# EU RISK MANAGEMENT PLAN FOR LIBTAYO® (CEMIPLIMAB)

| | |
|---|---|
| **Active substance(s) (INN or common name)** | CEMIPLIMAB |
| **Pharmaco-therapeutic group (ATC Code)** | Antineoplastic agents, monoclonal antibodies.<br>ATC code: L01FF06 |
| **Name of Marketing Authorisation Holder or Applicant** | Regeneron Ireland DAC |
| **Medicinal product(s) to which this Risk Management Plan (RMP) refers** | Cemiplimab |
| **Product(s) concerned (brand name(s))** | LIBTAYO® |
| **Data lock point for this RMP** | 04 October 2024 |
| **RMP Version number** | Version 4.3 |
| **Date of final sign-off** | 05 Aug 2025 |
| **Rationale for submitting an updated RMP** | Revision of additional risk minimisation measures of "Patient Guide and Patient Alert Card" to include only the Patient Card as Requested by PRAC, Procedure no.: EMEA/H/C/PSUSA/00010780/202209<br>Addition of indication: LIBTAYO as monotherapy is indicated for the adjuvant treatment of adult patients with cutaneous squamous cell carcinoma (CSCC) at high risk of recurrence after surgery and radiation (see section 5.1 for selection criteria). |
| **Summary of significant changes in this RMP** | Part I: Updated pharmacotherapeutic group (ATC code) to match PBRER; provided additional details on product composition; provided proposed dosage and indication for adjuvant |

| | |
|---|---|
| | treatment of patients with high-risk CSCC.<br><br>Part II Module SI: Updated epidemiology (i.e., incidence and prevalence, demographics, risk factors, existing treatment options, natural history, and important comorbidities) of CSCC.<br><br>Part II Module SIII: Updated with clinical trial exposure data for Study 1423, Study 1540, Study 1620, and Study 1676, and Study 1788 (C-POST).<br><br>Part II Module SIV: updated to include Study 1788 (C-POST).<br><br>Part II Module SV: Updated post-authorisation exposure data<br><br>Part II Module SVII: Risk frequencies updated for Study 1423, Study 1540, Study 1620, Study 1676, and added for Study 1788 (C-POST).<br><br>Removed long-term safety data from Presentation of the Missing Information<br><br>Part II Module SVIII<br><br>Removed long-term safety data.<br><br>Rationale: On 12 Jul 2022, the MAH submitted updated and final analysis data for Study 1540 group 1-3 and primary analysis data for group 6 (Type II variation assessment report, Procedure No. EMEA/H/C/004844/II/0031). In addition, considering Study 1540 has been completed and no new safety |

| | |
|---|---|
| | findings have been identified in patients after long term follow up, the MAH proposes to remove the missing information 'long term safety data'<br><br>Part IV: Table for post-authorisation efficacy; Study 1620 was removed since the study was completed and the final CSR was submitted to EMA, Procedure No., EMEA/H/C/000484/REC/012<br><br>Part V: Updated to remove Patient Guide from additional risk minimisation measures as requested by PRAC, Procedure no.: EMEA/H/C/PSUSA/00010780/202209<br><br>Part VI: Updated to reflect changes elsewhere<br><br>Part VII: Annex 2 updated to reflect completion of Study 1540 and Study 1620 |
| **Other RMP versions under evaluation** | Not applicable |
| **Details of the currently approved RMP** | EU RMP version 4.0<br><br>Approved with Procedure: EMEA/H/C/004844/II/0028<br><br>Date of Approval (CHMP Opinion date): 23 February 2023 |
| **QPPV name** | Suzanne Green, MBChB |
| **QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.** | |

# TABLE OF CONTENTS

## LIST OF TABLES

# LIST OF ABBREVIATIONS

| Abbreviation | Definition of Term |
|---|---|
| 1L | First-line treatment |
| ADA | Anti-drug antibody |
| AE | Adverse event |
| ALP | Alkaline phosphatase |
| ALK | Anaplastic lymphoma kinase |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| BCC | Basal cell carcinoma |
| BRAF | Serine/threonine-protein kinase B-Raf |
| CC | Cervical cancer |
| CHO | Chinese Hamster Ovary |
| CI | Confidence interval |
| CNS | Central nervous system |
| CSCC | Cutaneous squamous cell carcinoma |
| CT | Computed tomography |
| DLP | Data lock point |
| DLT | Dose-limiting toxicity |
| ECG | Electrocardiogram |
| EGFR | Epidermal Growth Factor Receptor |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| GLP | Good laboratory practice |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HHI | Hedgehog pathway inhibitors |
| HIV | Human immunodeficiency virus |
| HPV | Human papillomavirus |
| IC | Investigator’s choice |
| ICH | International Council for Harmonisation |
| IgG | Immunoglobulin G |
| imAE | Immune-mediated adverse event |
| imAR | Immune-mediated adverse reaction |
| IRR | Infusion-related reactions |
| IV | Intravenous |

| Abbreviation | Definition of Term |
|---|---|
| laCSCC | Locally advanced cutaneous squamous cell carcinoma |
| MAA | Marketing authorisation application or marketing authorisation applicant |
| MAH | Marketing authorisation holder |
| mCSCC | Metastatic cutaneous squamous cell carcinoma |
| MRI | Magnetic resonance imaging |
| NAb | Neutralizing antibody |
| NSCLC | Non-small cell lung cancer |
| ORR | Overall response rate |
| OS | Overall survival |
| PD-1 | Programmed cell death-1 (receptor) |
| PD-L1, PD-L2 | Programmed cell death ligand 1, programmed cell death ligand 2 |
| PFS | Progression-free survival |
| PK | Pharmacokinetic(s) |
| PSA | Prostate-specific antigen |
| PTCH | Protein patched homologue |
| PSUR | Periodic safety update report |
| Q2W | Every 2 weeks |
| Q3W | Every 3 weeks |
| R/M | Recurrent or metastatic |
| RMP | Risk Management Plan |
| ROS1 | c-ROS oncogene 1 |
| SC | Subcutaneous |
| SCC | Squamous cell carcinoma |
| SEER | Surveillance, Epidemiology, and End Results |
| SmPC | Summary of product characteristics |
| SJS | Stevens-Johnson syndrome |
| SMO | Smoothened |
| TEN | Toxic epidermal necrolysis |
| ULN | Upper limit of normal |
| US | United States |
| UV | Ultraviolet |

# PART I: PRODUCT(S) OVERVIEW

## Table Part I. 1 Product Overview

| | |
|---|---|
| **Active substance(s)**<br>**(INN or common name)** | Cemiplimab |
| **Pharmacotherapeutic group(s) (ATC Code)** | Antineoplastic agents, PD-1/PD-L1 (Programmed cell death protein-1/death ligand 1) inhibitors. ATC code: L01FF06 |
| **Marketing Authorisation Holder or Applicant** | Regeneron Ireland DAC |
| **Medicinal products to which this Risk Management Plan (RMP) refers** | Cemiplimab |
| **Invented name(s) in the European Economic Area (EEA)** | LIBTAYO® |
| **Marketing authorisation procedure** | Centralised procedure |
| **Brief description of the product** | Chemical class: Anti-neoplastic agent, monoclonal antibody |
| | Summary of mode of action: Cemiplimab is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody that binds specifically to programmed cell death-1 (PD-1) and blocks its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). |
| | Important information about its composition:<br>Concentrate for solution for infusion (sterile concentrate).<br>Clear to slightly opalescent, colourless to pale yellow solution with a pH of 6.0 and osmolality between 300 and 360 mmol/kg. The solution may contain trace amounts of translucent to white particles in a single-use vial.<br>Cemiplimab is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture. Cemiplimab has an approximate molecular weight of 146 kDa. |
| **Hyperlink to the Product Information** | Module 1.3.1 English Approved Product Information |

| | |
|---|---|
| **Indication(s) in the EEA** | **Current:**<br>**Cutaneous squamous cell carcinoma (CSCC)**<br>LIBTAYO® as monotherapy is indicated for the treatment of adult patients with metastatic (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation.<br>**Basal Cell Carcinoma (BCC)**<br>LIBTAYO as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic basal cell carcinoma (laBCC or mBCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI).<br>**Non-small cell lung cancer (NSCLC)**<br>LIBTAYO as monotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:<br>• locally advanced NSCLC who are not candidates for definitive chemoradiation, or<br>• metastatic NSCLC<br>**Non-small cell lung cancer (NSCLC) in combination therapy**<br>LIBTAYO in combination with platinum-based chemotherapy is indicated for the first-line treatment of adult patients with NSCLC expressing PD-L1 (in ≥ 1% of tumour cells) with no EGFR, ALK or ROS1 aberrations, who have:<br>• locally advanced NSCLC who are not candidates for definitive chemoradiation, or<br>• metastatic NSCLC.<br>**Cervical cancer (CC)**<br>LIBTAYO as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy. |
| | **Proposed:**<br>**Cutaneous squamous cell carcinoma (CSCC)**<br>LIBTAYO as monotherapy is indicated for the adjuvant treatment of adult patients with CSCC at high risk of recurrence after surgery and radiation (see section 5.1 for selection criteria). |
| **Dosage in the EEA** | **Current:** The approved recommended dose is 350 mg cemiplimab every 3 weeks (Q3W) administered as an intravenous (IV) infusion over 30 minutes<br>Treatment may be continued until disease progression or unacceptable toxicity<br>**Proposed dosage:**<br>*Locally Advanced or Metastatic CSCC, NSCLC, BCC and Recurrent or Metastatic Cervical Cancer*<br>The recommended dose is 350 mg cemiplimab every 3 weeks (Q3W) administered as an intravenous infusion over 30 minutes.<br>Treatment may be continued until disease progression or unacceptable toxicity.<br>*Adjuvant treatment of high-risk CSCC* |

| | |
|---|---|
| | The recommended dose of LIBTAYO administered as an intravenous infusion over 30 minutes is:<br>• 350 mg every 3 weeks for 12 weeks followed by 700 mg every 6 weeks, or<br>• 350 mg every 3 weeks.<br>Treatment may be continued until disease recurrence, unacceptable toxicity, or for up to 48 weeks of total therapy. |
| **Pharmaceutical form(s) and strengths** | **Current:** Concentrate for solution for infusion (sterile concentrate)<br>Each mL of concentrate contains 50 mg of cemiplimab<br>Cemiplimab 350 mg concentrate for solution for infusion<br>One vial contains 350 mg of cemiplimab in 7 mL<br>**Proposed:** No change |
| **Is/will the product be subject to additional monitoring in the EU?** | Yes |

# PART II: SAFETY SPECIFICATION

## Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

### Cutaneous Squamous Cell Carcinoma

Cutaneous squamous cell carcinoma (CSCC) is a malignant proliferation of epidermal keratinocytes with invasion of the dermis. While most cases of CSCC are successfully treated with surgery, some patients have a heightened risk of recurrence, a subset referred to as high-risk CSCC. Cutaneous squamous cell carcinoma that involves regional lymph nodes, but not other distant sites, is referred to as locally advanced CSCC (laCSCC). Locally advanced CSCC may be amenable to surgical resection (resectable) or not (unresectable). Cutaneous squamous cell carcinoma that involves distant (non-regional) lymph nodes and/or other distant sites is referred to as metastatic CSCC (mCSCC).

### Incidence and Prevalence:

CSCC is the second most common non-melanoma skin cancer and its incidence has steadily increased in recent decades for many geographic regions (Stratigos, 2015) (Rogers, 2010) (Que, 2018) (Lomas, 2012) (Olsen, 2024). Worldwide incidence varies widely, with the highest age-standardized incidences observed in the North America (324.2/100,000 persons) and Australasia (249.7/100,000 persons) regions. Among western European countries, the annual age-standardized incidence is estimated to be 6.9 cases per 100,000 persons. Between 1990 and 2019, the largest increases in incidence were noted in East Asia (+159.2%) and North America (+80.5%) (Huang, 2024). The Australasia region also had the highest CSCC mortality rate in 2019 (Guo, 2023).

Aligning with recent global trends, many European countries have reported a steady increase in the incidence of CSCC over the last several decades, particularly in the northern and western regions. In Finland, the crude incidence of CSCC increased from 19/100,000 persons in 2006 to 42 in 2020 (Lounas, 2024). Between 1989 and 2017, the age-standardized incidence rate of CSCC in situ increased from 11.1/100,000 person-years to 67.8 for men and 9.3/100,000 person-years to 71.7 for women in the Netherlands (Tokez, 2020). Over a period of 30 years, the Danish cancer registry reported an annual increase in CSCC incidence of 3.1% for men and 4.3% for women (Birch-Johansen, 2010). A similar increase in incidence was observed in Norway between 1963 and 2011 (Robsahm, 2015). Germany reported an even more pronounced annual increase in CSCC incidence between 2007 and 2015, with increases of 7.9% for men (54/100,000 person-years in 2015) and 9.8% for women (26/100,000 person-years in 2015) (Stang, 2019). Consistently across the literature, Ireland had the highest age-standardized incidence rate in Europe, which was approximately 105/100,000 person-years in 2015 (Carsin, 2011) (Guo, 2023) (Venables, 2019b).

The estimated prevalence rate of CSCC in 2019 for the United States, Europe (including France, Germany, Italy, Spain, and the United Kingdom), and Japan are summarised in Table Part II.SI.1. Among these countries, the United States had the highest prevalence of CSCC, while Japan experienced the most significant increase in prevalence from 1990 to 2019.

**Table Part II.SI. 1 Estimated Prevalence Rate of CSCC Worldwide in 2019**

| Country | Prevalence rate (95% CI) [per 100,000 population] | Percentage change in prevalence rate between 1990 and 2019 (95% CI) [per 100,000 population] |
|---|---|---|
| France | 9.3 (7.9 to 11.1) | 12 (0 to 26.5) |
| Germany | 5.7 (4.8 to 6.8) | 55.2 (38 to 73.1) |

| | | |
|---|---|---|
| Italy | 7.7 (6.4 to 9.3) | 28.8 (23.2 to 35.8) |
| Japan | 1.2 (1 to 1.4) | 116.7 (104.1 to 131.4) |
| Spain | 7.7 (6.6 to 9) | 5.1 (-8.8 to 20.5) |
| UK | 8.6 (7.2 to 10.2) | 22.4 (20.1 to 24.5) |
| US | 314.3 (270.4 to 368.1) | 13.3 (-1.3 to 30.3) |
| **Worldwide** | 39.3 (34 to 45.8) | 14.1 (0.1 to 31.3) |

Prevalence rates are age-standardized based on the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019 standard population structure.
UK, United Kingdom; US, United States.
Source: (Guo, 2023)

**Demographics of the CSCC Population and Risk Factors for the Disease:** Incidence of CSCC is associated with demographic characteristics including male gender, advanced age, and light-skinned, white race and ethnicity.

- Sun exposure: Cumulative sun exposure (principally ultraviolet B [UVB] radiation) is the most important environmental cause of CSCC. In one prospective cohort study of 172,472 Norwegian women, fewer than 40 years of high sunburn frequency throughout life was linked to a 51% greater risk of CSCC compared with low exposure [hazard ratio: 1.51, 95% CI: 1.22-1.87] (Lergenmuller, 2022). Tanning beds, which primarily emit ultraviolet A [UVA] radiation, cause skin changes like those seen with sun damage. A 2012 meta-analysis of observational studies found a 67% higher risk for CSCC among persons with a history of any tanning bed use compared with those who had never used tanning beds (relative risk: 1.67, 95% CI: 1.29 to 2.17) (Wehner, 2012).
- Immunosuppression: Chronic immunosuppression may increase the incidence of CSCC. In the Netherlands and Norway, the rates of CSCC were 65 to 250 times more frequent in kidney and heart transplant recipients than in the general population (Hartevelt, 1990) (Jensen, 1999) (Blue, 2022). In the United States, approximately 35% of heart transplant recipients will develop a skin cancer within 10 years after transplantation (Lampros, 1998) (Brewer, 2009). Among patients in Australia with chronic lymphocytic leukaemia, 11.2% developed CSCC, of which 10.3% progressed to metastatic disease (Lai, 2023). Immunosuppressed individuals with CSCC also face a heightened risk of mortality, likely attributed to a more aggressive phenotype and an increased risk of recurrence and metastasis (Blue, 2022).
- Age: Globally, the greatest age-standardized incidence for CSCC is observed in those aged 70 to 74 years (Guo, 2023). For high-risk and advanced CSCC cases, the median age is moderately higher at ≥75 years (Burton, 2016).
- Race and ethnicity: Light-skinned, non-Hispanic white populations have the highest reported rates, while blacks, dark-skinned Asians, and other non-whites have low reported rates of CSCC (Armstrong, 2001) (Koh, 2003) (Halder, 1988).
- Gender: CSCC is significantly more prevalent in males than in females. Research indicates that the male-to-female ratio for high-risk and advanced tumors is approximately 3:1 (Soleymani, 2023) (Venables, 2019a).

**Existing Treatment Options for CSCC**:

The first-line treatment of CSCC is surgical excision with histopathological control of excision margins. Surgical interventions are the centerpiece of clinical management of resectable

CSCC. The primary goal is complete resection of cancer, and acceptable functional and cosmetic outcomes are important additional objectives (Madan, 2010).

A subset of CSCC tumors is considered to have a high-risk for recurrence following surgery due to underlying clinicopathologic factors, including extent of nodal involvement, presence of extracapsular extension, disease stage, perineural involvement (PNI), in-transit metastases (ITM), recurrent disease, and immunosuppression, among others (Carter, 2013) (Ebrahimi, 2020) (Karia, 2018) (Lin, 2012) (Stratigos, 2023) (Xu, 2018). Adjuvant radiation therapy may be recommended for high-risk tumors following surgical resection (Kim, 2018); however, CSCC may still recur with locoregional and/or distant metastases (Porceddu, 2018). Adjuvant systemic treatment following radiotherapy, including chemotherapy, targeted therapies, or immunotherapy, have been evaluated. Most notably, the phase III trial assessing adjuvant carboplatin following surgery and radiation in patients with high-risk head and neck CSCC was unable to demonstrate therapeutic benefit (Porceddu, 2018). Thus, there is a critical unmet medical need to lower the risk of CSCC recurrence and metastasis in these patients with a poor prognosis.

