for resectable NSCLC
Studies included in the IMFINZI monotherapy pan-tumour pool			
Study 1108 (CD-ON-MEDI4736-1108 [NCT01693562]) 16 Oct 2017	Phase I/IIb first-time-in-human, open-label, 3 + 3 dose-escalation, dose-expansion	• D (NSCLC) • D (UC)	Patients with advanced solid tumours, including NSCLC, that are refractory to standard therapy and for which no standard therapy exists

Table II-11 Summary of Studies Included in the RMP

Study name (number) Data cut-off	Study design	Treatment arms	Patient population
Japan 002 (D4190C00002 [NCT01938612]) 31 Mar 2018	Phase I Open-label, multicentre	• D • D + T	Patients with advanced solid tumours, including NSCLC, that are refractory to standard therapy and for which no standard therapy exists
ATLANTIC (D4191C00003 [NCT02087423]) 03 Jun 2016	Phase II Non-comparative, open-label, multicentre, international	• D	Patients with locally advanced or metastatic NSCLC (Stage IIIB-IV) who have received at least 2 prior systemic treatment regimens
PACIFIC (D4191C00001 [NCT02125461]) 22 Mar 2018	Phase III Randomised, double-blind, placebo-controlled, multicentre, international	• D • Placebo	Patients with locally advanced, unresectable, Stage III NSCLC who have not progressed after definitive platinum-based concurrent chemoradiation
ARCTIC (D4191C00004 [NCT02352948]) 09 Feb 2018	Phase III Randomised, open-label, multicentre, international	Substudy A: • D • Chemotherapy Substudy B: • D • Chemotherapy • T • D + T	Patients with locally advanced or metastatic NSCLC (Stage IIIB-IV) who received at least 2 prior systemic treatments and do not have EGFR or ALK target mutations
MYSTIC (D419AC00001 [NCT02453282]) 04 Oct 2018	Phase III Randomised, open-label, multicentre, international	• D • D + T • Chemotherapy	Patients with Stage IV NSCLC who have not received prior chemotherapy or other systemic therapy and who do not have EGFR or ALK target mutations
HAWK (D4193C00001 [NCT02207530]) 05 Oct 2018	Phase II Single-arm, multicentre, international	• D	Patients with recurrent or metastatic HNSCC not amenable to therapy with curative intent
CONDOR (D4193C00003 [NCT02319044]) 27 Aug 2018	Phase II Randomised, open-label, multicentre, international	• D • T • D + T	Patients with recurrent or metastatic HNSCC not amenable to therapy with curative intent
EAGLE (D4193C00002 [NCT02369874]) 10 Sep 2018	Phase III Randomised, open-label, multicentre, international	• D • T	Patients with recurrent or metastatic HNSCC not amenable to therapy with curative intent

II: 3.1 Exposure to IMFINZI for LS-SCLC

The pivotal safety dataset in support of the use of IMFINZI monotherapy for the treatment of patients with LS-SCLC was derived from the D arm of ADRIATIC study (see Table II-11 for details). Patients were to receive IMFINZI 1500 mg via iv infusion Q4W until clinical/RECIST 1.1-defined radiological progression, intolerable toxicity, or for a maximum of 24 months, whichever occurred first.

Exposure to IMFINZI in the D arm of the ADRIATIC study by weeks, age group and sex, and race is presented in Table II-12, Table II-13, and Table II-14, respectively.

Table II-12 Duration of Exposure to IMFINZI (D Arm; ADRIATIC Study) (N = 262)

Duration of exposure (weeks)	n	Patient-years exposure
≥ 0	262	273.6
≥ 8	246	271.9
≥ 12	221	267.9
≥ 16	201	262.9
≥ 24	173	253.1
≥ 32	153	242.8
≥ 40	132	229.0
≥ 48	122	220.8
≥ 52	114	213.2
≥ 60	110	209.0
≥ 72	106	203.9
≥ 104	46	92.1
Total	**262**	**273.6**

Total treatment duration = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/7. X is defined as the planned frequency in dosing (in days) - 1. Patient-years exposure = Total treatment duration (years) summed across all patients within a group. Where treatment duration (years) = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/365.25. X is defined as the planned frequency in dosing (in days) - 1. For Q4W, X = 27.

Table II-13 Exposure to IMFINZI by Age Group and Gender (D Arm; ADRIATIC Study) (N = 262)

	Male		Female	
Age group (years)	n	Patient-years exposure	n	Patient-years exposure
< 65	110	112.8	49	57.6
≥ 65	68	69.9	35	33.2
Total	**178**	**182.7**	**84**	**90.9**

Patient-years exposure = Total treatment duration (years) summed across all patients within a group. Where treatment duration (years) = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/365.25. X is defined as the planned frequency in dosing (in days) - 1. For Q4W, X = 27.

Table II-14 Exposure to IMFINZI by Race (D Arm; ADRIATIC Study) (N = 262)

Race	n	Patient-years exposure
Asian	131	144.2
White	128	125.5
Other	2	3.0
Black or African American	1	0.9
Total	**262**	**273.6**

Patient-years exposure = Total treatment duration (years) summed across all patients within a group. Where treatment duration (years) = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/365.25. X is defined as the planned frequency in dosing (in days) - 1. For Q4W, X = 27.

II: 3.2 Exposure to IMFINZI + Neoadjuvant Platinum-based Chemotherapy in Patients with Resectable NSCLC

The pivotal safety dataset in support of the use of IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy after surgery in patients with resectable NSCLC was derived from the D + CTx arm of the AEGEAN study (see Table II-11 for details). Patients were to receive up to 4 cycles of neoadjuvant platinum-based doublet chemotherapy in combination with IMFINZI 1500 mg via iv infusion, Q3W, pre-surgery. Post-surgery, patients were to receive an additional 12 cycles of IMFINZI 1500 mg Q4W as monotherapy.

Exposure to IMFINZI in the D + CTx arm of the AEGEAN study by weeks, age group and sex, and race is presented in Table II-15, Table II-16, and Table II-17, respectively.