For patients who develop advanced CSCC (mCSCC or unresectable laCSCC), (Shin, 2002, Maubec, 2011) immunotherapy, including anti-PD-1 and anti-PD-L1 monotherapies, has become the first-line standard of care (Queirolo, 2024) (Stratigos, 2023). Cemiplimab monotherapy was the first anti-PD-1 approved for advanced CSCC, with an ORR as high as 47.2% (95% CI: 39.9% to 54.4%) observed in the phase II EMPOWER-CSCC-1 study (Hughes, 2025). Pembrolizumab and cosibelimab have also been used for the treatment of advanced CSCC (Grob, 2020) (Clingan, 2023), and other PD-1 and PD-L1 inhibitors are being evaluated for use in the advanced setting (Lang, 2023).

**Natural History of CSCC**

While the probability of surgical cure for most patients with CSCC is high, the risk of nodal metastasis or CSCC-related mortality can be as great as 5.8% and 3.4%, respectively (Brantsch, 2008) (Schmults, 2013) (Czarnecki, 1994) (Eigentler, 2017) (Joseph, 1992). High-risk CSCC tumors are likely to result in the poorest outcomes, including locoregional metastasis, distant metastasis, or death. In a study evaluating 782 primary CSCC tumors with high-risk features, approximately 55% of local recurrences, nodal metastasis, in-transit metastasis, distant metastasis, and disease-specific deaths occurred within the first year, 80% by the second year, and 89% by the third year (Granger, 2024). Among patients categorized using NCCN risk groups, one study reported a 5-year cumulative incidence of nodal and distant metastasis of 0.5% and 0.1% in high-risk patients, and of 7.3% and 3.9% in very high-risk patients (Stevens, 2023). The 5-year disease-specific death was 0.5% for high-risk and 10.5% for very high-risk patients.

Locally advanced CSCC can invade local anatomic structures, resulting in additional symptoms (Poulalhon, 2015) (Brotherston, 2015). Furthermore, the prognosis for patients with laCSCC or mCSCC is considered to be very poor with a 2-year overall survival of 52.8% to 67.1%, respectively, following treatment with PD-1 or PD-L1 inhibitors in the real-world settings (Salzmann, 2020) (Verkerk, 2024).

**Important Comorbidities:**

As the median age of patients with high-risk and advanced CSCC is ≥75 years old (Soleymani, 2023) (Hanna, 2020), comorbidities are common and include those typically observed in an elderly population.

**Basal Cell Carcinoma**

**Advanced Basal Cell Carcinoma**

Basal cell carcinoma (BCC) is a malignant proliferation arising from the basal layer of the epidermis. Virtually all BCCs are characterised by aberrant signalling of the hedgehog signalling pathway, most commonly due to sporadic loss-of-function mutation in the gene encoding protein patched homologue (PTCH), a tumour suppressor. A PTCH mutation results in loss of patched-mediated inhibition of the G protein coupled receptor Smoothened (SMO), thereby enhancing downstream signalling that results in uncontrolled cellular proliferation (Sekulic, 2016). A small percentage of patients develop advanced BCC for which systemic therapy with hedgehog inhibitors (HHI) is administered, and these patients can be divided into 2 groups. Basal cell carcinoma that is metastatic to lymph nodes (regional or distant) or other distant sites is referred to as metastatic BCC. Basal cell carcinoma that has not metastasised to lymph nodes (regional or distant) or other distant sites in patients who are not candidates for curative surgery or radiotherapy is referred to as locally advanced BCC. The combined populations of metastatic BCC and locally advanced BCC are referred to as advanced BCC (Mohan, 2014).

**Incidence and Prevalence:**

Worldwide incidence varies widely, with the highest incidence in Australia and the lowest incidence in parts of Africa (Lomas, 2012). Basal cell carcinoma is the most common malignancy in the US, with an estimated incidence of over 3 million, and ultraviolet (UV) exposure is the major risk factor (Wu, 2013). Accurate incidence numbers and mortality estimates are not available because the disease is not tracked in the Surveillance, Epidemiology, and End Results (SEER) program. In a prospective cohort study in Minnesota, USA (2000-2010), the age- and sex-adjusted incidence rate of BCC was reported at 321 per 100,000 person-years (Muzic, 2017). In a retrospective cohort analysis of electronic health record in California, USA, the age-, sex-, and race-adjusted incidence rate of BBC was 535 per 100,000 person-years in 2012 (Asgari, 2015). Data from prospective studies suggest that the incidence of BCC in the US has doubled in the last 2 decades (Wu, 2013). Basal cell carcinoma incidence also appears to be increasing slightly in European Union (EU) nations, with approximately 50 to 90 new patients per 100,000 individuals annually in EU (Madan, 2010) (Leiter, 2017). A systematic review and meta-analysis of published records (between 1985 and 2007) from Spanish Network of Cancer Registries (REDECAN) and the International Agency for Research on Cancer reported an overall incidence of 113.05 (95% CI, 89.03-137.08) cases per 100 000 person-year for studies based on registration methodologies and an incidence of 253 per 100,000 person-years when incidence was calculated based on histological and clinical data (Tejera-Vaquerizo, 2016).

There is a paucity of information on the incidence of locally advanced BCC or metastatic BCC. A retrospective study using linked data from Danish registries from 1997 to 2010 assessed the incidence of metastatic BCC. Cumulative incidence of metastatic BCC was reported at 0.004% among patients with a history of BCC and 1 per 1,000,000 in the general population (Nguyen-Nielsen, 2015). Similar to the incidence reported from the Danish data, a retrospective cohort study using electronic health records in the Department of Veterans Affairs (VA) metastatic BCC was reported in 0.1% of patients with primary BCC (Stevens, 2018). Using claims data of privately insured patients, the 2012 age-standardised incidence for locally advanced BCC and metastatic BCC in the US was estimated at 2.3 and 0.04 per 100,000 persons, respectively (Goldenberg, 2016).

Mortality: Given the rarity of advanced BCC, there is a paucity of data regarding survival rates. One study of 100 metastatic BCC cases, median survival after diagnosis was 54 months, with patients with distant metastatic disease having shorter survival (24 months; 95% CI 12-34, n=50) than those with regional metastatic disease (87 months; 95% CI 63-not evaluable, n=50) (McCusker, 2014).

**Demographics of the Population in the BCC Indication and Risk Factors for the Disease:**

Incidence of BCC is associated with demographic characteristics including male gender, advanced age, and light skin. Risk factors include UV exposure (Wong, 2003).

- Gender: Age-standardised incidence rates in white populations is generally between 18% and 40% higher in men (Diepgen, 2002).
- Age: BCC is rarely found before the age of 20 and incidence rate doubles from 40 to 70 years of age (Lomas, 2012).
- Skin pigmentation: Type 1 skin has been shown to be risk factors for the development of BCC with a relative risk of 1.6 (Lear, 1997).
- UV exposure: Skin exposure to UV light is the main causative factor for BCC, though the relationship between cumulative exposure, timing of exposure and development of BCC is complex (Zanetti, 1996).

**Existing Treatment Options for BCC:**

The first-line treatment of BCC includes Mohs micrographic surgery, curettage and cautery and cryosurgery. For the small percentage of patients who develop advanced BCC (metastatic BCC or locally advanced BCC), systemic treatment with HHIs have been approved.

- ERIVANCE was a non-randomised phase 2 study that led to regulatory approval of vismodegib in the US, EU, and several other countries, for the treatment of locally advanced BCC and metastatic BCC. Vismodegib yielded overall response rates (ORRs) of 30% and 43% in metastatic and locally advanced BCC, respectively, in the original report (Sekulic, 2012). At the 12-month update, median durations of response were 7.6 months for metastatic BCC and 9.5 months for locally advanced BCC. Median OS was 33.4 months in the metastatic BCC cohort and not estimable in the locally advanced BCC cohort (Sekulic, 2015). The most common adverse events (AEs) were muscle spasms (71.2%), alopecia (65.4%), dysgeusia (53.8%), weight decrease (50.0%), fatigue (40.4%), and nausea (32.7%).
- BOLT was a phase 2 study of two doses of sonidegib, another orally available HHI, that led to the regulatory approval in the US, EU, and several other countries, at the dose of 200 mg per day, for locally advanced BCC, based on demonstration of ORR of 47% (31 responses among 66 patients) in this population (Migden, 2018). Median OS was not reported in the primary or 12-month analyses. The most common AEs at the approved dose were muscle spasms (49%), alopecia (43%), and dysgeusia (38%).

For BCC patients who progress on vismodegib, subsequent treatment with sonidegib appears to be inactive (Danial, 2016). There is no approved agent for BCC in patients who experienced progression of disease on HHI therapy, or who are intolerant of prior HHI therapy. As such, there is a significant unmet medical need for treatments for patients who develop advanced BCC disease.

**Natural History of Advanced BCC:**

Advanced BCCs are typified by their local invasiveness, proximity to vital structures or the presence of metastasis (Mohan, 2014). While HHI therapy have demonstrated high initial response rates, the majority of patients eventually discontinue therapy either due to progression of disease or intolerance (Sekulic, 2012) (Migden, 2015).

**Important Comorbidities:**

As the mean age of patients with advanced BCC in the clinical study of cemiplimab in BCC is 68 years old, common comorbidities include those expected in an elderly population with the most common (>20%) being hypertension and fatigue. Muscle spasms, a commonly associated side effect of HHI therapy was also common within this population. In a retrospective cohort study on metastatic BCC patients, the median age was 72 years old (Stevens, 2018). The same study reported pulmonary disease (19.6%), diabetes (18.1%), and cerebrovascular disease (10.5%) as the most commonly reported comorbidities in this patient population (Stevens, 2018).

**Non-small Cell Lung Cancer**

Lung cancer was the second most commonly diagnosed type of cancer in 2020, representing 11.4% of all new cancer diagnoses and over 2 million new cases worldwide (Sung, 2021). Notably, lung cancer was the leading cause of cancer death in 2020, at 18.40% of all cancer-related mortality and roughly 1.8 million deaths (Sung, 2021).

**Incidence and Prevalence:**

The highest incidence rate among males is reported from Micronesia/Polynesia at 51.6 per 100,000 males, whereas for females, the highest incidence rate was observed in North America at 30.1 per 100,000 females (Sung, 2021). In 2020, an estimated 228,820 new cases of lung cancer were to be diagnosed in the US and 135,720 people were to die from the disease (American Cancer Society, 2020). The estimated prevalence, incidence, and mortality of lung cancer (all types combined) in 2020 for the US, Europe (France, Germany, Italy, Spain, and the United Kingdom), and Japan are summarised in Table Part II.SI. 1.

**Table Part II.SI. 1 Estimated Prevalence, Incidence, and Mortality of Lung Cancer (All Types) in 2020**

| Country | Prevalence (5-year) | Incidence | Mortality |
|---|---|---|---|
| France | 91.5 per 100,000 | 34.9 per 100,000 | 25.4 per 100,000 |
| Germany | 101.0 per 100,000 | 31.9 per 100,000 | 23.1 per 100,000 |
| Italy | 81.7 per 100,000 | 25.3 per 100,000 | 18.0 per 100,000 |
| Japan | 171.3 per 100,000 | 32.1 per 100,000 | 14.7 per 100,000 |
| Spain | 76.4 per 100,000 | 29.0 per 100,000 | 20.9 per 100,000 |
| UK | 97.0 per 100,000 | 32.3 per 100,000 | 20.8 per 100,000 |
| US | 89.2 per 100,000 | 33.1 per 100,000 | 18.9 per 100,000 |
| **Worldwide** | **33.4 per 100,000** | **22.4 per 100,000** | **18.0 per 100,000** |

Incidence and mortality rates are age-adjusted based on the WHO world standard population. Prevalence estimates are scaled using Human Development Index (HDI) ratios.
UK, United Kingdom; US, United States; WHO, World Health Organization.
Source: (Ferlay J, 2018)

Non-small cell lung cancer is the most common subtype of lung cancer, accounting for 80% to 90% of cases (Howlader, 2019) (Planchard, 2018) (National Cancer Institute, 2019). Nonsmall cell lung cancer represents- a heterogenous group of tumours of varying histological type (Planchard, 2018) (Osmani, 2018). Histological subtypes of NSCLC are broadly grouped

under the categories of adenocarcinoma, squamous cell carcinoma, large cell carcinoma (including giant cell, clear cell, and large undifferentiated cell carcinoma), and others. According to data from SEER National Program of Cancer Registries (NPCR), the annual incidence of NSCLC in the US has declined from 46.4 new cases per 100,000 in 2010 to 40.9 cases per 100,000 in 2017, a decline largely attributable to a reduction in incidence among males (Ganti, 2021). Between 2010 and 2017, the incidence of NSCLC decreased from 56.0 to 46.5 per 100,000 for men, and from 39.1 to 36.6 per 100,000 for women. Despite the general decreases in lung cancer incidence worldwide, diagnoses of NSCLC are estimated to rise by 25% over the next 10 years, driven by increased incidence in low-income regions including Africa and parts of the Asia-Pacific region. The estimated new cases of NSCLC in 2020 in the US, Europe countries, and Japan is presented in Table Part II.SI. 2. As noted in the table, advanced NSCLC constitutes >50% of all new cases of NSCLC (Cerner Enviza, 2021).

**Table Part II.SI. 2 Estimated New Cases of NSCLC in 2020, All and Advanced NSCLC**

| Country | All NSCLC, n | Advanced NSCLC (ie, stage IIIb or IV)*, n (% of NSCLC) | Stage IIIb, n | Stage IV, n |
|---|---|---|---|---|
| **Europe** | | | | |
| France | 42,521 | 22,124 (52) | 2,347 | 19,777 |
| Germany | 49,983 | 26,098 (52) | 2,645 | 23,453 |
| Italy | 40,693 | 19,608 (53) | 2,093 | 19,608 |
| Spain | 26,169 | 13,765 (53) | 1,487 | 12,278 |
| UK | 46,093 | 23,922 (52) | 2,360 | 21,562 |
| **North America** | | | | |
| US | 192,787 | 98,024 (51) | 10,547 | 87,477 |
| **Asia** | | | | |
| Japan | 119,320 | 40,900 (35) | 8,947 | 37,911 |

NSCLC, non-small cell lung cancer; UK, United Kingdom; US, United States.
*These projections are based on 2017 historical data, thus, the staging of advanced NSCLC was based on the American Joint Committee on Cancer (AJCC) 7th edition. Using the historic age-adjusted incidence rates by gender, incidence is forecasted using a conservative approach without incorporating any assumptions about future changes in rates other than what is indicated by the historical curve.
Source: (Cerner Enviza, 2021).

Prevalence (5-year) by stage is presented in Table Part II.SI. 3, showing that approximately 45% of patients living with NSCLC in Europe and North America have advanced NSCLC (Cerner Enviza, 2021).

**Table Part II.SI. 3 Estimated Prevalence (5-Year) of NSCLC in 2020, by Stage**

| Country | NSCLC, n | Advanced (ie, stage IIIb or IV) NSCLC, n (% of NSCLC) | Stage IIIb, n | Stage IV, n |
|---|---|---|---|---|
| **Europe** | | | | |
| France | 107,816 | 49,054 (45) | 4,156 | 44,898 |
| Germany | 129,283 | 58,523 (45) | 4,783 | 53,740 |
| Italy | 102,864 | 47,346 (46) | 3,753 | 43,593 |
| Spain | 65,518 | 30,338 (46) | 2,607 | 27,731 |
| UK | 116,480 | 52,225 (45) | 3,861 | 48,364 |
| **North America** | | | | |
| US | 486,680 | 217,385 (45) | 18,062 | 199,323 |
| **Asia** | | | | |
| Japan | 391,894 | 128,094 (33) | 14,421 | 113,673 |

NSCLC, non-small cell lung cancer; UK, United Kingdom; US, United States.
The staging of advanced NSCLC was based on the American Joint Committee on Cancer (AJCC) 7th edition.
Source: (Cerner Enviza, 2021).

**Demographics of the Population in the Locally Advanced NSCLC or Metastatic NSCLC and Risk Factors for the Disease:**

- Age: Median age of diagnosis is 70 years for both genders with approximately 90% of cases occurring in patients 55 years and older (de Groot, 2018).
- Gender: The male to female ratio is approximately 2:1 worldwide (Sung, 2021), ranging from 1.2 in North America to 5.6 in North Africa. The geographic variation in male to female ratio and the reported sex-specific differences in the incidence of lung cancer is largely attributed to worldwide tobacco consumption. With the decline in tobacco use, the rates are converging in women and men. The rate of change in incidence, however, varies by region and closely follows the tobacco epidemic. Countries with active tobacco control measures are observing a decline in incidence of lung cancer in men and a plateau in incidence rate in women. While in other countries where tobacco consumption is increasing or peaked, lung cancer incidence rate continues to rise for the next few decades. Data from population-based cancer registries in Europe show a decline in incidence rate of lung cancer in men between 35 to 64 years of age (Lortet-Tieulent, 2015). Similarly, incidence and death rate from lung cancer has been decreasing among men in the US (Bray, 2018). For women, the tobacco epidemic is less advanced and despite the observed trend in men, most countries are still observing a rising trend in the incidence of lung cancer (Lortet-Tieulent, 2015) (Bray, 2018). In the US, lung cancer rates among women reached a plateau around early 2000 and began levelling off since then (Duma, 2019).
- Race and ethnicity: The incidence of lung cancer is greatest for non-Hispanic black men, whereas the lowest incidence rates are observed in Hispanic women (Siegel, 2021). While lung cancer has the highest rates among non-Hispanic black men, lung cancer incidence rates are greater among white women compared with African-American women (Siegel, 2021). Incidence and mortality rates of lung cancer by race and gender in the US for years 2013 to 2018 are presented in Table Part II.SI.4.

**Table Part II.SI. 4 Incidence and Mortality Rate of Lung Cancer by Race and Gender**

| | | All races combined | Non-Hispanic white | Non-Hispanic black | Asian/ Pacific Islander | American Indian/Alaska Native | Hispanic |
|---|---|---|---|---|---|---|---|
| **Incidence** | Male | 67.6 | 70.8 | 79.8 | 43.2 | 59.2 | 37.1 |
| | Female | 51.3 | 56.4 | 47.9 | 27.9 | 47.9 | 24.3 |
| | All | 58.4 | 62.6 | 60.9 | 34.4 | 52.7 | 29.7 |
| **Mortality** | Male | 46.9 | 49.4 | 57.0 | 28.0 | 38.4 | 23.0 |
| | Female | 32.0 | 35.6 | 30.6 | 16.3 | 27.4 | 12.3 |
| | All | 38.5 | 41.7 | 41.3 | 21.2 | 32.1 | 16.8 |

Rates are presented per 100,000 population and age-adjusted to the 2000 US standard population.
Source: (Siegel, 2021).

- Socioeconomic factors: Incidence of lung cancer is disproportionate across education levels. Men who did not graduate from high school have an incidence rate of 166 per 100,000, while the rate among college graduates is 57.6 (de Groot, 2018). Lower education and income are associated with higher smoking prevalence. However, some studies have shown an independent association between lower socioeconomic status and lung cancer controlling for smoking status. This observation suggests a role for possibly other environmental factors (de Groot, 2018).
- Smoking: Tobacco use is the primary risk factor for lung cancer and approximately 90% of cases are attributable to smoking (de Groot, 2018). While nicotine is not considered a carcinogenic agent, tobacco combustion creates over 60 carcinogens (de Groot, 2018).
- Radon: Exposure to radon is the second largest risk factor for the development of lung cancer in the US and includes exposure from domestic residential sources and passive emission from the soil (Ridge, 2013).
- Other risk factors for the development of lung cancer include (National Cancer Institute, 2019) (Ridge, 2013): Radiation exposure (including radiotherapy), chronic exposure to toxic metals such as nickel, exposure to certain industrial substances such as radon and asbestos, familial history of lung cancer, air pollution, and infection with human immunodeficiency virus (HIV).

**Existing Treatment Options for the Locally Advanced NSCLC or Metastatic NSCLC:**

Overall, treatment goals for all patients diagnosed with advanced (ie, stage IIIb/IIIc unresectable or stage IV) NSCLC are symptom control, improvement in quality of life, and extension of survival (Zarogoulidis, 2013).

Systemic therapy with platinum-based doublet regimens, with or without maintenance therapy, was until recently the standard of care for first-line treatment of patients with advanced NSCLC whose tumours do not have an epidermal growth factor receptor (EGFR) mutation, an anaplastic lymphoma kinase (ALK) mutation, or a c-ROS oncogene 1 (ROS1) fusion (Besse, 2014) (Ettinger, 2016) (Reck, 2014).

This is still the standard of care for these patients in countries where anti-PD-1 therapy is not approved or available. Chemotherapy for metastatic NSCLC is not curative, and despite optimal treatment, patients have a median OS of approximately 8 to 12 months, and a 5-year survival rate of approximately 4% (Howlader, 2019) (Siegel, 2016).

For patients with unresectable stage III NSCLC, standard of care includes chemoradiotherapy (CRT) with the addition of the immunotherapy durvalumab (National Comprehensive Cancer Network (NCCN), 2021). Additional trials are ongoing to evaluate the combination of other immune checkpoint inhibitors such as pembrolizumab, nivolumab, and atezolizumab with CRT, irrespective of PD-L1 expression (Jabbour, 2021) (Peters, 2019) (Lin, 2020). Systemic treatment with PD-1/PD-L1 inhibitors is also recommended for PD-L1 expression positive patients with stage III NSCLC who are ineligible for chemoradiation (National Comprehensive Cancer Network (NCCN), 2021).

The recommended first-line therapy for patients with stage IV NSCLC who are PD-L1 expression positive (≥1%) and negative for EGFR, ALK, or ROS1 aberrations is a PD-1/PD-L1 inhibitor in combination with a platinum doublet therapy eg, pembrolizumab or atezolizumab in combination with platinum-based doublet chemotherapy, atezolizumab plus

bevacizumab plus platinum-based doublet chemotherapy, or nivolumab plus ipilimumab alone or in combination with platinum-based doublet chemotherapy (National Comprehensive Cancer Network (NCCN), 2021). In addition, patients with PD-L1 expression ≥50% (ie, high expressors) may be candidates for atezolizumab or cemiplimab monotherapy. Patients who respond or exhibit stable disease may initiate maintenance therapy including bevacizumab, pemetrexed, or atezolizumab monotherapy, pembrolizumab monotherapy or in combination with pemetrexed for those receiving pembrolizumab in combination with platinum-based doublet chemotherapy, atezolizumab plus bevacizumab if receiving combination therapy with these agents, bevacizumab plus pemetrexed if bevacizumab was used with a platinum-based doublet chemotherapy, or nivolumab plus ipilimumab; patients may also be switched to pemetrexed or docetaxel monotherapy. If progression occurs while receiving a PD-1/PD-L1 inhibitor, switching to another PD-1/PD-L1 inhibitor is not recommended and the options are supportive care or a clinical trial.

**Natural History of the Locally Advanced NSCLC or Metastatic NSCLC:**

Non-small cell lung cancer is composed of several histopathological subtypes, the most common of which are adenocarcinoma (40% to 60%) and squamous cell carcinoma (30%) (Dela Cruz, 2011). At the time of initial diagnosis, approximately 60% of patients with NSCLC are found to have widespread metastatic disease, whilst approximately 30% to 35% of all patients present with locally advanced, non-metastatic disease (locally advanced NSCLC) that, due to its local extension within the thorax, is not resectable with curative intent. Absence of symptoms and aggressive biology of the tumour is often the underlying cause of late stage diagnosis. Frequent respiratory symptoms include cough, haemoptysis, chest pain, and dyspnoea (Kocher, 2015). Metastasis can occur to any body organs, but is commonly manifested in liver, bone, adrenal glands, and brain (Stenbygaard, 1997). For advanced NSCLC, the clinical outcome of NSCLC is closely related to the disease stage at time of diagnosis, and molecular characterisation of tumour to allow for novel targeted therapies (Planchard, 2018). Recent advancements to characterise NSCLC by subtypes according to mutation in ROS1, EGFR, or ALK, and presentation of PD-L1 have resulted in significant improvement in survival.

**Important Comorbidities:**

In a registry of NSCLC patients in Austria, cardiovascular disease (62.1%), chronic obstructive pulmonary disease (62.0%), and diabetes (13.2%) were reported as chronic comorbidities (Kocher, 2015). In a Danish Lung Cancer Registry (2009-2011), chronic obstructive pulmonary disease (8.1%), previous cancer (6.7%), and cerebrovascular conditions (3.8%) were the most common comorbidities among NSCLC patients (Iachina, 2015). Patients with each of the comorbidities had 20% to 30% higher risk of mortality compared to patients without comorbid conditions (Iachina, 2015).

**Cervical Cancer**

**Disease Background**

Cervical cancer had an estimated global incidence of 604,000 new cases and 342,000 deaths in 2020 (Sung, 2021). Developing parts of the world exhibit the greatest burden of cervical cancer, with roughly 90% of cervical cancer deaths occurring in developing countries (Marth, 2017). In most cases, causation is due to infection with human papillomavirus (HPV). Although vaccination against high risk strains of HPV is projected to gradually decrease the global incidence of cervical cancer in the coming decades, the burden of this disease remains profound (Simms, 2019).

Screening with the Papanicolaou (Pap) test since the 1950s, with subsequent incorporation of HPV DNA testing, has been associated with decreased cervical cancer mortality in the US and other developed countries (Wang, 2004). Approximately 95% of cervical cancers are caused by persistent infections with carcinogenic HPVs (Schiffman, 2011). Among the 13 known carcinogenic HPV types, initial vaccination efforts were directed against HPV 16 and HPV18 types (Arbyn, 2007). The subsequent Gardasil 9 vaccine, which protects against 9 HPV types, offers the potential to prevent approximately 90% of cervical cancers (Joura, 2015). It is estimated that, in the setting of widespread screening and vaccination against carcinogenic HPV strains, cervical cancer incidence may decrease 2% annually by 2030, potentially culminating in the elimination of cervical cancer by the end of the century (Bray, 2012) (Simms, 2019).

**Incidence and Prevalence:**

Cervical cancer is the fourth most common cancer among women after breast, colorectal, and lung cancer (Arbyn, 2020). In 2018, approximately 570,000 cases of cervical cancer were registered around the world and the global estimated age-standardized incidence was roughly 13.1 per 100,000 women (Arbyn, 2020). In North America, the 2018 age-standardized (to the global age distribution) incidence was an estimated 6.4 per 100,000 women while that for Eastern Asia, Central-Eastern, Northern, Southern, and Western Europe was 10.9%, 16.0%, 9.5%, 7.8%, and 6.8% (per 100,000 women), respectively (Arbyn, 2020). In terms of the proportion across all cancers among women, cervical cancer represents 6.9% of all cancers diagnosed among women around the world, with the following burden across key regions: North America (1.7%), Eastern Asia (5.1%), Central-Eastern Europe (5.9%), Northern Europe (2.1%), Southern Europe (2.3%), and Western Europe (1.7%) (Arbyn, 2020). Among women in the United States, the probability of developing cervical cancer in the United States across key age intervals was as follows: Birth to 49 years (0.3%), 50 to 59 years (0.1%), 60 to 69 years (0.1%), and 70 and older (0.2%) (Siegel, 2021).

In the United States, the incidence rate of cervical cancer has remained relatively stable since at least 2005, and in 2018, there were an estimated 293,394 (0.18% of all females in United States) women living with cervical cancer (SEER*Explorer: An interactive website for SEER cancer statistics). At diagnosis, 44% of cervical cancer cases in the United States are classified as localized (tumour site only), 36% as regional (tumour has spread to regional lymph nodes), and 16% as distant (tumour has metastasized) (SEER*Explorer: An interactive website for SEER cancer statistics). In a 2006 to 2012 sample from a Spanish cancer registry, the tumour stage (International Federation of Gynaecology and Obstetrics) breakdown, by comparison, was: Stage I (42.6%), Stage II (24.0%), Stage III (19.9%), and Stage IV (13.4%) (Amengual, 2020).

Mortality: In 2018, there were an estimated 311,365 deaths from cervical cancer around the globe, representing 7.5% of all cancer-related deaths (Arbyn, 2020). The global age-standardized mortality rate was roughly 6.9 per 100,000 women while the regional age-standardized mortality rate (per 100,000 women) was as follows: North America (1.9), Eastern Asia (4.1) Central-Eastern Europe (6.1), Northern Europe (2.1), Southern Europe (2.2), and Western Europe (2.1) (Arbyn, 2020). In the United States, the age-adjusted mortality rate was 2.2 per 100,000 women and the 5-year relative survival was 66.3% (SEER*Explorer: An interactive website for SEER cancer statistics). As with incidence, the mortality rate in the United States has been stable since 2005 (SEER*Explorer: An interactive website for SEER cancer statistics). By stage, the 5-year relative survival in the United States was 91.9% for localized cervical cancer, 58.2% for regional cervical cancer, and 17.4% for distant cervical cancer (SEER*Explorer: An interactive website for SEER cancer statistics). In terms of

survival proportions, the 5-year age-standardized survival proportions (2004 to 2009) were: localized (85.9%), regional (55.8%), and distant (16.3%) (Benard, 2017). By comparison, 5-year survival proportions in a Spanish cancer registry (2006-2012) were: Stage I (92%), Stage II (59%), Stage III (37%), and Stage IV (18%) (Amengual, 2020).

**Demographics of the Population in the Cervical Cancer Indication and Risk Factors for the Disease:**

Incidence of cervical cancer is associated with demographic characteristics including middle age and Non-Hispanic black and Hispanic populations.

- Age: Globally, the average diagnostic age of cervical cancer was 53 years with the earliest peak occurring at ages 30 to 34 years in the United Kingdom (Arbyn, 2020). In the US, the incidence of histologically-confirmed cervical cancer was highest among those aged 60 to 69 years at 16.8 per 100,000 women, followed by ages 40 to 49 and 50 to 59 years (16.6 per 100,000 women and 16.1 per 100,000 women) (Islami, 2019).
- Race and ethnicity: Non-Hispanic black and Hispanic populations have the greatest reported rates of cervical cancer, while Non-Hispanic whites, Asians, and Pacific Islanders exhibit significantly lower rates (Adegoke, 2012) (Simard, 2012) (Siegel, 2021).
- Human papillomavirus (HPV) infection: Exposure to the approximately 14 carcinogenic HPV subtypes is responsible for virtually all cervical cancers, with over 70% of cervical cancer cases globally stemming from HPV types 16 and 18 (Crosbie, 2013).
- Exposure to DES (diethylstilbestrol) in utero: Women exposed in utero to DES, a synthetic, nonsteroidal form of oestrogen prescribed between 1940 and 1970 in order to prevent miscarriages and pregnancy complications, are at an increased risk for clear cell adenocarcinoma of the cervix and vagina, irrespective of HPV-positivity (Huo, 2017) (Verloop, 2017).
- Parity: Multiparity, defined as 3 or more full-term pregnancies, has been linked to increased risk of squamous cell carcinoma of the cervix in HPV-positive women (Muñoz, 2002).
- Long-term use of oral contraceptives: Among women positive for HPV, use of oral contraceptives for 5 years or longer resulted in at least a 3-fold increased risk for invasive squamous cervical cancer and carcinoma in situ (relative risk for 5 to 9 years of oral contraceptive use: 2.82 [95% CI: 1.46 to 5.42]; ≥10 years: 4.03 [95% CI: 2.09 to 8.02]) (Moreno, 2002).
- Infection with HIV: HIV-positive women have a greater incidence and reduced viral clearance of HPV, although risk was mitigated among antiretroviral treatment (ART)-adherent women (Liu, 2018). Due to this increased HPV persistence, HIV-positivity was associated with a 32% increased risk of high-grade squamous intraepithelial lesions (HSIL), and a 4-fold increased risk of cervical cancer (Liu, 2018).
- Sexual activity: Early age at first sexual intercourse and the lifetime number of sexual partners have been linked to risk of cervical cancer given the appreciable propensity for exposure to HPV (Louie, 2009).

- Smoking: Tobacco smoking increases the risk of HPV persistence and subsequent likelihood of cervical carcinogenesis (Fonseca-Moutinho, 2011). Compared with never smokers, the risk of HPV-positivity was 2-fold among women who reported smoking ≥15 cigarettes daily (Vaccarella, 2008). Further, current smokers had a greater baseline viral load of high-risk HPV subtypes (HPV16 and HPV18) compared with never smokers (Xi, 2009).

**Existing Treatment Options for Recurrent/Metastatic Cervical Cancer**

Initial management of cervical cancer is directed by disease stage, according to either the FIGO or UICC system (Marth, 2017). The first-line treatment (1L) for microinvasive disease (stages IA1-IIA) is surgical excision, including conisation, simple or radical hysterectomy with or without sentinel lymph node (SLN) dissection, and trachelectomy (Marth, 2017) (Cohen, 2019). Following surgical intervention, patients at intermediate or high risk of recurrence are recommended to undergo adjuvant treatment with either radiotherapy alone or chemoradiotherapy consisting of a cisplatin, carboplatin, or cisplatin + fluorouracil-based regimen. The 1L treatment for locally advanced disease (stages IIB-IVA) includes chemoradiotherapy with or without intracavitary brachytherapy (Marth, 2017) (Cohen, 2019). Although roughly one third of all locally advanced cervical cancer patients will experience disease recurrence after chemoradiation, treatment options for this group, as well as metastatic disease, are limited (Rose, 2007).

Cisplatin was the first established systemic therapy for R/M cervical cancer, but low response rates and survival indicated that single agent activity was modest (Eskander, 2014) (Tewari, 2014a). Consequently, cisplatin-based doublets with topotecan or paclitaxel, as well as the 3-drug combination of paclitaxel + ifosfamide + cisplatin, have shown superiority to cisplatin monotherapy. In addition, the combination regimen of paclitaxel + carboplatin is an alternative for patients not considered candidates for cisplatin-based treatment (Kitagawa, 2015).

A phase 3 study evaluated the cisplatin + paclitaxel regimen (N=130) compared with cisplatin monotherapy (N=134). Overall response rate was 36% in the cisplatin + paclitaxel arm, compared with 19% in the monotherapy arm. Median progression free survival (PFS) for patients receiving cisplatin + paclitaxel versus cisplatin alone was 4.8 and 2.8 months (Moore, 2004).

One phase 3 study comparing a cisplatin + topotecan regimen (N=147) to cisplatin alone (N=146) indicated that patients receiving combination therapy had better OS (9.4 vs 6.5 months), PFS (4.6 vs 2.9 months), and response rates (27% vs 13%) (Long, 2005).

A single-arm study (N=42) evaluating the paclitaxel + ifosfamide + cisplatin combination regimen found a response rate of 62% (95% CI: 47.3% to 76.7%) and median OS of 16.5 (range: 3 to 36) months (Kosmas, 2009).

Platinum-based chemotherapy combined with the angiogenesis inhibitor bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor A (VEGF-A), is the preferred 1L treatment for R/M cervical cancer.