Table II-15 Duration of Exposure to IMFINZI (D + CTx Arm; AEGEAN Study) (N = 401)

Duration of exposure (weeks)	n	Patient-years exposure
≥ 0	401 (100)	263.2
≥ 6	390 (97.3)	262.6
≥ 12	362 (90.3)	257.6
≥ 20	248 (61.8)	228.7
≥ 28	216 (53.9)	214.6
≥ 36	186 (46.4)	196.6
≥ 44	156 (38.9)	174.3
≥ 52	128 (31.9)	148.9

Total treatment duration = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/7. X is defined as the planned frequency in dosing (in days) - 1. For Q2W, X = 13. For Q3W, X = 20. For Q4W, X = 27. Patient Year exposure = Total treatment duration (years) summed across all patients within a group. Where treatment duration (years) = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/365.25. X is defined as the planned frequency in dosing (in days) - 1. For Q2W, X = 13. For Q3W, X = 20. For Q4W, X = 27.

Table II-16 Exposure to IMFINZI by Age Group and Gender (D + CTx Arm; AEGEAN Study) (N = 401)

Age group (years)	Male		Female	
	n	Patient-years exposure	n	Patient-years exposure
< 50	14 (3.5)	8.7	8 (2.0)	5.6
≥ 50 to < 65	110 (27.4)	76.9	60 (15.0)	43.6
≥ 65 to < 75	108 (26.9)	63.7	52 (13.0)	34.6
≥ 75	30 (7.5)	19.4	19 (4.7)	10.6
Total	**262 (65.3)**	**168.7**	**139 (34.7)**	**94.5**

Patient Year exposure = Total treatment duration (years) summed across all patients within a group. Where treatment duration (years) = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/365.25. X is defined as the planned frequency in dosing (in days) - 1. For Q2W, X = 13. For Q3W, X = 20. For Q4W, X = 27.

Table II-17 Exposure to IMFINZI by Race (D + CTx Arm; AEGEAN Study) (N = 401)

Race	n	Patient-years exposure
White	217 (54.1)	136.1
Asian	165 (41.1)	114.8
Other	14 (3.5)	9.6
Black or African American	5 (1.2)	2.7
Total	**401 (100)**	**263.2**

Patient Year exposure = Total treatment duration (years) summed across all patients within a group. Where treatment duration (years) = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/365.25. X is defined as the planned frequency in dosing (in days) - 1. For Q2W, X = 13. For Q3W, X = 20. For Q4W, X = 27.

II: 3.3 Exposure to IMFINZI + SoC Chemotherapy Followed by IMFINZI ± Olaparib as Maintenance Treatment for Endometrial Cancer

The pivotal safety dataset in support of the use of IMFINZI in combination with SoC chemotherapy (carboplatin and paclitaxel), followed by maintenance with IMFINZI as monotherapy or in combination with olaparib in patients with endometrial cancer was derived from the SoC + D and SoC + D + O arms of the DUO-E study (see Table II-11 for details). Patients were to receive SoC chemotherapy and IMFINZI 1120 mg via iv infusion Q3W for 4 to 6 cycles during the chemotherapy phase. Patients who achieved and maintained disease control were subsequently to receive IMFINZI 1500 mg Q4W in conjunction with olaparib or placebo (2 × 150 mg tablets twice daily) in the maintenance phase.

Exposure to IMFINZI in the SoC + D and SoC + D + O arms of the DUO-E study by weeks, age group, and race is presented in Table II-18, Table II-19, and Table II-20, respectively. Of note, all patients were female.

Table II-18 Duration of Exposure to IMFINZI (SoC + D and SoC + D + O Arms; DUO-E Study [Overall Period])

Duration of exposure (weeks)	SoC + D (N = 235)		SoC + D + O (N = 238)	
	n	Patient-years exposure	n	Patient-years exposure
≥ 0	235	224.7	238	265.2
≥ 6	225	224.2	233	265.0
≥ 12	211	222.2	218	262.3
≥ 24	182	212.2	198	255.6
≥ 32	152	195.3	178	244.4
≥ 40	128	179.0	162	233.4
≥ 48	103	158.2	135	210.4
≥ 52	96	151.5	129	204.6
≥ 76	51	96.4	70	132.6
≥ 104	18	40.3	21	48.3
≥ 132	3	7.8	6	15.7

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.
Overall period = Chemotherapy phase + Maintenance phase.

Table II-19 Exposure to IMFINZI by Age Group (SoC + D and SoC + D + O Arms; DUO-E Study [Overall Period])

Age group (years)	SoC + D (N = 235)		SoC + D + O (N = 238)	
	n	Patient-years exposure	n	Patient-years exposure
< 65	120	118.8	134	151.9
≥ 65 to < 75	87	80.4	85	96.2
≥ 75	28	25.5	19	17.1
Total	**235**	**224.7**	**238**	**265.2**

Patient-years exposure = Total treatment duration (years) summed across all patients within a group. Where treatment duration (years) = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/365.25. X is defined as the planned frequency in dosing (in days) - 1. For Q3W, X = 20. For Q4W, X = 27.
Overall period = Chemotherapy phase + Maintenance phase.

Table II-20 Exposure to IMFINZI by Race (SoC + D and SoC + D + O Arms; DUO-E Study [Overall Period])

Race	SoC + D (N = 235)		SoC + D + O (N = 238)	
	n	Patient-years exposure	n	Patient-years exposure
White	134	135.5	133	147.0
Asian	71	64.3	69	80.6

Table II-20 Exposure to IMFINZI by Race (SoC + D and SoC + D + O Arms; DUO-E Study [Overall Period])

Race	SoC + D (N = 235)		SoC + D + O (N = 238)	
	n	Patient-years exposure	n	Patient-years exposure
Black or African American	11	7.6	14	15.5
Other	14	12.5	19	18.0
Not reported	5	4.8	3	4.1
Total	**235**	**224.7**	**238**	**265.2**

Patient-years exposure = Total treatment duration (years) summed across all patients within a group. Where treatment duration (years) = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/365.25. X is defined as the planned frequency in dosing (in days) - 1. For Q3W, X = 20. For Q4W, X = 27.
Overall period = Chemotherapy phase + Maintenance phase.