A phase 3 study assessing whether doublet chemotherapy regimens (paclitaxel + cisplatin and paclitaxel + topotecan) with or without bevacizumab improved survival in R/M cervical cancer demonstrated that the addition of bevacizumab to chemotherapy increased OS (17.0 vs 13.3 months) and improved response rates (48% vs 36%) compared with chemotherapy alone (Tewari, 2014b). The bevacizumab arm was associated with higher risk of gastrointestinal fistula in previously irradiated patients, but this was not associated with any significant reduction of quality of life (Penson, 2015). Subgroup analysis of GOG-240 demonstrated that

the survival benefit associated with the addition of bevacizumab was greatest in high risk patients (those with negative prognostic factors), and small in low risk patients. Therefore, "a previously irradiated low-risk patient who is carefully counselled may reasonably choose not to receive bevacizumab." (Tewari, 2015).

After first line (1L) chemotherapy for R/M cervical cancer, no systemic therapy has been associated with improvement in OS. Phase 2 studies describe palliative activity for pemetrexed (Miller, 2008), (Lorusso, 2010), gemcitabine (Schilder, 2005), vinorelbine (Muggia, 2004) (Muggia, 2005), topotecan (Bookman, 2000), (Muderspach, 2001), and irinotecan (Takeuchi, 1991), (Verschraegen, 1997). Generally, these agents were associated with ORR ≤15% and median OS of 6 to 9 months. There has never been a randomized trial to compare any of these agents as second line or greater therapy among patients with R/M cervical cancer, and all cytotoxic chemotherapy regimens have low clinical activity in this setting.

Based on results from the uncontrolled phase 2 KEYNOTE-158 study, the US Food and Drug Administration granted accelerated approval of pembrolizumab for patients with advanced PD-L1-positive cervical cancer. In this trial, R/M cervical cancer patients with PD-L1-positive tumours had a response rate of 14.3% (95% CI: 7.4% to 24.1%) (Chung, 2019).

**Natural History of Recurrent or Metastatic Cervical Cancer:**

The subset of cervical cancer tumours likely to result in the poorest prognosis are classified as R/M cervical cancer. Microinvasive disease (stages IA1 to IIA) has the lowest risk of recurrence, with a roughly 5-year recurrence rate of 6.4% (95% CI: 4.9% to 7.9%) (Taarnhøj, 2018). While the probability of surgical cure for patients with locally advanced cervical cancers (stages IIB to IVA) is relatively good, roughly one third of patients will experience disease recurrence after chemoradiation (Rose, 2007). Characteristics indicating intermediate-to-high risk locally advanced disease include lymphovascular space invasion (LVSI), large tumour size (>4 cm), deep stromal invasion, positive or close surgical margins, positive lymph nodes, and microscopic parametrial involvement (Marth, 2017). Further, the prognosis of recurrent cervical cancer, excluding isolated centropelvic operable lesions, is dismal with 5-year survival rates of 3% to 13% (Legge, 2015).

Cervical cancer tumours with even poorer prognosis include the approximately 5% of cervical neoplasms categorized as metastatic disease (stage IVB), which currently has a 5-year survival rate of 16.5% compared with 91.5% for localized disease (Li, 2016) (Oishi, 2016). Given that the metastatic patient population is heterogeneous, ranging from patients with metastasis confined to the lymph nodes to those with numerous organ metastases, treatment is quite variable. As a consequence, the treatment of R/M cervical disease remains a complex clinical challenge with limited options.

**Important Comorbidities:**

Poor adherence to cervical Pap screening is associated with greater risk for cervical cancer, and factors such as obesity, arthritis, diabetes mellitus, hypertension, and sociodemographic and health access factors have all been linked to worse screening adherence (Modesitt, 2005) (Liu, 2014). In addition, several studies suggest a moderate increased risk of cervical adenocarcinoma among obese women, as well as greater cervical cancer mortality (Modesitt, 2005).

## Part II: Module SII – Nonclinical Part of the Safety Specification

Repeated-dose toxicity of cemiplimab was evaluated during the 2 Good Laboratory Practice (GLP)-compliant toxicology studies in which male and female cynomolgus monkeys were

given 0, 2, 10, or 50 mg/kg/week of cemiplimab by intravenous (IV) infusion. REGN2810-TX-14059 was a 4-week, repeated-dose, GLP-compliant toxicology study, and REGN2810-TX-14153 was a 26-week, repeated-dose, GLP-compliant toxicology study. Independent safety pharmacology studies were not conducted with cemiplimab. Instead, safety pharmacology endpoints were integrated into these repeated-dose toxicology studies in cynomolgus monkeys (Module 2.6.6.3 of the initial marketing authorisation application [MAA] Dossier). In addition, REGN2810-TX-15151 was a 13-week GLP fertility assessment study in which male and female cynomolgus monkeys were given 0, 10, or 50 mg/kg/week of cemiplimab by IV infusion. Results from these studies are included in Table Part II.SII. 1.

**Table Part II.SII. 1 Nonclinical Studies**

| Nonclinical Studies | Relevance to Humans |
|---|---|
| **Toxicity: Repeated Dose Studies**<br>• REGN2810-TX-14059: In this study, significant findings directly attributable to cemiplimab were limited to dose-independent reversible increases in the frequency and absolute counts of proliferating T-lymphocytes and increased T cell dependent antibody secondary responses.<br>There were also cemiplimab related microscopic findings most likely due to anti-drug antibody (ADA) immune responses to repeated administration of a heterologous human IgG protein to monkeys. Anti-cemiplimab antibodies were detected in the majority of animals dosed with cemiplimab.<br>• REGN2810-TX-14153: In this study, clinical signs consistent with the formation of ADA (immune complex deposition and associated tissue damage) led to the early death of 1 animal in each of the 10 and 50 mg/kg/week dose groups. | Yes.<br>Due to its mechanism of action, cemiplimab can increase the risk of immune-mediated response in normal tissues known as immune-mediated adverse reactions (imARs). imARs are included as an important identified risk.<br>Yes<br>ADA was reflective of the administration of a heterologous human protein to cynomolgus monkeys and is not necessarily predictive of human responses to cemiplimab.<br>Cemiplimab is a fully humanised antibody and advanced CSCC patients tend to be immune-compromised. Therefore, the risk of developing ADAs to cemiplimab in the advanced CSCC patient population is negligible (Shankar, 2007) (van Brummelen, 2016).<br>Data on ADA based on data locks of 20 Sep 2018 for Groups 1 and Group 3 and 10 Oct 2018 for Group 2 were reviewed. One hundred forty-three patients were included in the ADA population from Study 1540, including 41 patients from Group 1 (3 mg/kg cemiplimab in mCSCC), 61 patients from Group 2 (3 mg/kg cemiplimab in laCSCC) and 41 patients from Group 3 (350 mg cemiplimab in mCSCC patients). None of these patients (0%) experienced ADA or neutralizing antibody (NAb) to cemiplimab.<br>Overall, the results indicate that the immunogenicity associated with the current dosing regimen of cemiplimab is very low in adult patients with advanced CSCC. |

| Nonclinical Studies | Relevance to Humans |
|---|---|
| | Upon EMA request, lack of effect due to ADAs is included as an important potential risk for cemiplimab. |
| **Reproductive/Developmental Toxicity**<br>• The PD-1/PD-L1 signalling pathway plays a role in sustaining pregnancy by maintaining immunological tolerance, and previous studies have shown that PD-1 receptor blockade results in early termination of pregnancy (Guleria, 2005).<br>• REGN2810-TX-15151: No cemiplimab-related microscopic findings were observed in male or female reproductive tissues or fertility parameters after 13 weekly treatments at doses up to 50 mg/kg in sexually mature cynomolgus monkeys. | Yes.<br>Due to its mechanism of action, cemiplimab may increase the risk of miscarriage and stillbirth if administered during pregnancy. |
| **Carcinogenicity, Genotoxicity, and Mutagenicity**<br>• Carcinogenicity and genotoxicity studies were not conducted with cemiplimab, which is consistent with the fact that it is an antibody and its use in patients with advanced malignancy (International Council for Harmonisation - ICH S6(R1), 2012 and ICH S9, 2009). | N/A |
| **Safety Pharmacology**<br>• There were no cemiplimab-related central nervous system (CNS) clinical signs or body temperature effects noted in the repeated dose toxicology studies in monkeys receiving cemiplimab (Section 2.6.6 of Toxicology Written Summary).<br>• No cemiplimab-related changes in heart rate, blood pressure or electrocardiogram (ECG) parameters in any of the repeated dose toxicology studies in monkeys were observed (Section 2.6.6 of Toxicology Written Summary).<br>• There were no cemiplimab-related respiratory clinical signs noted in the repeated dose toxicology studies in monkeys (Section 2.6.6 of Toxicology Written Summary). | N/A<br>As stated in Part II: Module SVI, there is no evidence of CNS effect, so the potential for intentional misuse is minimal. Additionally, there were no preclinical findings in vital signs that would have relevance to safety in humans. |

### Other Toxicity-related Information or Data as Applicable

Local tolerability following IV administration was evaluated as part of the repeated dose toxicology studies in monkeys, and tolerability following SC administration was evaluated in the single-dose pharmacokinetic (PK) study. Following both IV and SC administration,

minimal local findings observed at the injection sites were considered to be either incidental and/or procedure related and not a direct consequence of cemiplimab exposure.

No dedicated drug abuse liability assessment studies of cemiplimab were conducted as there was no evidence of cemiplimab-related effects on the central nervous system (CNS) of cynomolgus monkeys or other evidence from the animal toxicology or pharmacology studies that suggested a dependence potential and abuse liability for cemiplimab. Furthermore, in addition to physicochemical properties that preclude facile permeation of the blood brain barrier (eg, high molecular weight and hydrophilicity) and the unlikely possibility of forming active metabolites, there is no evidence that cemiplimab binds to CNS receptors or transporters associated with abuse liability (eg, opiate, dopaminergic, noradrenergic, serotoninergic, NMDA-ergic, sigma, and GABA-ergic).

**Conclusions on Non-clinical Data**

Nonclinical toxicology studies in monkeys of up to 26 weeks in duration with cemiplimab demonstrated that there were no adverse effects at doses up to 50 mg/kg/week.

No cemiplimab-related findings were observed in male or female reproductive tissues or fertility parameters after 13 weekly treatments at doses up to 50 mg/kg/week in sexually mature cynomolgus monkeys. However, due to its mechanism of action, cemiplimab may increase the risk of miscarriage and stillbirth if administered during pregnancy.

Additionally, in nonclinical toxicology studies, findings included dose-independent, reversible increases in the frequency and absolute counts of proliferating T-lymphocytes and increased T-cell-dependent antibody secondary response. Due to its mechanism of action, cemiplimab can increase the risk of immune-mediated adverse reactions (imARs), which are included in this Risk Management Plan (RMP) as important identified risks.

Development of anti-drug antibody (ADA) was reflective of the administration of a heterologous human protein to cynomolgus monkeys and is not necessarily predictive of human responses to cemiplimab. However, upon EMA request, lack of effect due to human development of ADAs has been included as an important potential risk and is discussed in this RMP.

## Part II: Module SIII - Clinical Trial Exposure

The safety profile of cemiplimab monotherapy in advanced malignancies was characterised in 3 uncontrolled clinical studies: R2810-ONC-1423 (Study 1423), R2810-ONC-1540 (Study 1540), and R2810-ONC-1620 (Study 1620), and 2 randomised controlled clinical studies, R2810-ONC-1624 (Study 1624) and R2810-ONC-1676 (Study 1676).

The safety profile of cemiplimab monotherapy in the adjuvant setting was characterised in clinical study R2810-ONC-1788 (C-POST).

The safety profile of cemiplimab in combination therapy (cemiplimab/chemotherapy) was characterised in clinical study R2810-ONC-16113 Part 2 (Study 16113).

First-in-Human Study:

Study 1423 is a phase 1, open-label, multicentre, dose-escalation, and cohort expansion study of cemiplimab as a single therapy and in combination with other cancer therapies in patients with advanced solid malignancies. The primary objective of the study is to characterise the safety, tolerability, and dose-limiting toxicities (DLTs) of cemiplimab, as well as to evaluate in select indications the preliminary efficacy of cemiplimab as monotherapy or in combination

with other anti-cancer therapies. Study 1423 included patients with CSCC, BCC, NSCLC, and CC patients. Data cutoff for the RMP was 30 Apr 2019 for Study 1423.

Recurrent or Metastatic Cervical Cancer*:

Study 1676 is an open-label, randomized, multicentre, phase 3 trial comparing cemiplimab versus investigator's choice (IC) chemotherapy in patients with recurrent, persistent* or metastatic cervical cancer that had progressed after platinum-containing chemotherapy.

*Persistent cervical cancer is included within the recurrent cervical cancer group; hence we henceforth refer to "recurrent or metastatic cervical cancer"

In the experimental group, cemiplimab was administered IV as a fixed dose of 350 mg Q3W. In the control group, IC chemotherapy options were 4 classes: (1) antifolate - pemetrexed, (2) topoisomerase 1 inhibitor topotecan or irinotecan, (3) nucleoside analogue – gemcitabine, and (4) vinca alkaloid - vinorelbine. The primary objective of the study was to compare OS in patients treated with either cemiplimab or IC chemotherapy. The duration of the study treatment period for a patient was up to 96 weeks (up to 16 cycles of 6 weeks each). The cutoff for data inclusion in the RMP from this study was 04 Jan 2021.

Advanced Basal Cell Carcinoma:

Study 1620 is a phase 2, non-randomised, 2-group, multicentre study of cemiplimab at a dose of 350 mg administered IV Q3W in patients with advanced BCC who experienced progression of disease on HHI therapy or were intolerant of prior HHI therapy. The study has 2 groups. Group 1 is for patients with metastatic BCC. Group 2 is for adult patients with locally advanced BCC. The primary objective of the study is to estimate the ORR for metastatic BCC (Group 1) or locally advanced BCC (Group 2), when treated with cemiplimab monotherapy. The cutoff for data inclusion in the RMP from this study was 20 May 2021.

Advanced Non-small Cell Lung Cancer:

A. Cemiplimab Monotherapy:

Study 1624 is a randomised, multicentre, open-label, pivotal phase 3 study of cemiplimab monotherapy versus platinum-based doublet chemotherapy in patients with stage IIIB, stage IIIC, or stage IV squamous or non-squamous NSCLC who are not candidates for treatment with definitive concurrent chemoradiation, whose tumours express PD-L1 in ≥50% of tumour cells, and who have received no prior systemic treatment for their advanced disease. Eligible patients are randomised to 1 of the following 2 treatment groups: cemiplimab 350 mg monotherapy or chemotherapy. Patients with NSCLC randomised to chemotherapy may receive 1 of the following regimens for 4 to 6 cycles:

- Paclitaxel + cisplatin or carboplatin,
- Gemcitabine + cisplatin or carboplatin, or
- Pemetrexed + cisplatin or carboplatin followed by optional pemetrexed maintenance

Patients assigned to the cemiplimab treatment group will receive cemiplimab 350 mg as an IV infusion on day 1 of every treatment cycle Q3W for up to 108 weeks.

Patients who experience progressive disease on therapy may continue treatment with cemiplimab 350 mg Q3W for up to 108 additional weeks, with the addition of histology-specific chemotherapy for 4 cycles, provided they meet specific criteria and the patient has not completed the 108-week treatment period. Patients who experience disease progression while on or after completion of chemotherapy will be offered the option to crossover to cemiplimab

at the time of confirmed progression to receive cemiplimab 350 mg Q3W for up to 108 weeks, provided they meet specific criteria. The cutoff for data inclusion in the RMP from this study was 01 Mar 2020.

The primary objectives of the study are:

- To compare the OS of cemiplimab versus standard-of-care platinum-based chemotherapies in the first-line treatment of patients with advanced or metastatic NSCLC whose tumours express PD-L1 in ≥50% of tumour cells.
- To compare the progression-free survival of cemiplimab versus standard-of-care platinum-based chemotherapies in the first-line treatment of patients with advanced or metastatic NSCLC whose tumours express PD-L1 in ≥50% of tumour cells.

B. Cemiplimab in Combination Therapy (cemiplimab/chemotherapy):

Study 16113 Part 2 is a randomised, multi-centre, double-blind, active-controlled Phase 3 study of cemiplimab in combination with platinum-based chemotherapy versus placebo in combination with platinum-based chemotherapy in patients with locally advanced NSCLC (Stage IIIB and IIIC) who were not candidates for definitive chemoradiation, or with metastatic (Stage IV) NSCLC, regardless of PD-L1 tumour expression status and who had not previously received systemic treatment for advanced NSCLC. Eligible patients were randomised (2:1) to receive either cemiplimab 350 mg IV Q3W for 108 weeks plus platinum-based chemotherapy Q3W for 4 cycles or placebo IV Q3W for 108 weeks plus platinum-based chemotherapy Q3W for 4 cycles. The cutoff date for data inclusion in the RMP from this study was 14 June 2021.

The primary objective of the study was to determine if cemiplimab/chemotherapy improved OS over placebo/chemotherapy in this patient population.

Advanced Cutaneous Squamous Cell Carcinoma:

Study 1540 is a phase 2, non-randomised, multicentre study of the efficacy and safety of cemiplimab at a dose of 3 mg/kg administered IV every 2 weeks (Q2W, Groups 1 and 2), 350 mg IV every 3 weeks (Q3W, Groups 3 and 6), 600 mg IV every 4 weeks (Q4W), and 1 dose of cemiplimab 438 mg SC, followed by 350 mg IV Q3W (Group 5) administered to patients with advanced CSCC. Groups 1 and 3 include patients with mCSCC. Group 2 includes patients with laCSCC. Groups 4, 5 and 6 include patients with advanced (metastatic or unresectable locally advanced) CSCC. The primary objective of the study is to estimate the clinical benefit of cemiplimab monotherapy (as measured by ORR) for Groups 1 to 4. For Group 6, the primary objective is to provide additional efficacy and safety data for cemiplimab monotherapy. Data included in the RMP from this study are from the final analysis for Group 1, Group 2, and Group 3 and data as of 25 October 2021 for Group 6.