II: 3.4 Exposure to IMFINZI + SoC Chemotherapy for BTC

The pivotal safety dataset in support of the use of IMFINZI in combination with SoC chemotherapy (gemcitabine and cisplatin) in patients with previously untreated, unresectable locally advanced or metastatic BTC was derived from the D + Gem/Cis arm of the TOPAZ-1 study (see Table II-11 for details), in which IMFINZI 1500 mg was administered in combination with cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 (each administered on Days 1 and 8; Q3W) via iv infusion (on Day 1; Q3W); starting on Cycle 1, for up to 8 cycles. After completing the chemotherapy treatment period, patients received IMFINZI 1500 mg monotherapy via iv infusion Q4W until clinical or radiological (per RECIST v1.1) disease progression or until unacceptable toxicity, withdrawal of consent, or any other discontinuation criteria were met. Patients who were clinically stable at initial disease progression could continue to receive study treatment at the discretion of the investigator and patient.

Exposure to IMFINZI in the D + Gem/Cis arm of the TOPAZ-1 study by weeks, age group and sex, and race is presented in Table II-21, Table II-22, and Table II-23, respectively.

Table II-21 Duration of Exposure to IMFINZI (D + Gem/Cis Arm; TOPAZ-1 Study) (N = 338)

Duration of exposure (weeks)	n	Patient-years exposure
≥ 0	338	215.2
≥ 8	304	212.5
≥ 16	257	202.0
≥ 24	225	190.0
≥ 32	176	164.0
≥ 40	110	119.3
≥ 48	60	78.5
≥ 50	53	72.0

Table II-21 Duration of Exposure to IMFINZI (D + Gem/Cis Arm; TOPAZ-1 Study) (N = 338)

Duration of exposure (weeks)	n	Patient-years exposure
≥ 52	49	68.2
Total	**338**	**215.2**

Total exposure months = (min(last IMFINZI dose date where dose > 0 + [20 if last dose in period 1 or 27 if last dose in period 2], date of death, date of DCO) - first IMFINZI dose date + 1)/(365.25/12). Note: For each subject, weeks and years of exposure are derived from months of exposure.

Table II-22 Exposure to IMFINZI by Age Group and Gender (D + Gem/Cis Arm; TOPAZ-1 Study) (N = 338)

	Male		Female	
Age group (years)	n	Patient-years exposure	n	Patient-years exposure
< 65	94	60.5	86	55.2
≥ 65	75	45.2	83	54.3
Total	**169**	**105.7**	**169**	**109.6**

Total exposure months = (min (last IMFINZI dose date where dose > 0 + [20 if last dose in period 1 or 27 if last dose in period 2], date of death, date of DCO) - first IMFINZI dose date + 1)/(365.25/12).
Note: For each subject, years of exposure is derived from months of exposure.

Table II-23 Exposure to IMFINZI by Race (D + Gem/Cis Arm; TOPAZ-1 Study) (N = 338)

Race	n	Patient-years exposure
Asian	184	123.1
White	129	77.0
Other	17	10.7
Black or African American	8	4.5
Total	**338**	**215.2**

Total exposure months = (min (last IMFINZI dose date where dose > 0 + [20 if last dose in period 1 or 27 if last dose in period 2], date of death, date of DCO) - first IMFINZI dose date + 1)/(365.25/12).
Note: For each subject, years of exposure is derived from months of exposure.

II: 3.5 Exposure to IMFINZI + Tremelimumab + SoC Chemotherapy for Metastatic NSCLC

The pivotal dataset in support of the use of IMFINZI in combination with tremelimumab and platinum-based chemotherapy (SoC) for the first-line treatment of metastatic NSCLC was derived from the D + T + SoC chemotherapy arm of the POSEIDON study (see Table II-11 for details), in which IMFINZI 1500 mg plus tremelimumab 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, IMFINZI 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 was administered alongside IMFINZI dose 6 at Week 16.

Exposure to IMFINZI and tremelimumab in the D + T75 + SoC arm of the POSEIDON study by weeks, age group and gender, and race is presented in Table II-24, Table II-25, and Table II-26, respectively.

Table II-24 Duration of exposure to IMFINZI and Tremelimumab (D + T75 + SoC Arm; POSEIDON Study) (N = 330)

Duration of exposure (weeks)	IMFINZI (N = 330)		Tremelimumab (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 retreatment), date of death, date of DCO) – first infusion/dose date of first cycle + 1.

Table II-25 Exposure to IMFINZI and Tremelimumab by Age Group and Sex (D + T75 + SoC Arm; POSEIDON Study) (N = 330)

Age group (years)	IMFINZI (N = 330)				Tremelimumab (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 retreatment), date of death, date of DCO) – first infusion/dose date of first cycle + 1.

Table II-26 Exposure to IMFINZI and Tremelimumab by Race (D + T75 + SoC Arm; POSEIDON Study) (N = 330)

Race	IMFINZI (N = 330)		Tremelimumab (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 retreatment), date of death, date of DCO) – first infusion/dose date of first cycle + 1.

II: 3.6 Exposure to IMFINZI (± Tremelimumab) for HCC

The pivotal safety dataset in support of the use of IMFINZI in combination with tremelimumab in patients with unresectable HCC was derived from pooled data from patients who received a single priming dose of tremelimumab 300 mg in combination with IMFINZI 1500 mg via iv infusion on Day 1 (Week 0) in the T300 + D arms of the HIMALAYA study (n = 388) and Study 22 (n = 74) (see Table II-11 for details). After initial combination dosing, patients in both studies subsequently received IMFINZI 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.

The pivotal dataset in support of the use of IMFINZI as monotherapy in the same indication was derived from a pooled dataset of patients who received iv infusions of IMFINZI 1500 mg Q4W in the D arm of the HIMALAYA study (n = 388), and IMFINZI 1500 mg Q4W (n = 62) and 20 mg/kg Q4W (n = 42) in Study 22 (see Table II-11 for details). All patients received treatment until confirmed disease progression, unacceptable toxicity, or any discontinuation criterion was met.

Exposure to IMFINZI and tremelimumab (T300 + D) and IMFINZI (D) in the HCC tumour pool by weeks, age group and sex, and race is presented in Table II-27, Table II-28, and Table II-29, respectively.