High-risk Cutaneous Squamous Cell Carcinoma

Study 1788 (C-POST) is a randomised, double-blind, multicenter, placebo-controlled phase 3 trial in 415 patients. Study participants were at high risk of recurrence due to nodal features (extracapsular extension or ≥ 3 involved lymph nodes) and/or non-nodal features (in-transit metastases, T4 lesion, perineural invasion, or locally recurrent tumour with ≥ 1 additional adverse feature), and completed adjuvant radiation therapy within 2 to 10 weeks of randomisation. Eligible patients were randomised 1:1 to cemiplimab or placebo. Eighty-one patients were assigned to receive 350 mg cemiplimab or placebo IV every 3 weeks for up to 48 weeks. After a protocol amendment, patients were assigned to receive 350 mg cemiplimab or placebo IV every 3 weeks for 12 weeks, followed by 700 mg cemiplimab or placebo IV

every 6 weeks for an additional 36 weeks. Treatment continued until disease recurrence, unacceptable toxicity, or up to 48 weeks.

The primary endpoint was disease-free survival (DFS) defined as time from randomisation to the first documented disease recurrence or death due to any cause.

Cumulative Exposure Cemiplimab Monotherapy in advanced malignancies:

As of the cutoff dates of the 5 studies described above, the cumulative exposure for cemiplimab monotherapy included 1281 patients with advanced solid malignancies treated at doses of 1 mg/kg Q2W, 3 mg/kg Q2W, 3 mg/kg Q3W, 10 mg/kg Q2W, 200 mg Q2W, and 350 mg Q3W. These studies included 384 patients with advanced CSCC, 355 patients with advanced NSCLC, 138 patients with advanced BCC, 300 patients with recurrent or metastatic cervical cancer and 104 patients with other solid tumors. The median duration of exposure to cemiplimab monotherapy was 28 weeks (range: 2 days to 144 weeks). Among the 1281 patients, 53% were exposed for ≥ 6 months and 26% were exposed for ≥ 12 months. This cemiplimab monotherapy pool included 130 patients in Study 1423, 358 patients in Study 1540, 138 patients in Study 1620, 355 patients in Study 1624, and 300 patients in Study 1676.

Cumulative Exposure Cemiplimab in Combination Therapy (cemiplimab/chemo):

As of the cutoff date of the study 16113 Part 2 (14 June 2021) described above, the cumulative exposure for cemiplimab in combination with platinum-based chemotherapy included 312 patients with locally advanced NSCLC (Stage IIIB and IIIC) who were not candidates for definitive chemoradiation, or with metastatic (Stage IV) NSCLC, regardless of PD-L1 tumour expression status and who had not previously received systemic treatment for advanced NSCLC. Patients received cemiplimab 350 mg IV Q3W for 108 weeks plus platinum-based chemotherapy Q3W for 4 cycles.

For post-marketing exposure details, please refer to Part II, Module SV, Section SV.1.2.

**Clinical Trial Exposure in Patients with Recurrent or Metastatic (R/M) Cervical Cancer**

Clinical trial exposure data to cemiplimab for all patients with R/M cervical cancer are summarized in Table Part II.SIII.1. A total of 300 patients were treated with cemiplimab at a dose of 350 mg Q3W. The duration of exposure for all R/M cervical cancer patients was 152.30 patient years. Thirty-seven percent (37%) (111/300) cervical cancer patients were treated for at least 24 weeks and 19.3% (58/300) cervical cancer patients were treated for at least 48 weeks.

Clinical trial exposure data to cemiplimab by age for all R/M cervical cancer patients are summarised in Table Part II.SIII. 2. The majority of patients (88.7% [266/300]) with R/M cervical cancer were younger than 65 years, 9.7% (29/300) were 65 to 74 years and 1.7% (5/300) of patients were aged 75 years or older.

Clinical trial exposure data to cemiplimab by ethnic origin for all R/M cervical cancer patients are summarised in Table Part II.SIII. 3. Of 300 R/M cervical cancer patients, 82.3% (247/300) described themselves as Not Hispanic or Latino.

**Table Part II.SIII. 1 Duration of Exposure to Cemiplimab (Cervical Cancer) (Safety Analysis Set)**

| Duration of exposure (weeks) | Number of Patients Exposed (n) | Duration of Exposure (Patient-years) |
|---|---|---|
| < 12 weeks | 115 | 14.60 |
| ≥ 12 weeks | 185 | 137.71 |
| ≥ 24 weeks | 111 | 115.14 |

| Duration of exposure (weeks) | Number of Patients Exposed (n) | Duration of Exposure (Patient-years) |
|---|---|---|
| ≥ 36 weeks | 81 | 98.73 |
| ≥ 48 weeks | 58 | 81.33 |
| Total | 300 | 152.30 |

Data cutoff as of 04 Jan 2021 for Study 1676.
Duration of Exposure (weeks) = Minimum of [(last dose date - first dose date + 21)/7 AND (data cutoff date or death date - first dose date +1)/7] for 350 mg Q3W.
Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/365.25

**Table Part II.SIII. 2 Duration of Exposure by Age Group (Cervical Cancer) (Safety Analysis Set)**

| Age group | Number of Patients Exposed (n) | Duration of Exposure (Patient-years) |
|---|---|---|
| < 65 | 266 | 129.93 |
| 65 to 74 | 29 | 20.41 |
| ≥ 75 | 5 | 1.96 |
| Total | 300 | 152.30 |

Data cutoff as of 04 Jan 2021 for Study 1676.
Duration of Exposure (weeks) = Minimum of [(last dose date - first dose date + 21)/7 AND (data cutoff date or death date - first dose date +1)/7] for 350 mg Q3W.
Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/365.25

**Table Part II.SIII. 3 Duration of Exposure by Ethnic Origin (Cervical Cancer) (Safety Analysis Set)**

| Ethnic origin | Number of Patients Exposed (n) | Duration of Exposure (Patient-years) |
|---|---|---|
| Not Hispanic or Latino | 247 | 128.54 |
| Hispanic or Latino | 47 | 19.79 |
| Not Reported | 6 | 3.98 |
| Total | 300 | 152.30 |

Data cutoff as of 04 Jan 2021 for Study 1676.
Duration of Exposure (weeks) = Minimum of [(last dose date - first dose date + 21)/7 AND (data cutoff date or death date - first dose date +1)/7] for 350 mg Q3W.
Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/365.25

### Clinical Trial Exposure in Patients with Advanced Basal Cell Carcinoma

Clinical trial exposure data to cemiplimab for all patients with advanced BCC are summarised in Table Part II.SIII. 4. The duration of exposure for all advanced BCC patients was 126.18 patient-years. A total of 68.8% (95/138) advanced BCC patients were treated for at least 24 weeks (114.41 patient-years of exposure) and 40.6% (56/138) advanced BCC patients were treated for at least 48 weeks (87.55 patient-years of exposure).

A total of 138 patients were treated with cemiplimab at a dose of 350 mg Q3W for 126.18 patient-years.

Clinical trial exposure data to cemiplimab by age and gender for all advanced BCC patients are summarised in Table Part II.SIII.5. Across the age groups, more males have been treated compared to females (94 vs. 44). The majority of patients (42.0% [58/138]) with advanced BCC were younger than 65, 31.2% (43/138) of patients were aged 75 years or older.

Clinical trial exposure data to cemiplimab by ethnic origin for all advanced BCC patients are summarised in Table Part II.SIII.6. Of 138 advanced BCC patients, 102 patients did not describe themselves as Hispanic or Latino.

**Table Part II.SIII. 4 Duration of Exposure (Basal Cell Carcinoma) (Safety Analysis Set)**

| Duration of exposure (weeks) | Number of Patients Exposed (n) | Duration of Exposure (Patient-years) |
|---|---|---|
| < 12 weeks | 12 | 1.64 |
| ≥ 12 weeks | 126 | 124.54 |
| ≥ 24 weeks | 95 | 114.41 |
| ≥ 36 weeks | 76 | 103.91 |
| ≥ 48 weeks | 56 | 87.55 |
| Total number of patients exposed | 138 | 126.18 |

Data cutoff as of 30 Jun 2020 for Study 1620. BCC patients from Study 1423 have been included in the Overall Population table (Table Part II.SIII. 16).
[a] Duration of Exposure (weeks) = Minimum of (last dose date - first dose date +21 days)/7 and (data cutoff date or death date - first dose date + 1 day)/7 for 350 mg Q3W.
[b] Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/365.25.

**Table Part II.SIII.5 Duration of Exposure by Age Group and Gender (Advanced Basal Cell Carcinoma) (Safety Analysis Set)**

| | Number of Patients Exposed (n) | | | Duration of Exposure (Patient-years) | | |
|---|---|---|---|---|---|---|
| Age group | Male | Female | Total | Male | Female | Total |
| < 65 | 38 | 20 | 58 | 30.94 | 21.87 | 52.81 |
| 65 to 74 | 25 | 12 | 37 | 25.37 | 7.09 | 32.46 |
| ≥ 75 | 31 | 12 | 43 | 31.64 | 9.27 | 40.91 |
| Total | 94 | 44 | 138 | 87.96 | 38.22 | 126.18 |

Data cutoff as of 30 Jun 2020 for Study 1620. BCC patients from Study 1423 have been included in the Overall Population table (Table Part II.SIII.18).
[a] Duration of Exposure (weeks) = Minimum of (last dose date - first dose date +21 days)/7 and (data cutoff date or death date - first dose date + 1 day)/7 for 350 mg Q3W.
[b] Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/365.25

**Table Part II.SIII. 6 Duration of Exposure by Ethnic Origin (Advanced Basal Cell Carcinoma) (Safety Analysis Set)**

| Ethnic origin | Number of Patients Exposed (n) | Duration of Exposure (Patient-years) |
|---|---|---|
| Not Hispanic or Latino | 102 | 90.58 |
| Hispanic or Latino | 3 | 2.55 |
| Missing | 33 | 33.05 |
| Total | 138 | 126.18 |

Data cutoff as of 30 Jun 2020 for Study 1620. BCC patients from Study 1423 have been included in the Overall Population table (Table Part II.SIII. 19).
[a] Duration of Exposure (weeks) = Minimum of (last dose date - first dose date +21 days)/7 and (data cutoff date or death date - first dose date + 1 day)/7 for 350 mg Q3W.
[b] Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/365.25.

### Clinical Trial Exposure to Cemiplimab Monotherapy in Patients with Advanced Non-small Cell Lung Cancer

Clinical trial exposure data to cemiplimab for all patients with advanced NSCLC are summarised in Table Part II.SIII.7. One-hundred ninety-seven advanced NSCLC patients were treated for at least 24 weeks (191.44 patient-years of exposure) and 84 advanced NSCLC patients were treated for at least 48 weeks (115.60 patient-years of exposure).

A total of 355 patients were treated with cemiplimab at a dose of 350 mg Q3W for 224.07 patient-years.

Clinical trial exposure data to cemiplimab by age and gender for all advanced NSCLC patients are summarised in Table Part II.SIII.8. Across the age groups, more males have been treated compared to females (312 vs. 43). The majority of patients (56.0% [199/355]) with advanced NSCLC were younger than 65, 9.3% (33/355) of patients were aged 75 years or older.

Clinical trial exposure data to cemiplimab by ethnic origin for all advanced NSCLC patients are summarised in Table Part II.SIII.9. Of 355 advanced NSCLC patients, 319 patients did not describe themselves as Hispanic or Latino.

**Table Part II.SIII.7 Duration of Exposure (Advanced Non-small Cell Lung Cancer) (Safety Analysis Set)**

| Duration of exposure (weeks) | Number of Patients Exposed (n) | Duration of Exposure (Patient-years) |
|---|---|---|
| < 12 weeks | 88 | 9.94 |
| ≥ 12 weeks | 267 | 214.13 |
| ≥ 24 weeks | 197 | 191.44 |
| ≥ 36 weeks | 139 | 158.69 |
| ≥ 48 weeks | 84 | 115.60 |
| Total number of patients exposed | 355 | 224.07 |

Data cutoff for Study 1624 was of 01 Mar 2020. NSCLC patients from Study 1423 have been included in the Overall Population table (Table Part II.SIII. 16).
[a] Duration of Exposure (weeks) = Minimum of (last dose date - first dose date +21 days)/7 and (data cutoff date or death date - first dose date + 1 day)/7 for 350 mg Q3W.
[b] Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/365.25.

**Table Part II.SIII.8 Duration of Exposure by Age and Gender (Advanced Non-small Cell Lung Cancer) (Safety Analysis Set)**

| | Number of Patients Exposed (n) | | | Duration of Exposure (Patient-years) | | |
|---|---|---|---|---|---|---|
| Age group | Male | Female | Total | Male | Female | Total |
| < 65 | 171 | 28 | 199 | 115.30 | 20.52 | 135.82 |
| 65 to 74 | 111 | 12 | 123 | 61.56 | 8.18 | 69.74 |
| ≥ 75 | 30 | 3 | 33 | 17.45 | 1.05 | 18.50 |
| Total | 312 | 43 | 355 | 194.31 | 29.75 | 224.07 |

Data cutoff for Study 1624 was of 01 Mar 2020. NSCLC patients from Study 1423 have been included in the Overall Population table (Table Part II.SIII.18).
[a] Duration of Exposure (weeks) = Minimum of (last dose date - first dose date +21 days)/7 and (data cutoff date or death date - first dose date + 1 day)/7 for 350 mg Q3W.
[b] Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/365.25.

**Table Part II.SIII.9 Duration of Exposure by Ethnic Origin (Advanced Non-small Cell Lung Cancer) (Safety Analysis Set)**

| Ethnic origin | Number of Patients Exposed (n) | Duration of Exposure (Patient-years) |
|---|---|---|
| Not Hispanic or Latino | 319 | 204.29 |
| Hispanic or Latino | 36 | 19.77 |
| Total | 355 | 224.07 |

Data cutoff for Study 1624 was of 01 Mar 2020. NSCLC patients from Study 1423 have been included in the Overall Population table (Table Part II.SIII. 19).
[a] Duration of Exposure (weeks) = Minimum of (last dose date - first dose date +21 days)/7 and (data cutoff date or death date - first dose date + 1 day)/7 for 350 mg Q3W.
[b] Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/365.25.

### Clinical Trial Exposure to Cemiplimab in Combination Therapy (Cemiplimab/Chemotherapy) in Patients with Advanced Non-small Cell Lung Cancer

Clinical trial exposure data to cemiplimab in combination therapy (cemiplimab/chemotherapy) for patients with advanced NSCLC are summarised in Table Part II.SIII.10. One-hundred and seventy-nine (179) advanced NSCLC patients were treated for at least 36 weeks (206.12 patientyears of exposure) and 119 advanced NSCLC patients were treated for at least 48 weeks (158.88 patient-years of exposure).

Clinical trial exposure data to cemiplimab in combination therapy (cemiplimab/chemotherapy) by age and gender for all advanced NSCLC patients are summarised in Table Part II.SIII.11. Across the age groups, more males have been treated compared to females (268 vs. 44). The majority of patients (58.9 % [184/312]) with advanced NSCLC were younger than 65, 5.8% (18/312) of patients were aged 75 years or older.

**Table Part II.SIII.10 Duration of Exposure to Cemiplimab in Combination Therapy (Cemiplimab/Chemotherapy) (Advanced Non-small Cell Lung Cancer) (Safety Analysis Set)**

| Duration of Exposure (weeks) | Number of Patients Exposed (n) | Duration of Exposure (patient-years) |
|---|---|---|
| < 12 weeks | 44 | 5.02 |
| >=12 weeks | 268 | 246.00 |
| >=24 weeks | 224 | 231.22 |
| >=36 weeks | 179 | 206.12 |
| >=48 weeks | 119 | 158.88 |
| Total number of patients exposed | 312 | 251.03 |

Data cutoff for Study 16113 Part 2 was 14 Jun 2021.

**Table Part II.SIII.11 Duration of Exposure to Cemiplimab in Combination Therapy (Cemiplimab/Chemotherapy) by Age Group and Gender (Advanced Non-small Cell Lung Cancer) (Safety Analysis Set)**

| | Number of Patients Exposed (n) | | | Duration of Exposure (Patient-years) | | |
|---|---|---|---|---|---|---|
| Age group | M | F | Total M+F | M | F | Total M+F |
| < 65 | 157 | 27 | 184 | 128.18 | 19.70 | 147.87 |
| 65 to 74 | 96 | 14 | 110 | 76.24 | 11.40 | 87.63 |
| >= 75 | 15 | 3 | 18 | 11.97 | 3.55 | 15.52 |
| Total | 268 | 44 | 312 | 216.38 | 34.65 | 251.03 |

Data cutoff for Study 16113 Part 2 was 14 Jun 2021.

### Clinical Trial Exposure in Patients with Advanced Cutaneous Squamous Cell Carcinoma

Clinical trial exposure data to cemiplimab for all patients with advanced CSCC are summarised in Table Part II.SIII.12. The duration of exposure for all advanced CSCC patients was 298.47 patient years. Two-hundred thirty-two advanced CSCC patients were treated for at least 24 weeks (272.71 patient-years of exposure) and 153 advanced CSCC patients were treated for at least 48 weeks (217.50 patient-years of exposure).

Clinical trial exposure data to cemiplimab by dose level and frequency for all advanced CSCC patients are summarised in Table Part II.SIII.13. Of 358 patients, 137 patients were treated with cemiplimab 3 mg/kg Q2W and 221 patients were treated with cemiplimab 350 mg Q3W.