Table II-27 Duration of Exposure to IMFINZI Monotherapy and in Combination with Tremelimumab (HCC Tumour Pool)

Duration of exposure (weeks)	T300 + D (N = 462)				D (N = 492)	
	IMFINZI		Tremelimumab			
	n	Patient-years exposure	n	Patient-years exposure	n	Patient-years exposure
≥ 0	462	370.5	462	42.7	492	358.6
≥ 4	455	370.1	455	42.3	487	358.4
≥ 8	378	362.9	36	10.2	425	352.4
≥ 12	327	354.4	6	5.6	359	341.4
≥ 16	286	343.7	6	5.6	296	325.5
≥ 20	242	329.6	6	5.6	246	309.4
≥ 24	222	321.5	NA	NA	225	301.0
≥ 28	197	309.4	NA	NA	196	286.9
≥ 32	189	304.9	NA	NA	173	273.6
≥ 36	173	294.8	NA	NA	155	262.1
≥ 40	160	285.5	NA	NA	144	254.3
≥ 44	149	276.9	NA	NA	138	249.6
≥ 48	141	270.0	NA	NA	134	246.1
≥ 52	131	260.8	NA	NA	120	233.1
≥ 104	66	167.8	NA	NA	53	138.6
≥ 156	10	32.2	NA	NA	11	36.4

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-28 Exposure to IMFINZI Monotherapy and in Combination with Tremelimumab by Age Group and Sex (HCC Tumour Pool)

Age group (years)	T300 + D (N = 462)								D (N = 492)			
	IMFINZI				Tremelimumab							
	Male		Female		Male		Female		Male		Female	
	n	PYE	n	PYE	n	PYE	n	PYE	n	PYE	n	PYE
< 65	193	153.1	33	19.3	193	16.5	33	3.0	208	145.0	46	31.0
≥ 65	194	160.3	42	37.8	194	20.0	42	3.3	205	159.9	33	22.8
Total	**387**	**313.4**	**75**	**57.1**	**387**	**36.4**	**75**	**6.3**	**413**	**304.8**	**79**	**53.8**

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.
PYE, Patient-years exposure.

Table II-29 Exposure to IMFINZI Monotherapy and in Combination with Tremelimumab by Race (HCC Tumour Pool)

Race	T300 + D (N = 462)				D (N = 492)	
	IMFINZI		Tremelimumab			
	n	Patient-years exposure	n	Patient-years exposure	n	Patient-years exposure
Asian	238	185.6	238	21.4	268	179.4
White	204	165.0	204	19.8	194	160.0
Black or African American	11	6.7	11	0.8	11	5.4
Other [a]	8	13.0	8	0.6	19	13.8
Missing	1	0.3	1	0.1	0	0
Total	**462**	**370.5**	**462**	**42.7**	**492**	**358.6**

[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: 3.7 Exposure to IMFINZI + EP for ES-SCLC

Data presented in this section are from the D + EP arm of the CASPIAN study (see Table II-11 for details).

Exposure to IMFINZI in the D + EP arm of the CASPIAN study by weeks, age group and gender, and race is presented in Table II-30, Table II-31, and Table II-32, respectively.

Table II-30 Duration of Exposure to IMFINZI (D + EP Arm; CASPIAN Study) (N = 265)

Duration of exposure (weeks)	n	Patient-years exposure
≥ 0	265	167.3
≥ 8	242	166.0
≥ 16	223	161.7
≥ 24	166	139.6
≥ 32	108	109.7
≥ 40	77	88.7
≥ 48	52	67.9
≥ 50	51	67.0
≥ 52	46	62.0
Total	**265**	**167.3**

Total exposure = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/7. X is defined as the planned frequency in dosing (in days) - 1. For Caspian, if last dose is during EP, X = 20; if last dose is post-EP, X = 27.

Table II-31 Exposure to IMFINZI by Age Group and Gender (D + EP Arm; CASPIAN Study) (N = 265)

Age group (years)	Male		Female	
	n	Patient-years exposure	n	Patient-years exposure
< 65	113	69.2	51	34.4
≥ 65	75	45.1	26	18.7
Total	**188**	**114.3**	**77**	**53.1**

Total exposure = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/7. X is defined as the planned frequency in dosing (in days) - 1. For Caspian, if last dose is during EP, X = 20; if last dose is post-EP, X = 27.

Table II-32 Exposure to IMFINZI by Race (D + EP Arm; CASPIAN Study) (N = 265)

Race	n	Patient-years exposure
White	226	148.0
Black or African American	2	1.4
Asian	36	17.5
Other	1	0.5
Missing	0	0.0
Total	**265**	**167.3**

Total exposure = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/7. X is defined as the planned frequency in dosing (in days) - 1. For Caspian, if last dose is during EP, X = 20; if last dose is post-EP, X = 27.

II: 3.8 IMFINZI Monotherapy Exposure Across Indications

The studies included in the monotherapy pan-tumour pool are detailed in Table II-11.

Exposure to IMFINZI monotherapy by weeks, age and gender, and race is presented in Table II-33, Table II-34, and Table II-35, respectively.

Table II-33 Duration of Exposure to IMFINZI Monotherapy (Pan-Tumour Pool) (N = 3006)

Duration of exposure (weeks)	n	Patient-years exposure
≥ 0	3006	1474.2
≥ 8	2248	1409.7
≥ 16	1554	1266.7
≥ 24	1221	1146.6
≥ 32	976	1020.3
≥ 40	836	927.2
≥ 48	718	830.4
≥ 50	685	799.5
≥ 52	567	683.2

Table II-33 Duration of Exposure to IMFINZI Monotherapy (Pan-Tumour Pool) (N = 3006)

Duration of exposure (weeks)	n	Patient-years exposure
Total	**3006**	**1474.2**

Total exposure = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/7. X is defined as the planned frequency in dosing (in days) – 1. For studies with IMFINZI Q4W, X = 27. For studies with IMFINZI Q2W, X = 13.

Table II-34 Exposure to IMFINZI Monotherapy by Age Group and Gender (Pan-Tumour Pool) (N = 3006)

Age group (years)	Male		Female	
	n	Patient-years exposure	n	Patient-years exposure
< 65	1087	531.2	641	287.8
≥ 65	861	465.2	417	190.0
Total	**1948**	**996.4**	**1058**	**477.8**

Total exposure = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/7. X is defined as the planned frequency in dosing (in days) - 1. For studies with IMFINZI Q4W, X = 27. For studies with IMFINZI Q2W, X = 13.