Clinical trial exposure data to cemiplimab by age and gender for all advanced CSCC patients are summarised in Table Part II.SIII. 14. Across the age groups, more males have been treated compared to females (289 vs. 69). The majority of patients (78.2% [280/358]) with advanced CSCC were aged 65 years or older, including 171 patients (47.8%) that were aged 75 years or older.

**Table Part II.SIII.12 Duration of Exposure (Advanced CSCC Indication) (Safety Analysis Set)**

| Duration of exposure (weeks) | Number of Patients Exposed (n) | Duration of Exposure (Patient-years) |
|---|---|---|
| < 12 weeks | 75 | 9.32 |
| ≥12 weeks | 283 | 289.15 |
| ≥24 weeks | 232 | 272.71 |
| ≥36 weeks | 195 | 251.24 |
| ≥48 weeks | 153 | 217.50 |
| Total number of patients exposed | 358 | 298.47 |

Final analysis for Study 1540 Groups 1-3; Data cut-off as of 25 Oct 2021 for Study 1540 Group 6.
Duration of Exposure (weeks) = Minimum of [(last dose date - first dose date + 14 or 21 based on Q2W or Q3W dosing schedule)/7 AND (data cut-off date or death date - first dose date +1)/¬7].
Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/¬365.25.

**Table Part II.SIII.13 Duration of Exposure by Dose Level and Frequency (Advanced CSCC Indication) (Safety Analysis Set)**

| Dose level and frequency | Number of Patients Exposed (n) | Duration of Exposure (Patient-years) |
|---|---|---|
| 3 mg/kg Q2W | 137 | 138.22 |
| 350 mg Q3W | 221 | 160.25 |
| Total | 358 | 298.47 |

Final analysis for Study 1540 Groups 1-3; Data cut-off as of 25 Oct 2021 for Study 1540 Group 6.
Duration of Exposure (weeks) = Minimum of [(last dose date - first dose date + 14 or 21 based on Q2W or Q3W dosing schedule)/7 AND (data cut-off date or death date - first dose date +1)/¬7].
Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/¬365.25.

**Table Part II.SIII. 14 Duration of Exposure by Age Group and Gender (Advanced CSCC Indication) (Safety Analysis Set)**

| | Number of Patients Exposed (n) | | | Duration of Exposure (Patient-years) | | |
|---|---|---|---|---|---|---|
| Age group | Males | Females | Total M+F | Males | Females | Total M+F |
| < 65 | 64 | 14 | 78 | 58.79 | 11.33 | 70.12 |
| >=65 to <75 | 85 | 24 | 109 | 85.38 | 17.80 | 103.18 |
| >=75 to <85 | 105 | 18 | 123 | 79.95 | 12.41 | 92.35 |
| >= 85 | 35 | 13 | 48 | 25.37 | 7.46 | 32.82 |
| Total | 289 | 69 | 358 | 249.48 | 48.99 | 298.47 |

Final analysis for Study 1540 Groups 1-3; Data cut-off as of 25 Oct 2021 for Study 1540 Group 6.
Duration of Exposure (weeks) = Minimum of [(last dose date - first dose date + 14 or 21 based on Q2W or Q3W dosing schedule)/7 AND (data cut-off date or death date - first dose date +1)/¬7].

### Clinical Trial Exposure to Cemiplimab Monotherapy in the Overall Population (Including CSCC, BCC, NSCLC, and Cervical Cancer in the Advanced Setting)

Clinical trial exposure data to cemiplimab monotherapy for the overall population (including CSCC, BCC, NSCLC and CC patients) are summarised in Table Part II.SIII. 15. The overall duration of exposure was 880.87 patient-years. Seven-hundred one (701) patients were treated for at least 24 weeks (761.13 patient-years of exposure) and 400 patients were treated for at least 48 weeks (557.28 patient-years of exposure).

Clinical trial exposure data to cemiplimab monotherapy by dose level and frequency for patients in all indications are summarised in Table Part II.SIII. 16. A total of 1014 patients were treated with cemiplimab at a dose of 350 mg Q3W, 235 patients were treated with

cemiplimab at a dose of 3 mg/kg Q2W and 32 patients were treated with cemiplimab at other doses.

Clinical trial exposure data to cemiplimab by age and gender for the overall population (including CSCC, BCC, NSCLC, and CC patients) are summarised in Table Part II.SIII. 17. Across the age groups, more males have been treated compared to females (784 vs. 497). The majority of patients (52.2% [669/1281]) were younger than 65, 21.9% (280/1281) of patients were aged 75 years or older.

Clinical trial exposure data to cemiplimab by ethnic origin for the overall population (including CSCC, BCC, NSCLC, and CC patients) are summarised in. Of 1281 patients, 1112 patients did not describe themselves as Hispanic or Latino.

**Table Part II.SIII. 15 Duration of Exposure (Overall Population) (Safety Analysis Set)**

| Duration of exposure (weeks) | Number of Patients exposed (n) | Duration of Exposure (Patient-years) |
|---|---|---|
| < 12 weeks | 330 | 40.42 |
| ≥ 12 weeks | 951 | 840.45 |
| ≥ 24 weeks | 701 | 761.13 |
| ≥ 36 weeks | 548 | 674.65 |
| ≥ 48 weeks | 400 | 557.28 |
| Total number of patients exposed | 1281 | 880.87 |

Final analysis for Study 1540 Groups 1-3; Data cut-off was 11 Oct 2020 for Study 1540 Groups 1-3 and 25 Oct 2021 for Study 1540 Group 6. Data cut-off was 4 Jan 2021 for Study 1676; Data cut-off was 20 May 2021 for Study 1620; Data cut-off was 1 Mar 2020 for Study 1624; Data cut-off was 30 Apr 2019 for Study 1423.
Duration of Exposure (weeks) = Minimum of [last dose date - first dose date +(14 or 21 based on Q2W or Q3W dosing schedule)]/7 AND (data cut-off date or death date - first dose date +1)/7]
Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/365.25

**Table Part II.SIII. 16 Duration of Exposure by Dose Level and Frequency (Overall Population) (Safety Analysis Set)**

| Dose Level and Frequency | Number of Patients exposed (n) | Duration of Exposure (Patient-years) |
|---|---|---|
| 3 mg/kg Q2W | 235 | 191.59 |
| 350 mg Q3W | 1014 | 671.72 |
| Other Doses | 32 | 17.56 |
| Total | 1281 | 880.87 |

Final analysis for Study 1540 Groups 1-3; Data cut-off was 11 Oct 2020 for Study 1540 Groups 1-3 and 25 Oct 2021 for Study 1540 Group 6. Data cut-off was 4 Jan 2021 for Study 1676; Data cut-off was 20 May 2021 for Study 1620; Data cut-off was 1 Mar 2020 for Study 1624; Data cut-off was 30 Apr 2019 for Study 1423.
Duration of Exposure (weeks) = Minimum of [last dose date - first dose date +(14 or 21 based on Q2W or Q3W dosing schedule)]/7 AND (data cut-off date or death date - first dose date +1)/7]
Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/365.25.

**Table Part II.SIII. 17 Duration of Exposure by Age Group and Gender (Overall Population) (Safety Analysis Set)**

| | Number of Patients exposed (n) | | | Duration of Exposure (Patient-years) | | |
|---|---|---|---|---|---|---|
| **Age group** | **Male** | **Female** | **Total** | **Male** | **Female** | **Total** |
| < 65 | 318 | 351 | 669 | 231.33 | 195.75 | 427.08 |
| >=65 to <75 | 247 | 85 | 332 | 187.65 | 61.37 | 249.02 |
| >=75 to <85 | 174 | 43 | 217 | 132.56 | 27.98 | 160.54 |
| >= 85 | 45 | 18 | 63 | 33.83 | 10.41 | 44.24 |
| Total | 784 | 497 | 1281 | 585.37 | 295.50 | 880.87 |

Final analysis for Study 1540 Groups 1-3; Data cut-off was 11 Oct 2020 for Study 1540 Groups 1-3 and 25 Oct 2021 for Study 1540 Group 6. Data cut-off was 4 Jan 2021 for Study 1676; Data cut-off was 20 May 2021 for Study 1620; Data cut-off was 1 Mar 2020 for Study 1624; Data cut-off was 30 Apr 2019 for Study 1423.
Duration of Exposure (weeks) = Minimum of [last dose date - first dose date +(14 or 21 based on Q2W or Q3W dosing schedule)]/7 AND (data cut-off date or death date - first dose date +1)/7]
Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/365.25

**Table Part II.SIII. 18 Duration of Exposure by Ethnicity Origin (Overall Population) (Safety Analysis Set)**

| **Ethnic origin** | **Number of Patients exposed (n)** | **Duration of Exposure (Patient-years)** |
|---|---|---|
| Not Hispanic or Latino | 1112 | 771.94 |
| Hispanic or Latino | 109 | 57.54 |
| Not reported | 27 | 18.24 |
| Missing | 33 | 33.14 |
| Total | 1281 | 880.87 |

Final analysis for Study 1540 Groups 1-3; Data cut-off as of 25 Oct 2021 for Study 1540 Group 6. Data cut-off as of 04 Jan 2021 for Study 1676; Data cut-off as of 20 May 2021 for Study 1620; Data cut-off as of 01 Mar 2020 for Study 1624; Data cut-off as of 30 Apr 2019 for Study 1423.
Duration of Exposure (weeks) = Minimum of [(last dose date - first dose date +14 or 21 based on Q2W or Q3W dosing schedule)]/7 AND (data cut-off date or death date - first dose date +1)/7]
Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/365.25.

### Clinical Trial Exposure to Cemiplimab Monotherapy as Adjuvant Treatment in the High Risk CSCC Population

In Study R2810-ONC-1788 (C-POST), a total of 205 patients with high-risk CSCC were exposed to cemiplimab monotherapy in the adjuvant setting. Clinical trial exposure data to cemiplimab for all patients with high-risk CSCC are summarised in Table Part II.SIII.19. One-hundred eighty-one high-risk CSCC patients were treated for at least 12 weeks (144.61 patient-years of exposure) and 102 high-risk CSCC patients were treated for at least 48 weeks (94.38 patient-years of exposure).

A total of 65 patients were treated with cemiplimab at a dose of 350 mg Q3W for 32.55 patient-years. One-hundred forty patients were treated with cemiplimab at a dose of 350 mg Q3W for 12 weeks then switched to 700 mg Q6W thereafter for 114.89 patient years. The total exposure from these 2 groups was 147.44 patient years (Table Part II.SIII.20).

Clinical trial exposure data to cemiplimab by age and gender for all high-risk CSCC patients are summarised in Table Part II.SIII.21 and Table Part II.SIII.22. More males have been treated compared to females (171 vs. 34). The majority of patients with high-risk CSCC were aged 65 years or older, including seventy-one patients who were aged 75 years or older.

Clinical trial exposure data to cemiplimab by ethnic origin for all high-risk CSCC patients are summarised in Table Part II.SIII.23. Of 205 high-risk CSCC patients, 169 patients did not describe themselves as Hispanic or Latino.

**Table Part II.SIII. 19 Duration of Exposure (Adjuvant Treatment of High-risk CSCC) (Safety Analysis Set)**

| Duration of exposure (weeks) | Number of Patients exposed (n) | Duration of Exposure (Patient-years) |
|---|---|---|
| < 12 weeks | 24 | 2.83 |
| ≥ 12 weeks | 181 | 144.61 |
| ≥ 24 weeks | 158 | 137.46 |
| ≥ 36 weeks | 143 | 128.95 |
| ≥ 48 weeks | 102 | 94.38 |
| Total number of patients exposed | 205 | 147.44 |

Data cut-off as of 04 Oct 2024

Duration of treatment exposure (weeks) is defined as [minimum (date of last dose + 21 days,¬ data cutoff date+1,¬ date of death+1,¬ date of 1st dose of Part 2 cemiplimab) - date of first dose]/¬7 for participants who received 350mg Q3W only and [minimum (date of last dose + 42 days,¬ data cutoff date+1,¬ date of death+1,¬ date of 1st dose of Part 2 cemiplimab) - date of first dose]/¬7 for participants who received 350 mg Q3W followed by 700 mg Q6W.

Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/¬365.25

**Table Part II.SIII. 20 Duration of Exposure by Dose Level and Frequency (Adjuvant Treatment of High-risk CSCC) (Safety Analysis Set)**

| Dose Level and Frequency | Number of Patients exposed (n) | Duration of Exposure (Patient-years) |
|---|---|---|
| Cemiplimab 350mg Q3W Only | 65 | 32.55 |
| Cemiplimab 350mg Q3W + 700mg Q6W | 140 | 114.89 |
| Total | 205 | 147.44 |

Data cut-off as of 04 Oct 2024.

Duration of treatment exposure (weeks) is defined as [minimum (date of last dose + 21 days,¬ data cutoff date+1,¬ date of death+1,¬ date of 1st dose of Part 2 cemiplimab) - date of first dose]/¬7 for participants who received 350mg Q3W only and [minimum (date of last dose + 42 days,¬ data cutoff date+1,¬ date of death+1,¬ date of 1st dose of Part 2 cemiplimab) - date of first dose]/¬7 for participants who received 350 mg Q3W followed by 700 mg Q6W.

Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/¬365.25

**Table Part II.SIII. 21 Duration of Exposure by Age Group (Adjuvant Treatment of High-risk CSCC) (Safety Analysis Set)**

| Age Group | Number of Patients exposed (n) | Duration of Exposure (Patient-years) |
|---|---|---|
| < 65 | 54 | 41.55 |
| 65 to 74 | 80 | 58.99 |
| >= 75 | 71 | 46.90 |
| Total | 205 | 147.44 |

Data cut-off as of 04 Oct 2024.

Duration of treatment exposure (weeks) is defined as [minimum (date of last dose + 21 days,¬ data cutoff date+1,¬ date of death+1,¬ date of 1st dose of Part 2 cemiplimab) - date of first dose]/¬7 for participants who received 350mg Q3W only and [minimum (date of last dose + 42 days,¬ data cutoff date+1,¬ date of death+1,¬ date of 1st dose of Part 2 cemiplimab) - date of first dose]/¬7 for participants who received 350 mg Q3W followed by 700 mg Q6W.

Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/¬365.25

**Table Part II.SIII. 22 Duration of Exposure by Gender (Adjuvant Treatment of High-risk CSCC) (Safety Analysis Set)**

| | Number of Patients exposed (n) | | | Median Duration of Exposure (Weeks) | | |
|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Total |
| Cemiplimab 350 mg Q3W Only | 55 | 10 | 64 | - | - | - |
| Cemiplimab 350 mg Q3W + 700 mg Q6W | 116 | 24 | 140 | - | - | - |
| Total | 171 | 34 | | 48.0 | 47.0 | 47.9 |

Data cut-off as of 04 Oct 2024.
Duration of treatment exposure (weeks) is defined as [minimum (date of last dose + 21 days, data cutoff date+1, date of death+1, date of 1st dose of Part 2 cemiplimab) - date of first dose]/7 for participants who received 350 mg Q3W only and [minimum (date of last dose + 42 days, data cutoff date+1, date of death+1, date of 1st dose of Part 2 cemiplimab) - date of first dose]/7 for participants who received 350 mg Q3W followed by 700 mg Q6W

**Table Part II.SIII. 23 Duration of Exposure by Ethnic Origin (Adjuvant Treatment of High-risk CSCC) (Safety Analysis Set)**

| Ethnic origin | Number of Patients exposed (n) | Duration of Exposure (Patient-years) |
|---|---|---|
| HISPANIC OR LATINO | 19 | 12.74 |
| NOT HISPANIC OR LATINO | 169 | 125.05 |
| UNKNOWN | 10 | 7.44 |
| NOT REPORTED | 7 | 2.21 |
| Total | 205 | 147.44 |

Data cut-off as of 04 Oct 2024.
Duration of treatment exposure (weeks) is defined as [minimum (date of last dose + 21 days, data cutoff date+1, date of death+1, date of 1st dose of Part 2 cemiplimab) - date of first dose]/7 for participants who received 350 mg Q3W only and [minimum (date of last dose + 42 days, data cutoff date+1, date of death+1, date of 1st dose of Part 2 cemiplimab) - date of first dose]/7 for participants who received 350 mg Q3W followed by 700 mg Q6W.
Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients *7/365.25
.