Table II-35 Exposure to IMFINZI Monotherapy by Race (Pan-Tumour Pool) (N = 3006)

Race	n	Patient-years exposure
White	2076	1028.1
Black or African American	67	31.6
Asian	739	357.3
Other	48	21.0
Missing	76	36.2
Total	**3006**	**1474.2**

Total exposure = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/7. X is defined as the planned frequency in dosing (in days) - 1. For studies with IMFINZI Q4W, X = 27. For studies with IMFINZI Q2W, X = 13.

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

II: 4.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Patients with prior Grade ≥ 3 imAE while receiving immunotherapy, including anti-CTLA-4 treatment, or any unresolved imAE >Grade 1

Reason for exclusion: Patients with any prior Grade ≥ 3 imAE while receiving immunotherapy may be at a higher risk of recurrence of immune-mediated events of the same type.

Is it considered to be included as missing information: No

Rationale: The SmPC warns that this population has not been studied and/or that the effect of IMFINZI is unknown. As further characterisation of this population is neither feasible nor warranted, it is not relevant for inclusion as missing information.

Patients requiring systemic immunosuppressive medication (except physiological dose of systemic corticosteroids) before starting IMFINZI

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 MOA of IMFINZI.

Is it considered to be included as missing information: No

Rationale: This population was excluded for concerns regarding efficacy not safety. Experience to date has indicated that treatment with IMFINZI has been well tolerated by patients receiving physiological and high doses of systemic corticosteroids. Use of other immunosuppressive medications in the target population is not anticipated to lead to an increased risk of imAEs.

Patients with pre-existing autoimmune disease

Reason for exclusion: IMFINZI, 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). IMFINZI 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 SmPC warns that this population has not been studied and/or that the effect of IMFINZI is unknown. As further characterisation of this population is neither feasible nor warranted, it is not considered relevant for inclusion as missing information.

Patients with untreated CNS metastatic disease, leptomeningeal disease, or cord compression

Reason for exclusion: Patients with these conditions have significantly worse prognoses and are excluded in the initial clinical development to ensure interpretability of efficacy. However, patients with stable CNS metastases or cord compression are not excluded from IMFINZI clinical trials.

Is it considered to be included as missing information: No

Rationale: Based on the MOA of IMFINZI, components of the immune system (eg, T cells) are capable of crossing the blood brain barrier and possibly exerting an antitumour response. Consequently, this population was excluded for concerns regarding efficacy, not safety. Patients previously treated for CNS metastases that are radiographically and neurologically stable and do not require corticosteroids (of any dose) for symptomatic management for at least 14 days prior to the first dose of IMFINZI are included in clinical trials with IMFINZI. No evidence of a different safety profile in patients with stable CNS metastases has been evident in the clinical development program to date, and the further investigation of IMFINZI in patients with untreated metastatic CNS disease, leptomeningeal disease, or cord compression is not feasible due to the poor prognosis in this patient population.

Paediatric and adolescent patients < 18 years of age

Reason for exclusion: This population was excluded from this 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: Paediatrics and adolescents are out of scope for the target indications, as these are primarily diseases of adults, with only exceptional occurrence in the paediatric population (Dishop and Kuruvilla 2008, Karatzas and Tzortzis 2019, Khanna and Verma 2018, Newsome et al 2018).

Females who are pregnant or lactating

Reason for exclusion: It is unknown whether IMFINZI is secreted in human milk, and pregnant and lactating females are excluded to avoid potential harm to the unborn foetus or breastfeeding newborn.

Is it considered to be included as missing information: No

Rationale: The SmPC warns that this population has not been studied and/or that the effect of IMFINZI is unknown. As further characterisation of this population is neither feasible nor warranted, it is not considered relevant for inclusion as missing information.

Patients with active primary immunodeficiency

Reason for exclusion: IMFINZI treatment may not be effective due to underlying immune deficiency.

Is it considered to be included as missing information: No

Rationale: The safety profile is not expected to be less favourable for patients with primary immune deficiency than in the intended population because, by their MOA, immune checkpoint inhibitors can only alter existing immune mechanisms.

Patients with pre-existing active infection/co-infection including tuberculosis, hepatitis B, hepatitis C, or HIV

Reason for exclusion: PD-L1 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 SmPC warns that this population has not been studied and/or that the effect of IMFINZI is unknown. As further characterisation of this population is neither feasible nor warranted, it is not considered relevant for inclusion as missing information.

Patients receiving live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving IMFINZI

Reason for exclusion: This population is excluded due to concern of live attenuated vaccine complications. PD-1/PD-L1 blockade could lead to more vigorous inflammation. In analogy, immune reconstitution in HIV patients was associated with BCG vaccine complications (Nuttall et al 2008).

Is it considered to be included as missing information: No

Rationale: The SmPC warns that this population has not been studied and/or that the effect of IMFINZI is unknown. As further characterisation of this population is neither feasible nor warranted, it is not considered relevant for inclusion as missing information.

II: 4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program 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 Programs

Table II-36 Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of special population	Exposure (number of patients)									
	IMFINZI monotherapy pan-tumour pool[a]	CASPIAN (D + EP)	POSEIDON (D + T75 + SoC)	HCC tumour pool		TOPAZ-1 (D + Gem/Cis)	DUO-E		AEGEAN (D + CTx)	ADRIATIC (D)
				T300 + D	D		SoC + D	SoC + D + O		
Pregnant women	Not included in the clinical development program									
Breastfeeding women										
Patients with relevant comorbidities:										
Moderate hepatic impairment [b]	9	1	1	4	20	16	2	0	1	0
Severe hepatic impairment [b]	2	0	0	0	0	0	0	0	0	0
Severe renal impairment [c]	3	0	0	1	0	0	0	0	0	0
Patients with uncontrolled cardiovascular disorders (including congestive heart failure, hypertension, unstable angina, or cardiac arrhythmia)	Not included in the clinical development program									
Patients with active autoimmune diseases requiring systemic immunosuppressive treatment	Not included in the clinical development program									
Patients with relevant different ethnic origin:										
Black or African American	67	2	8	11	11	8	11	14	5	1
Asian	739	36	97	238	268	184	71	69	165	131
Other [d]	48	1	11	8	19	17	14	19	14	2
Subpopulations carrying relevant genetic polymorphisms	No data are available regarding relevant genetic polymorphisms									

[a] The studies included in the IMFINZI monotherapy pan-tumour pool and their data cut-off dates are summarised in Table II-11.

[b] 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; and severe hepatic impairment = BIL > 3 × ULN and any AST (where ULN of BIL is 1.9 IU/L and ULN of AST is 34 IU/L).

[c] 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.

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

II: 5 MODULE SV: POST-AUTHORISATION EXPERIENCE

II: 5.1.1 Method Used to Calculate Exposure

The post-marketing patient exposure data presented is estimated based on monthly actual ex-factory sales volume from each local marketing company. These data represent all IMFINZI formulation delivered to various distribution channels (for example wholesalers, pharmacies etc) worldwide.

The sales volume is provided as the total sales in mg, calculated by number of vials sold multiplied by strength of formulation. The approved strengths and dosage forms for this product are 500 mg/10 mL (50 mg/mL) and 120 mg/2.4 mL (50 mg/mL) solutions for iv infusion. The recommended dose as per the Core Data Sheet for the indications of UC and NSCLC is 10 mg/kg administered as an iv infusion over 60 minutes Q2W as long as clinical benefit is observed or until unacceptable toxicity for UC patients or until disease progression or unacceptable toxicity for locally advanced NSCLC patients. Assuming the average patient weight is 75 kg the dose becomes 75 × 10 = 750 mg/60 mins/2 weeks. To calculate the patient exposure both the sales figures and recommended dose should be in the same units. Hence, below is the methodology for converting the recommended dose to mg:

- 1 year has 365 days and 52 weeks (365/7 = 52 weeks)
- Since recommended dose is given Q2W hence, number of weeks' patient is exposed to drug is 26 weeks (52/2 = 26 weeks)
- If in 2 weeks, the patient is exposed to 750 mg then in 26 weeks the patient is exposed to 19500 mg (750 × 26 = 19500 mg). Therefore, the recommended dose as per the label is 19500 mg in a year.
- Number of patient-years = sales in mg divided by recommended dose 19500 mg.

Although a flat dose regimen is also recommended for locally-advanced NSCLC, UC and HCC patients (1500 mg Q4W) and alternative dosing regimens are used for patients receiving IMFINZI for metastatic NSCLC, ES-SCLC, and BTC (see Table I-1 for details), these regimens are not incorporated into exposure calculations to maintain consistency with previous data.

The current methodology does not distinguish between sales that are related to initial prescriptions versus those related to repeat prescriptions. Therefore, it is not possible to estimate the number of patients exposed to IMFINZI. Detailed patient-level data (eg, gender, ethnicity, age category, off-label use, specific populations etc) are not available.

II: 5.1.2 Exposure

The cumulative global post-marketing patient exposure to IMFINZI (10 mg/kg), since launch to 30 April 2023, has been estimated to be approximately 118467 patient-years.

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

Potential for misuse for illegal purposes

IMFINZI is a potent and highly selective human IgG1κ mAb designed to inhibit binding of PD-L1 to PD-1 and CD80. Based on its clinical setting of use, mode of action, physiological and pharmacological activity, and lack of stimulant and addictive properties, IMFINZI is unlikely to be abused.

II: 7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

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

II: 7.1.1 Risk Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reasons for not including an identified or potential risk in the list of safety concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated) include abdominal pain, cough/productive cough, dental and oral soft tissue infections, dysphonia, dysuria, influenza, myalgia, night sweats, oedema peripheral, oral candidiasis, pyrexia, and upper respiratory tract infections.

Pneumonia as a risk is not considered important because only low-grade events were more prevalent in the IMFINZI group compared to the placebo group. Low-grade events are not considered to impact the benefit-risk for IMFINZI in the target population.

There is potential risk of medication error for IMFINZI as a consequence of the different doses and frequency of administration specific to the 2 lung cancer indications. IMFINZI should be administered to NSCLC patients using a weight-based dose (10 mg/kg Q2W) and to ES-SCLC patients using a fixed dose (1500 mg) (Table II-37). The fixed dose of 1500 mg Q4W (equivalent to 20 mg/kg Q4W for an average body weight of 75 kg) is predicted to result in similar area under the concentration-time curve and only a modest difference in median peak and trough levels at steady state compared to 10 mg/kg Q2W based on population pharmacokinetics simulations. Therefore, the fixed dose is expected to demonstrate similar efficacy and safety profiles to the 10 mg/kg Q2W regimen. As the weight-based and fixed-dose regimens have shown similar safety profiles, the risk to the patient, should they receive the incorrect dosing regimen, is low.

In addition, the potential risk for medication error due to differences in frequency of IMFINZI administration between patients with NSCLC and ES-SCLC could eventually lead to under- or over-dosing. However, this risk is considered low because for patients with ES-SCLC, the difference in frequency of IMFINZI administration is driven by coadministration of chemotherapy.

Table II-37 IMFINZI Dosing and Duration of Therapy

Indication	Recommended IMFINZI dose	Duration of therapy
Locally advanced NSCLC	10 mg/kg every 2 weeks	Until disease progression, unacceptable toxicity, or a maximum of 12 months[a]

Table II-37 IMFINZI Dosing and Duration of Therapy

Indication	Recommended IMFINZI dose	Duration of therapy
ES-SCLC	1500 mg[b] in combination with chemotherapy[c,d] every 3 weeks (21 days) for 4 cycles, followed by 1500 mg every 4 weeks as monotherapy	Until disease progression or unacceptable toxicity

[a] It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.
[b] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg.
[c] Administer IMFINZI prior to chemotherapy on the same day.
[d] When IMFINZI is administered in combination with chemotherapy, refer to the Prescribing Information for etoposide and carboplatin or cisplatin for dosing information.
Source: IMFINZI SmPC.

The IMFINZI container label has been carefully designed to reduce confusion regarding product concentration, content, instructions for diluting with water, and the administration rate. Moreover, IMFINZI is not a self-administered medication, rather, it is to be administered as an iv infusion by highly trained, specialised healthcare professionals familiar with iv administration procedure. Therefore, the risk of medication error for IMFINZI is expected to be low and without significant impact on the overall benefit-risk profile of IMFINZI.

Medication errors will be reviewed through routine pharmacovigilance.

Obesity is viewed as a critical co-factor in cancer due to metabolic, inflammatory and immune perturbations (Mirsoian and Murphy 2015, Canter et al 2018). The evidence for an impact of obesity on safety outcomes with immunotherapies is, however, limited at this time. Based on patients with reported BMI in the exposure-safety analysis population (Study 1108, PACIFIC; n = 1324), 17.4% (n = 230) of patients were classified as obese, based on BMI of = 30. Higher IMFINZI exposure was observed in obese patients when compared to other BMI subgroups; however, there is no evidence of a different safety profile. An analysis across the pooled dataset assessed 3 safety endpoints (Grade 3 or 4 drug-related adverse event, Grade 3 or 4 drug-related adverse events of special interest and adverse event leading to treatment discontinuation) for all BMI subgroups. The results show that adverse event incidence rates were comparable across BMI subgroups for all 3 safety endpoints; therefore, safety data do not suggest an unfavourable impact on benefit-risk profile for the obese subpopulation.

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

Important identified risks: immune-mediated adverse events of pneumonitis, hepatitis, colitis or diarrhoea, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis or hypopituitarism, type 1 diabetes mellitus, nephritis, and rash or dermatitis.

Benefit-risk impact:

Overall, Grade 3/4 imAEs and fatal outcomes were observed in 2.4% and 0.4% of patients, respectively, treated with IMFINZI monotherapy. Although severe imAEs are of low frequency or rare, they can be potentially serious or life-threatening for the individual patient and require careful monitoring, early recognition and timely intervention by withholding/discontinuation of IMFINZI, and appropriate medical intervention, including systemic corticosteroids and/or hormone replacement therapy.

Important identified risk: Infusion-related reaction

Benefit-risk impact:

Severe or life-threatening infusion-related reaction may result in the need to interrupt or permanently discontinue IMFINZI therapy and requires careful monitoring, early recognition, and timely intervention.

Important potential risk: Immune-mediated pancreatitis

Benefit-risk impact:

Immune-mediated pancreatitis is associated with other anti-PD-1/PD-L1 agents and is being closely monitored in the IMFINZI program and is observed rarely. Pancreatitis can be potentially serious or life-threatening in the individual patient, and requires careful monitoring, early recognition and timely intervention by withholding/discontinuation of IMFINZI and appropriate medical intervention including systemic corticosteroids.

Important potential risk: Other potential immune-mediated adverse reactions (eg, myasthenia gravis and Guillain-Barré syndrome)

Benefit-risk impact:

Serious and rare risks of myasthenia gravis and Guillain-Barré syndrome are associated with other anti-PD-1/PD-L1 agents. Cases of myasthenia gravis and Guillain-Barré syndrome have been reported and are being closely monitored in the IMFINZI program. Other potential immune-mediated adverse reactions, such as myasthenia gravis and Guillain-Barré syndrome, can be potentially serious or life-threatening in the individual patient, and require careful monitoring, early recognition and timely intervention by withholding/discontinuation of IMFINZI and appropriate medical intervention including systemic corticosteroids.

Missing information: Patients with moderate or severe hepatic impairment

Benefit-risk impact:

There has been low exposure of patients with moderate or severe hepatic impairment in clinical trials. Data in these populations will be important to further understand the safety profile of IMFINZI.

Missing information: Patients with severe renal impairment

Benefit-risk impact:

There has been low exposure of patients with severe renal impairment in clinical trials. Data in these populations will be important to further understand the safety profile of IMFINZI.

Missing information: Patients with prior Grade ≥ 3 imAE while receiving immunotherapy, including anti-CTLA-4 treatment or any unresolved imAE > Grade 1

Benefit-risk impact:

These patients may be at a higher risk of recurrence of immune-mediated events of the same type. Data in these populations will be important to further understand the safety profile of IMFINZI.

Missing information: Patients with pre-existing autoimmune disease

Benefit-risk impact:

Patients with pre-existing autoimmune disease other than vitiligo, alopecia, hypothyroidism stable on hormone replacement, or chronic skin conditions not requiring systemic treatment were excluded from clinical studies. It is anticipated that treatment with IMFINZI could exacerbate pre-existing autoimmune diseases, with potentially detrimental consequences that lead to an unacceptable benefit-risk profile. Data in these populations will be important to further understand the safety profile of IMFINZI.

Missing information: Patients with pre-existing active infection including tuberculosis, hepatitis B, hepatitis C, or HIV

Benefit-risk impact:

These patients may be at risk of exacerbation of underlying infectious diseases or systemic inflammatory responses. Data in these populations will be important to further understand the safety profile of IMFINZI.

Missing information: Patients receiving live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving IMFINZI

Benefit-risk impact:

These patients may be at risk of vaccine complications. Data in these populations will be important to further understand the safety profile of IMFINZI. In analogy, immune

reconstitution in HIV patients was associated with BCG vaccine complications (Nuttall et al 2008).

Missing information: Female patients who are pregnant or breastfeeding

Benefit-risk impact:

Due to its mechanism of action, IMFINZI could potentially cause foetal harm when administered to a pregnant woman. It is unknown if IMFINZI is secreted in human milk but a risk to newborns/infants from breastfeeding women cannot be excluded. Use in this population is not anticipated due to recommendations in the label not to use during pregnancy or when breastfeeding.

II: 7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

There are no new safety concerns or reclassifications of safety concerns.

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

There are no safety concerns.

II: 8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

II: 8.1 Summary of the Safety Concerns

There are no safety concerns.

III: PART III: PHARMACOVIGILANCE PLAN

III: 1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

There are no safety concerns, so only routine pharmacovigilance activities are required.

III: 2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

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

A summary of the planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or are specific obligations is provided in Table IV-1.

Table IV-1 Planned and Ongoing Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or are Specific Obligations

Study code (name) / Short title Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates for EMA
Efficacy studies which are conditions of the marketing authorisation				
Study D9311C00001 (DUO-E) A study to assess the efficacy and safety of durvalumab in combination with platinum-based chemotherapy (paclitaxel + carboplatin) followed by maintenance durvalumab with or without olaparib for patients with newly diagnosed advanced or recurrent endometrial cancer. • ***Status:*** Ongoing	*Primary Objective:* • To demonstrate the efficacy of SoC + D or SoC + D + O when compared to SoC by assessment of PFS. *Secondary Objective:* • To determine the efficacy of SoC + D or SoC + D + O when compared to SoC by the assessment of PFS2, OS, ORR, DoR, TFST, TSST, and TDT.	• Further evidence of efficacy and safety in patients with advanced and recurrent endometrial cancer in the first-line treatment setting	Interim OS analysis	Q4 2025
			Final report	Q4 2026
Study D9106C00001 (AEGEAN) A study of neoadjuvant/ adjuvant durvalumab for the treatment of patients with resectable NSCLC. • ***Status***: Ongoing	*Primary Objectives:* • To compare the efficacy of D + CTx administered prior to surgery followed by D post-surgery compared with placebo + CTx administered prior to surgery followed by placebo post-surgery in terms of EFS • To compare the activity of D + CTx administered prior to surgery compared with placebo + CTx administered prior to surgery in terms of pCR *Secondary Objectives:* • To compare the efficacy of D + CTx administered prior to surgery followed by D post-surgery compared with placebo + CTx administered prior to surgery followed by placebo post-surgery in terms of DFS and OS	• Further evidence of long-term efficacy in patients with resectable NSCLC at high risk of recurrence	Final OS analysis	Q2 2029

Table IV-1 Planned and Ongoing Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or are Specific Obligations

Study code (name) / Short title Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates for EMA
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				

DFS, Disease-free survival; DoR, Duration of response; EFS, Event-free survival; ORR, Objective response rate; OS, Overall survival; pCR, Complete pathological response; PFS, Progression-free survival; PFS2, Second progression-free survival; TDT, Time to treatment discontinuation or death; TFST, Time to first subsequent therapy or death, TSST, Time to second subsequent therapy or death.

V: PART V: RISK MINIMISATION MEASURES

V: 1 ROUTINE RISK MINIMISATION MEASURES

Not applicable as there are no safety concerns.

V: 2 ADDITIONAL RISK MINIMISATION MEASURES

Not applicable as there are no safety concerns.

V: 3 SUMMARY OF RISK MINIMISATION MEASURES

Not applicable as there are no safety concerns.

VI: PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR IMFINZI (DURVALUMAB)

This is a summary of the Risk Management Plan (RMP) for IMFINZI (durvalumab). The RMP details important risks of IMFINZI, how these risks can be minimised, and how more information will be obtained about IMFINZI's risks and uncertainties (missing information).

IMFINZI's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients/carers on how IMFINZI should be used.

This summary of the RMP for IMFINZI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 IMFINZI's RMP.

VI: 1 THE MEDICINE AND WHAT IT IS USED FOR

IMFINZI is authorised:

- As monotherapy for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express programmed cell death ligand 1 (PD-L1) on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.
- In combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with extensive-stage small cell lung cancer.
- In combination with gemcitabine and cisplatin for the first-line treatment of adults with unresectable or metastatic biliary tract cancer.
- In combination with tremelimumab and platinum-based chemotherapy for the first-line treatment of adults with metastatic NSCLC with no sensitising epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) positive mutations.
- In combination with tremelimumab for the first-line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).
- As monotherapy for the first-line treatment of adults with advanced or unresectable HCC.

- In combination with carboplatin and paclitaxel for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with:
  - IMFINZI as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR)
  - IMFINZI in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR).
- As monotherapy for the treatment of adults with limited-stage small cell lung cancer whose disease has not progressed following platinum-based chemoradiation therapy.
- In combination with platinum-based chemotherapy as neoadjuvant treatment, followed by as monotherapy as adjuvant treatment, for the treatment of adults with resectable NSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements.

IMFINZI contains durvalumab as the active substance and is administered as an intravenous infusion.

Further information about the evaluation of IMFINZI's benefits can be found in IMFINZI's EPAR, including its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/imfinzi.

VI: 2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of IMFINZI, together with measures to minimise such risks and the proposed studies for learning more about risks of IMFINZI, are outlined below.

Measures to minimise the risks identified for medicinal products can be as follows:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and product information 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 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 addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report 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 IMFINZI 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 IMFINZI. 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).

There are no safety concerns for IMFINZI.

VI: 2.2 Summary of Important Risks

There are no safety concerns for IMFINZI.

VI: 2.3 Post-authorisation Development Plan

VI: 2.3.1 Studies that are Conditions of the Marketing Authorisation

The following studies are conditions of the marketing authorisation:

- **Study D9311C00001 (DUO-E) - A study to assess the efficacy and safety of IMFINZI in combination with platinum-based chemotherapy (paclitaxel + carboplatin) followed by maintenance IMFINZI with or without olaparib for patients with newly diagnosed advanced or recurrent endometrial cancer**
  - *Purpose of the study*: To investigate the efficacy of IMFINZI in combination with standard-of-care platinum-based chemotherapy (carboplatin and paclitaxel) followed by IMFINZI with or without olaparib, compared to standard-of-care platinum-based chemotherapy, by the assessment of progression-free survival in patients with newly diagnosed advanced or recurrent endometrial cancer.
- **Study D9106C00001 (AEGEAN) - A study of neoadjuvant/adjuvant IMFINZI for the treatment of patients with resectable NSCLC**
  - *Purpose of the study*: To investigate the efficacy of IMFINZI and platinum-based chemotherapy administered prior to surgery followed by IMFINZI monotherapy post-surgery, compared with placebo and platinum-based chemotherapy administered prior to surgery followed by placebo post-surgery in terms of event-free survival; and to compare the activity of IMFINZI and platinum-based chemotherapy administered

prior to surgery with placebo and platinum-based chemotherapy administered prior to surgery in terms of complete pathological response, in patients with resectable NSCLC.

VI: 2.3.2 Other Studies in the Post-Authorisation Development Plan

There are no studies required for IMFINZI.

VII: PART VII: ANNEXES

Annex 4 Specific Adverse Drug Reaction Follow-Up Forms *(Not Applicable)*

Annex 6 Details of Proposed Additional Risk Minimisation Activities *(Not Applicable)*

Annex 4: Specific Adverse Drug Reaction Follow-Up Forms (Not Applicable)

Not applicable.

Annex 6: Details of Proposed Additional Risk Minimisation Activities (Not Applicable)

Not applicable.