# Part II: Module SIV - Populations not Studied in Clinical Trials

## SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

### Table Part II.SIV. 1 Important Exclusion Criteria

| Exclusion Criteria | Reason for Exclusion | Identified as Missing Information (Yes/No) | Rationale for not Being Included as Missing Information |
|---|---|---|---|
| Paediatric patients<br>(<18 years old). This exclusion criterion applies to Study 1540 (Section 4.2.2), Study 1620 (Section 6.2.2, BCC), Study 1624 (Section 6.2.2, NSCLC), Study 1676 (Section 6.2.2, R/M Cervical Cancer), Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy) and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC). | The safety of cemiplimab in children under 18 years of age is not known. | No | CSCC, BCC, NSCLC, and R/M cervical cancer are rare in paediatric patients.<br>Adequately addressed in Section 4.2 of the SmPC. |
| Ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for immune-mediated adverse events (imAEs). This exclusion criterion applies to Study 1540 (Section 4.2.2, CSCC), Study 1620 (Section 6.2.2, BCC), Study 1676 (Section 6.2.2, R/M Cervical Cancer), Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy), and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC). It does not apply to Study 1624 (NSCLC).<br>Prior treatment with other immune modulating agents that was (a) within fewer than 4 weeks (28 days) prior to the first dose of cemiplimab, or (b) associated with imAEs that were grade ≥1 within 90 days prior to the first dose of cemiplimab, or (c) associated with toxicity that resulted in discontinuation of the immune-modulating agent. Examples of immune modulating agents include therapeutic anti-cancer vaccines, cytokine treatments (other than granulocyte colony stimulating factor [G-CSF] or erythropoietin), or agents that target cytotoxic T-lymphocyte antigen 4, 4-1BB (CD137), PI 3-K-delta, or OX-40. This exclusion criterion applies to Study 1540 (Section 4.2.2, CSCC), Study 1676 (Section 6.2.2, R/M Cervical Cancer), Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy), and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC). It does not apply to Study 1620 (BCC) or Study 1624 (NSCLC). | These patients were excluded to avoid confounding the safety and/or efficacy of cemiplimab in the study population in order to better characterise the safety and efficacy profile of cemiplimab. | No | Adequately addressed in Section 4.4 of the SmPC. |

| Exclusion Criteria | Reason for Exclusion | Identified as Missing Information (Yes/No) | Rationale for not Being Included as Missing Information |
|---|---|---|---|
| Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of cemiplimab.<br><br>Note: Patients who required brief course of steroids (eg, as prophylaxis for imaging studies due to hypersensitivity to contrast agents) were not excluded. This exclusion criterion applies to Study 1540 (Section 4.2.2, CSCC), Study 1620 (Section 6.2.2, BCC) and Study 1676 (Section 6.2.2, R/M Cervical Cancer); it does not apply to Study 1624 (NSCLC) and to Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy), and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC). | | | |
| Pregnant and breastfeeding women, and sexually active men and women of childbearing potential who were unwilling to use highly effective contraception prior to the initial dose/start of the first treatment, during the study and up to 6 months after the last dose of cemiplimab. This exclusion criterion applies to Study 1624 (Section 6.2.2, NSCLC), Study 1676 (Section 6.2.2, R/M Cervical Cancer), Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy), and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC).<br><br>Positive serum pregnancy test (a false positive pregnancy test, if demonstrated by serial measurements and negative ultrasound, will not be exclusionary, upon communication with and approval from the medical monitor). This exclusion criterion applies to Study 1540 (Section 4.2.2, CSCC), Study 1620 (Section 6.2.2, BCC), Study 1676 (Section 6.2.2, R/M Cervical Cancer), and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC). | To avoid potential harm to an unborn foetus or a newborn through exposure to drug from breast milk.<br><br>Exposure of pregnant women to cemiplimab may potentially increase the frequency of early termination of pregnancy.<br><br>Cemiplimab, like other monoclonal antibodies may be secreted in breast milk. The safety of exposure to a newborn through breast milk is unknown. | No | Adequately addressed in sections 4.6 and 5.3 of the SmPC. |
| Patients with a history of solid organ transplant. This exclusion criterion applies to Study 1540 (Section 4.2.2, CSCC), Study 1620 (Section 6.2.2, BCC), Study 1624 (NSCLC), Study 1676 (R/M Cervical Cancer), Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy), and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC). | Patients with solid organ transplant may experience increased frequency of transplant rejection when exposed to anti-PD-1. | No | Adequately addressed in sections 4.2, 4.4. and 4.8 of the SmPC. |
| Patients with hepatic impairment<br>• Total bilirubin >1.5 × upper limit of normal (ULN; if liver metastases >3 × ULN) (Patients with Gilbert's Disease and total bilirubin up to 3 × ULN may have been | To ensure that patients in the study had adequate organ function and to avoid potential | No | Adequately addressed in sections 4.2 and 5.2 of the SmPC. |

| Exclusion Criteria | Reason for Exclusion | Identified as Missing Information (Yes/No) | Rationale for not Being Included as Missing Information |
|---|---|---|---|
| eligible after communication with and approval from the medical monitor.)<br>• Transaminases >3 × ULN (or >5.0 × ULN, if liver metastases)<br>• Alkaline phosphatase (ALP) >2.5 × ULN (or >5.0 × ULN, if liver or bone metastases)<br>• **Note for patients with hepatic metastases who wish to enrol:** If transaminase levels (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]) were >3 × but ≤5 × ULN, total bilirubin must have been ≤1.5 × ULN. If total bilirubin was >1.5 × but ≤3 × ULN, both transaminases (AST and ALT) must have been ≤3 × ULN.<br>This exclusion criterion applies to Study 1540 (Section 4.2.1, CSCC) and Study 1620 (Section 6.2.1, BCC), it does not apply to Study 1624 (NSCLC), Study 1676 (R/M Cervical Cancer), Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy), and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC). | confounding variables that may affect understanding and interpretation of the safety profile of cemiplimab. | | |
| Patients with renal impairment<br>Serum creatinine >1.5 × ULN or estimated creatinine clearance (CrCl) ≤30 mL/min. This exclusion criterion applies to Study 1540 (Section 4.2.2) (CSCC) and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC).<br>Renal function: Serum creatinine >2x ULN or estimated CrCl ≤35 mL/min (according the method of Cockcroft and Gault). This exclusion criterion applies to Study 1620 (Section 6.2.1, BCC); it does not apply to Study 1624 (NSCLC), and Study 1676 (R/M Cervical Cancer). | To ensure that patients in the study had adequate organ function and to avoid confounding safety in patients potentially requiring dialysis. | No | Adequately addressed in sections 4.2 and 5.2 of the SmPC |
| Prior treatment with an agent that blocks the PD-1/PD-L1 pathway. This exclusion criterion applies to Study 1540 (Section 4.2.2, CSCC), Study 1620 (Section 6.2.2, BCC), Study 1676 (Section 6.2.2, R/M Cervical Cancer), Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy), and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC); it does not apply to Study 1624 (NSCLC). | To avoid factors that may confound understanding of drug safety profile and efficacy | No | Adequately addressed in Section 4.4 of the SmPC. |
| Untreated brain metastasis(es) that may be considered active. (Note: patients with brain involvement of CSCC/BCC/cervical cancer due to | Risk minimisation for comorbidities and for possible | No | This is adequately addressed in |

| Exclusion Criteria | Reason for Exclusion | Identified as Missing Information (Yes/No) | Rationale for not Being Included as Missing Information |
|---|---|---|---|
| direct extension of invading tumour, rather than metastasis, may have been allowed to enrol if they did not require greater than 10 mg prednisone daily, after discussion and approval of the medical monitor). Patients with previously treated brain metastases may have participated provided that the lesion(s) was (were) stable (without evidence of progression for at least 6 weeks on imaging obtained in the screening period), and there was no evidence of new or enlarging brain metastases, and the patient did not require any immunosuppressive doses of systemic corticosteroids for management of brain metastasis(es) within 4 weeks of first dose of cemiplimab. This exclusion criterion applies to Study 1540 (Section 4.2.2, CSCC), Study 1620 (Section 6.2.2, BCC), Study 1676 (Section 6.2.2, R/M Cervical Cancer); it does not apply to Study 1624 (NSCLC) and Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy). | confounding of efficacy results and safety data. The activity of cemiplimab in untreated brain metastases remains unknown. | | sections 4.4 and 5.1 of the SmPC. |
| Concurrent malignancy other than CSCC or BCC or cervical cancer and/or history of malignancy other than CSCC within 3 years of date of first planned dose of cemiplimab, except for tumours with negligible risk of metastasis or death, such as adequately treated BCC or CSCC of the skin, carcinoma in situ of the cervix, or ductal carcinoma in situ of the breast, or low-risk early stage prostate adenocarcinoma (T1-T2aN0M0 and Gleason score ≤6 and prostate-specific antigen [PSA] ≤10 ng/mL) for which the management plan was active surveillance, or prostate adenocarcinoma with biochemical-only recurrence with documented PSA doubling time of >12 months for which the management plan was active surveillance (D'Amico, 2005) (Pham, 2016). Patients with hematologic malignancies (eg, chronic lymphocytic leukaemia) were excluded. This exclusion criterion applies to Study 1540 (Section 4.2.2, CSCC), Study 1620 (Section 6.2.2, BCC), Study 1676 (Section 6.2.2, R/M Cervical Cancer), and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC).<br><br>Another malignancy, other than NSCLC, that is progressing or requires treatment, with the exception of nonmelanomatous skin cancer that has undergone potentially curative therapy, or in situ cervical carcinoma or any other tumour that has been treated, and the patient is deemed to be in complete remission for at least 2 years prior to randomisation, and no additional therapy is required during the study period. This exclusion criterion applies to Study 1624 (Section 6.2.2, NSCLC) and | Risk minimisation for comorbidities and for possible confounding of efficacy results and safety data. | No | Anti-PD-1 monoclonal antibodies are approved for treatment of several other malignancies. It is not expected that use of cemiplimab in advanced CSCC, BCC or NSCLC patients with history of other malignancies will have a significant safety impact. |

| Exclusion Criteria | Reason for Exclusion | Identified as Missing Information (Yes/No) | Rationale for not Being Included as Missing Information |
|---|---|---|---|
| Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy). | | | |
| Active infection requiring therapy, including infection with HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV). This exclusion criterion applies to Study 1540 (Section 6.2.2, CSCC), Study 1620 (BCC), Study 1676 (Section 6.2.2, R/M Cervical Cancer), Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy), and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC); it does not apply to Study 1624 (NSCLC). | Comorbid hepatitis may confound safety data involving the risk of immune-mediated hepatitis. The impact of cemiplimab on HIV infection remains unknown | No | Adequately addressed in sections 4.4 and 5.1 of the SmPC. |
| History of pneumonitis within the last 5 years. This exclusion criterion applies to Study 1540 (Section 6.2.2, CSCC), Study 1620 (Section 6.2.2, BCC), Study 1676 (Section 6.2.2, R/M Cervical Cancer), Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy), and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC).<br><br>History of interstitial lung disease (eg, idiopathic pulmonary fibrosis, organizing pneumonia) or active, noninfectious pneumonitis that required immune-suppressive doses of glucocorticoids to assist with management. A history of radiation pneumonitis in the radiation field is permitted as long as pneumonitis resolved ≥6 months prior to randomisation. This exclusion criterion applies to Study 1624 (Section 6.2.2, NSCLC), Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy), and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC). | Risk minimisation for immune-mediated pneumonitis and for possible confounding of safety data. | No | Adequately addressed in Section 5.1 of SmPC. |
| Grade ≥3 hypercalcaemia at time of enrolment. This exclusion criterion applies to Study 1540 (Section 6.2.2, CSCC); it does not apply to Study 1620 (BCC), Study 1624 (NSCLC), Study 1676 (R/M Cervical Cancer) and Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy). It does not apply to Study 1788 (C-POST, high-risk CSCC). | To avoid factors that may confound understanding and interpreting the safety profile of cemiplimab. | No | It is not expected that grade ≥3 hypercalcaemia will have a significant impact on the safety of cemiplimab in the advanced CSCC population post-approval. |

| Exclusion Criteria | Reason for Exclusion | Identified as Missing Information (Yes/No) | Rationale for not Being Included as Missing Information |
|---|---|---|---|
| Any systemic anticancer treatment (chemotherapy, targeted systemic therapy, photodynamic therapy), investigational or standard of care, within 30 days of the initial administration of cemiplimab or planned to occur during the study period (patients receiving bisphosphonates or denosumab were not excluded), radiation therapy within 14 days of initial administration of cemiplimab or planned to occur during the study period. This exclusion criterion applies to Study 1540 (Section 6.2.2, CSCC), and Study 1676 (Section 6.2.2, R/M Cervical Cancer); it does not apply to Study 1620 (BCC), Study 1624 (NSCLC), Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy), and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC). | Risk minimisation for patient comorbidities.<br>To avoid factors that may confound understanding of drug safety profile and efficacy. | No | It is not expected that previous anticancer treatments will have significant impact on the safety of cemiplimab in the advanced CSCC population post-approval. (see below for possible differences with prior idelalisib exposure). |
| History of documented allergic reactions or acute hypersensitivity reaction attributed to antibody treatments. This exclusion criterion applies to Study 1540 (Section 6.2.2, CSCC), Study 1620 (Section 6.2.2, BCC), Study 1676 (Section 6.2.2, R/M Cervical Cancer), Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy), and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC); it does not apply to Study 1624 (NSCLC). | Possible confounding of safety data. | No | Infusion reactions are important identified risks for cemiplimab. Cemiplimab is contraindicated in patients with prior history of hypersensitivity to cemiplimab or any of its excipients. See Section 4.3 of the SmPC. |
| Any acute or chronic psychiatric problems that, in the opinion of the investigator, made the patient ineligible for participation. This exclusion criterion applies to Study 1540 (Section 6.2.2, CSCC), Study 1620 (Section 6.2.2, BCC), Study 1624 (Section 6.2.2, NSCLC), Study 1676 (Section 6.2.2, R/M Cervical Cancer), Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy), and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC). | Ensuring informed consent and appropriate patient participation. | No | The safety profile of cemiplimab is unlikely to be different in patients with acute or chronic psychiatric problems. |

| Exclusion Criteria | Reason for Exclusion | Identified as Missing Information (Yes/No) | Rationale for not Being Included as Missing Information |
|---|---|---|---|
| Prior treatment with a serine/threonine-protein kinase (BRAF) inhibitor. This exclusion criterion applies to Study 1540 (Section 6.2.2, CSCC); it does not apply to Study 1620 (BCC), Study 1624 (NSCLC), Study 1676 (Section 6.2.2, R/M Cervical Cancer), Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy), or study 1788 (C-POST) (Section 6.2.2, high-risk CSCC). | Possible confounding of efficacy results. | No | It is not expected that prior treatment with a BRAF inhibitor will have a significant impact on the safety of cemiplimab in the advanced CSCC population post approval. |
| Any medical comorbidity, physical examination finding, or metabolic dysfunction, or clinical laboratory abnormality that, in the opinion of the investigator, rendered the patient unsuitable for participation in a clinical trial due to high safety risks and/or potential to affect interpretation of results of the study.<br><br>Note in clarification: For Group 2 patients, the investigator must have contacted the sponsor's medical monitor regarding any patients that the investigator felt could not provide the required baseline tumour biopsies (Study 1540 Protocol, Section 3.1.1). This exclusion criterion applies to Study 1540 (Section 4.2.2, CSCC), Study 1620 (Section 6.2.2, BCC), Study 1676 (Section 6.2.2, R/M Cervical Cancer), and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC).; it does not apply to Study 1624 (NSCLC), or Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy). | Possible confounding of efficacy results and safety data. | No | CSCC and BCC indications affect elderly populations who may have several comorbidities. This exclusion criterion is based on the opinion of investigators for the purpose of clinical trials and will not represent a clearly distinct population in the post-approval setting. |

| Exclusion Criteria | Reason for Exclusion | Identified as Missing Information (Yes/No) | Rationale for not Being Included as Missing Information |
|---|---|---|---|
| Inability to undergo any contrast-enhanced radiologic response assessment.<br><br>Notes regarding imaging options: A patient who was unable to undergo computed tomography (CT) with iodinated contrast (eg, due to contrast allergy) was not excluded if his/her disease could be measured by magnetic resonance imaging (MRI) with gadolinium. A patient who was unable to undergo MRI with gadolinium was not excluded if his/her disease could be measured by CT scan with contrast.<br><br>Note regarding Group 2 patients: In selected cases, a patient in Group 2 who was unable to undergo any contrast enhanced radiographic imaging (neither CT with iodinated contrast nor MRI with gadolinium) may have been eligible if the patient's disease could be comprehensively assessed with digital medical photography, after communication with and approval from medical monitor. This exclusion criterion applies to Group 2, Study 1540 (Section 4.2.2, CSCC) and Group 2, Study 1620 (BCC); it does not apply to Study 1624 (NSCLC), Study 1676 (R/M Cervical Cancer), Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy), or Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC). | Ensuring that efficacy assessments can be obtained. | No | This exclusion criterion is only linked to assessment of clinical efficacy as specified in the protocol. The safety of cemiplimab in the population of patients excluded by this exclusion criterion is unlikely to differ from other patients. |
| Prior treatment with idelalisib. This exclusion criterion applies to Study 1620 (Section 6.2.2, BCC), Study 1624 (Section 6.2.2, NSCLC) and Study 1676 (Section 6.2.2, R/M Cervical Cancer). It does not apply to Study 1540 (CSCC), Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy), or Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC). | Risk minimisation for imARs before benefit in the indication was established. | No | imARs are included as important identified risks. Warning about use of cemiplimab in patients with prior exposure to idelalisib is adequately addressed in sections 4.2 and 4.4 of the SmPC. |
| Receipt of a live vaccine within 30 days of planned start of study medication. This exclusion criterion does not apply to Study 1540 (CSCC), it applies to Study 1620 (Section 6.2.2, BCC), Study 1624 (Section 6.2.2, NSCLC), Study 1676 (Section 6.2.2, R/M Cervical Cancer), Study 16113 Part 2 (Section 6.2.2, NSCLC combination cemiplimab/chemotherapy), and Study 1788 (C-POST) (Section 6.2.2, high-risk CSCC). | Possible confounding of safety data. | No | Standard medical practice for administration of biologics. |

### SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programme

The clinical development programme is unlikely to detect certain types of adverse reactions such as some rare (≥1/10,000 to <1/1000) adverse reactions or those caused by prolonged (>109 weeks) exposure.

### SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

**Table Part II.SIV. 2 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes**

| Type of Special Population | Exposure |
|---|---|
| Pregnant or breastfeeding women | Not included in the clinical development programme |
| Ongoing or recent (within 5 years) evidence of significant autoimmune disease | Not included in the clinical development programme |
| Patients with a history of solid organ transplant | Not included in the clinical development programme |
| Patients with moderate to severe hepatic impairment<br><br>Patients with severe renal impairment | Included but limited exposure in clinical development |
| Use in patients with an active infection with HIV, HBV, or HCV | Included in the clinical development programme but limited exposure in clinical development |
| Use in patients with a history of pneumonitis within the last 5 years | Not included in the clinical development programme |
| Populations with relevant different ethnic origin | Included but limited exposure in Hispanic or Latino ethnicity (107 patients exposed) |
| Subpopulations carrying known and relevant genetic polymorphisms | To date, there is no information suggesting the existence of polymorphism relevant to the efficacy or safety of cemiplimab in the currently proposed indication(s) |

## Part II: Module SV - Post-authorisation Experience

### SV.1.1 Method to Calculate Exposure

Post-authorisation exposure was estimated using the sales data by assuming that all the vials sold were administered to patients at the approved dose of 350 mg Q3W, ie,

Exposure in patient years = (number of vials sold x 21)/365.25

### SV.1.2 Exposure

Post-authorisation exposure from the cumulative experience is available from 28 Sep 2018 through 30 Sep 2024, ie, over the period of 6 years. The cumulative exposure to cemiplimab is estimated to be 39,208 patient years.

**Table Part II.SV. 1 Exposure Table by Region**

| Regional Patient Exposure (patient years) | Europe | United States | Rest of the World | Total (Worldwide) |
|---|---|---|---|---|
| | [redacted] | | | 39,208[a] |

[a] Due to rounding, the total may not correspond with the exact sum of the separate values.

Detailed usage data are not available; therefore, presentation of patient exposure by age and sex is not possible. Consequently, it is only presented by region.

The marketing authorisation holder (MAH) has not become aware of any patterns of use with cemiplimab, including overdose, drug abuse, and misuse considered relevant for risk identification.

# Part II: Module SVI - Additional EU Requirements for the Safety Specification

### Potential for Misuse for Illegal Purposes

The potential for misuse of cemiplimab for illegal purposes is minimal. Based on nonclinical studies and the physicochemical properties of cemiplimab, there is no evidence of direct CNS effect that could suggest dependence or abuse potential (see Part II, Module SII for detailed information). Additionally, cemiplimab is available by prescription only and is administered in a controlled clinical setting by healthcare professionals.

# Part II: Module SVII - Identified and Potential Risks

## SVII.1 Identification of Safety Concerns in the Initial RMP Submission

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

**Table Part II.SVII. 1 Risks With Minimal Clinical Impact on Patients in Relation to the Severity of the Indication Treated**

| Risks |
|---|
| Pruritus |
| Fatigue |
| Upper respiratory tract infection |
| Urinary tract infection |
| Anaemia |
| Headache |
| Hypertension |
| Decreased appetite |
| Cough |
| Dyspnoea |
| Diarrhoea |
| Nausea |

| Risks |
|---|
| Constipation |
| Abdominal pain |
| Vomiting |
| Musculoskeletal pain |
| Pyrexia |

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

#### Important Identified Risks

**Table Part II.SVII. 2 Important Identified Risk: Immune-Mediated Adverse Reactions (Immune-Mediated Pneumonitis, Colitis, Hepatitis, Endocrinopathies, Immune-Mediated Skin Reactions, Nephritis, and Other imARs)**

| | |
|---|---|
| **Scientific Evidence that has led to the Inclusion** | Cemiplimab is a recombinant human IgG4 monoclonal antibody that binds specifically to PD-1, thereby blocking the interaction with its ligands, PD-L1 and PD-L2. This blockade inhibits the immune checkpoint function of PD-1. While its therapeutic mechanism involves increasing T-cell specific immune responses against the tumour, cemiplimab's checkpoint protein inhibition can also result in cell and metabolic toxicities attributable to imbalances in immune tolerance (Naidoo, 2015). Clinical manifestations, which generally present as imARs, can lead to significant effects on individual patients. Please see Section SVII.3 for details regarding imARs and monitoring instructions. |
| **Risk-benefit Impact** | A total of 119 (20.1%) patients exposed to cemiplimab in clinical trials included in the RMP experienced at least 1 irAR including 4 patients [0.7%] with grade 5, 7 patients [1.2%] with grade 4 and 36 patients [6.1%] with grade 3 irARs. Twenty-six (4.4%) patients discontinued treatment due to irARs.<br><br>Additional details are provided in Section VII.3. |

### Table Part II.SVII. 3 Important Identified Risk: Infusion-Related Reactions

| | |
|---|---|
| **Scientific evidence that has led to the Inclusion** | Therapeutic foreign proteins are potential antigens that may invoke hypersensitivity reactions.<br><br>Cemiplimab can cause severe or life-threatening infusion-related reactions (IRRs) including pyrexia, chills, flushing, hypotension, dyspnoea, wheezing, back pain, abdominal pain, and urticaria. |
| **Risk-benefit Impact** | Of all patients in the clinical trials included in the RMP, 53 (9.0%) patients experienced IRRs. One (0.2%) patient experienced an IRR of grade 3; 2 (0.3%) patients discontinued treatment due to an IRR. All IRR cases were resolved at the data cut off of the RMP.<br><br>Additional details are provided in Section VII.3. |

**Important Potential Risks:**

### Table Part II.SVII.4: Important Potential Risk: Lack of Effect Due to Anti-drug Antibodies

| | |
|---|---|
| **Scientific Evidence that has led to the Inclusion** | As with all monoclonal antibodies, cemiplimab has the potential to induce immunogenicity. Throughout the cemiplimab clinical development programme, validated assays were used to assess the systemic exposure of functional cemiplimab and immunogenicity (including ADAs and NAbs) following the administration of cemiplimab.<br><br>Approximately 2.4% of 1229 patients developed treatment emergent antibodies to cemiplimab. Of the patients who developed treatment emergent antibodies to cemiplimab, none developed NAbs. None of the patients with CSCC developed treatment emergent antibodies.<br><br>Approximately 2.0% of all patients receiving cemiplimab had persistent antibody responses defined as having at least 2 consecutive positive post-baseline samples separated by at least 16 weeks. Antibody titers were low to moderate. |
| **Risk-benefit Impact** | In the few patients who developed anti-cemiplimab antibodies, there was no evidence of altered PK profile, impact on efficacy, or increased incidence of infusion reactions. There is a theoretical possibility that high-titer ADAs and NAbs may have a clinically meaningful impact on the efficacy and/or safety of cemiplimab. |

## SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

On 12 Jul 2022, the MAH submitted updated and final analysis data for study 1540 groups 1-3 and primary analysis data for group 6 (Type II variation assessment report, Procedure No. EMEA/H/C/004844/II/0031). Considering that study 1540 has been completed and no new

safety findings have been identified in patients after long term follow up, the MAH proposes to remove the missing information 'long term safety data'.

## SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

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

Safety data from Study 1788 (C-POST) are not included in this section. The important identified risks (imAEs and IRR) observed in Study 1788 (C-POST) were consistent with the known safety profile of cemiplimab monotherapy, and no new imAE categories or safety concerns were identified. In Study 1788 (C-POST), imARs were usually manageable with treatment interruption or discontinuation and administration of corticosteroids and/or hormone replacement therapy.

**Important Identified Risk: Immune-mediated Adverse Reactions**

Potential Mechanisms:

Cemiplimab, a recombinant human IgG4 monoclonal antibody that binds specifically to PD-1, is an inhibitory immune checkpoint molecule. While its therapeutic mechanism involves increasing T cell-specific immune responses against tumour, cemiplimab's checkpoint protein inhibition can also result in toxicities that are attributable to imbalances in immune tolerance. Clinical manifestations are generally inflammatory or autoimmune-like, and they must be detected, treated, and monitored during and after exposure to cemiplimab. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

Details of the specific imARs are as follows:

**Immune-mediated Pneumonitis**

Potential Mechanisms:

See potential mechanism above for imARs.

Evidence Source(s) and Strength of Evidence:

Immune-mediated pneumonitis, defined as requiring use of corticosteroids with no clear alternative aetiology, including fatal cases, has been observed in patients treated with cemiplimab.

In Studies 1423, 1540, 1620, 1624, and 1676 in which patients (N=1281) with advanced solid tumours (a variety of tumour types, including CSCC, BCC, NSCLC, and cervical cancer) were treated with cemiplimab, immune-mediated pneumonitis occurred in 2.6% (33/1281) of patients.

In Study 16113 Part 2 in which patients (N=312) with locally advanced and metastatic NSCLC irrespective of PDL-1 expression who had received no prior systemic treatment for their advanced disease were treated with cemiplimab in combination with platinum-based doublet chemotherapy (cemiplimab/chemotherapy), immune-mediated pneumonitis occurred in 1.9% (6/312) of patients.

Characterisation of the Risk with Cemiplimab Monotherapy:

Immune-mediated pneumonitis occurred in 33 (2.6%) of 1281 patients receiving cemiplimab, including 4 (0.3%) patients with grade 4 and 8 (0.6%) patients with grade 3 pneumonitis. Immune-mediated pneumonitis led to permanent discontinuation of cemiplimab in 17 (1.3%)

of 1281 patients. Among the 33 patients with immune-mediated pneumonitis, the median time to onset was 2.7 months (range: 7 days to 22.2 months) and the median duration of pneumonitis was 1.1 months (range: 5 days to 16.9 months). Twenty-seven of the 33 patients (81.8%) received high-dose corticosteroids for a median of 15 days (range: 1 day to 5.9 months). Resolution of pneumonitis had occurred in 20 (60.6%) of the 33 patients at the time of data cutoff.

Characterisation of the Risk with Cemiplimab in Combination Therapy (cemiplimab/chemotherapy):

Immune-mediated pneumonitis occurred in 6 (1.9%) of 312 patients receiving cemiplimab, including 1 (0.3%) patient with grade 5 and 1 (0.3%) patient with grade 3 pneumonitis. None of the immune-mediated pneumonitis led to permanent discontinuation of cemiplimab, however there was one grade 5 (fatal) case. Among the 6 patients with immune-mediated pneumonitis, the median time to onset was 5.0 months (range: 3.7 to 10.5 months) and the median duration of pneumonitis was 0.7 months (range: 0.2 to 2.1 months). All six patients (100.0%) received high-dose corticosteroids (defined as ≥40 mg of prednisone or equivalent per day) for a median of 0.6 months (range: 0.1 to 1.6 months). Resolution of pneumonitis had occurred in 4 (66.7%) of the 5 remaining evaluable patients (6 patients in total; 1 patient experienced a fatal event of immune-mediated pneumonitis) at the time of data cutoff.

Post-marketing data: As of the data lock point (DLP) of the last periodic benefit risk evaluation report (PBRER, 28 Sep 2022 to 27 Sep 2024) no new information impacting the characterisation of the important identified risk of pneumonitis was identified.

Risk factors and Risk Groups:

Patients with a history of, or ongoing, pneumonitis and significant autoimmune disease may be at higher risk of developing immune-mediated pneumonitis.

Preventability:

The risk of immune-mediated pneumonitis is due to the pharmacologic action of cemiplimab and therefore cannot be prevented entirely in patients exposed to cemiplimab. However, early detection and management, including discontinuation of cemiplimab and use of systemic corticosteroids, may reduce the severity, and accelerate recovery. Part V provides details of risk minimisation measures for patients exposed to cemiplimab.

Impact on the Risk-benefit Balance of the Product:

Immune-mediated pneumonitis can be fatal, especially if not identified early and managed by withholding treatment or permanent treatment discontinuation and/or use of systemic corticosteroids. It is expected that implementation of the routine and additional risk minimisation measures described in this RMP (see Part V) will minimise the number of reported life-threatening or fatal pneumonitis events. Therefore, the impact on the risk-benefit balance of cemiplimab will be minimal following successful implementation of the risk minimisation plan.

Public Health Impact:

This risk has minimal impact on public health outside the effect on individual patients.

**Immune-mediated Colitis**

Potential Mechanisms:

See potential mechanism above for imARs.

Evidence Source(s) and Strength of Evidence:

Immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternative aetiology, has been observed in patients treated with cemiplimab.

In Studies 1423, 1540, 1620, 1624, and 1676 in which patients (N=1281) with advanced solid tumours (a variety of tumour types, including CSCC, BCC, NSCLC, and cervical cancer) were treated with cemiplimab, immune- mediated colitis occurred in 2.0% (25/1281) of patients.

In Study 16113 Part 2 in which patients (N=312) with locally advanced and metastatic NSCLC irrespective of PDL-1 expression who had received no prior systemic treatment for their advanced disease were treated with cemiplimab in combination with platinum-based doublet chemotherapy (cemiplimab/chemotherapy), immune-mediated colitis occurred in 0.3% (1/312) of patients.

Characterisation of the Risk with Cemiplimab Monotherapy:

Immune-mediated diarrhoea or colitis occurred in 25 (2.0%) of 1281 patients receiving cemiplimab including 10 (0.8%) with grade 3 immune-mediated diarrhoea or colitis. Immune-mediated diarrhoea or colitis led to permanent discontinuation of cemiplimab in 5 (0.4%) of 1281 patients. Among the 25 patients with immune-mediated diarrhoea or colitis, the median time to onset was 3.8 months (range: 1 day to 16.6 months) and the median duration of immune-mediated diarrhoea or colitis was 2.1 months (range: 4 days to 26.8 months). Nineteen patients (76.0%) with immune-mediated diarrhoea or colitis received high-dose corticosteroids for a median of 22 days (range: 2 days to 5.2 months). Resolution of immune-mediated diarrhoea or colitis had occurred in 14 (56.0%) of the 25 patients at the time of data cutoff.

Characterisation of the Risk with Cemiplimab in Combination Therapy (cemiplimab/chemotherapy):

Immune-mediated colitis occurred in 1 (0.3%) of 312 patients receiving cemiplimab; the event of immune-mediated colitis was grade 3. Immune-mediated colitis did not lead to permanent discontinuation of cemiplimab. Time to onset was 0.4 months (range: 0.4 to 0.4 months) and the duration of colitis was 0.20 months (range: 0.2 to 0.2 months). The patient did not receive high-dose corticosteroids (defined as ≥40 mg of prednisone or equivalent per day) and received systemic corticosteroids for 0.2 months (range: 0.2 to 0.2 months). The case of immune-mediated colitis had resolved at the time of data cutoff.

Post-marketing data: As of the DLP of the last periodic benefit risk evaluation report (PBRER, 28 Sep 2022 to 27 Sep 2024) no new information impacting the characterisation of the important identified risk of colitis was identified.

Risk Factors and Risk Groups:

Patients with a history of or ongoing significant autoimmune disease may be at higher risk of developing immune-mediated colitis.

Preventability:

The risk of immune-mediated colitis is due to the pharmacologic action of cemiplimab and therefore cannot be prevented entirely from occurring in patients exposed to cemiplimab. However, early detection and prompt management, including withholding or permanent treatment discontinuation of cemiplimab and use of systemic corticosteroids, may reduce the severity when it occurs and may lead to full recovery. Part V provides the details of risk minimisation measures for patients exposed to cemiplimab.

Impact on the Risk-benefit Balance of the Product:

Immune-mediated colitis can be fatal especially if not identified early and managed by treatment modification and/or use of systemic corticosteroids and supportive care. It is expected that with the successful implementation of the routine and the additional risk minimisation described in this RMP, the number of reported life-threatening or fatal colitis events will be very low. Therefore, the impact of this risk on the risk-benefit balance of cemiplimab will be minimal following successful implementation of the risk minimisation plan.

Public Health Impact:

This risk has minimal impact on public health outside the effect on individual patients.

**Immune-mediated Hepatitis**

Potential Mechanisms:

See potential mechanism above for imARs.

Evidence Source(s) and Strength of Evidence:

Immune-mediated hepatitis, defined as requiring use of corticosteroids with no clear alternative aetiology, has been observed in patients treated with cemiplimab.

In Studies 1423, 1540, 1620, 1624, and 1676 in which patients (N=1281) with advanced solid tumours (a variety of tumour types, including CSCC, BCC, NSCLC and cervical cancer) were treated with cemiplimab, immune-mediated hepatitis occurred in 2.4% (31/1281) of patients receiving cemiplimab.

In Study 16113 Part 2 in which patients (N=312) with locally advanced and metastatic NSCLC irrespective of PDL-1 expression who had received no prior systemic treatment for their advanced disease were treated with cemiplimab in combination with platinum-based doublet chemotherapy (cemiplimab/chemotherapy), immune-mediated hepatitis occurred in 0.6% (2/312) of patients.

Characterisation of the Risk with Cemiplimab Monotherapy:

Immune-mediated hepatitis occurred in 31 (2.4%) of 1281 patients receiving cemiplimab including 1 (<0.1%) patient with grade 5, 4 (0.3%) patients with grade 4, and 21 (1.6%) patients with grade 3 immune-mediated hepatitis. Immune-mediated hepatitis led to permanent discontinuation of cemiplimab in 18 (1.4%) of 1281 patients. Among the 31 patients with immune-mediated hepatitis, the median time to onset was 2.8 months (range: 7 days to 22.5 months) and the median duration of hepatitis was 2.3 months (range: 5 days to 8.7 months). Twenty-seven (87.1%) patients with immune-mediated hepatitis received high dose corticosteroids for a median of 24 days (range: 2 days to 3.8 months). Resolution of hepatitis had occurred in 12 (38.7%) of the 31 patients at the time of data cutoff.

Characterisation of the Risk with Cemiplimab in Combination Therapy (cemiplimab/chemotherapy):

Immune-mediated hepatitis occurred in 2 (0.6%) of 312 patients receiving cemiplimab, both were grade 3. Immune-mediated hepatitis led to permanent discontinuation of cemiplimab in 2 (100.0%) of 2 patients. Among the 2 patients with immune-mediated hepatitis, the median time to onset was 5.1 months (range: 2.0 to 8.2 months) and the median duration of hepatitis was 6.0 months (range: 5.3 to 6.7 months). Both patients received high-dose corticosteroids (defined as ≥40 mg of prednisone or equivalent per day) for a median of 0.6 months (range: 0.1

to 1.1 months). Resolution of hepatitis had occurred in 1 (50.0%) of the 2 patients at the time of data cutoff.

Post-marketing data: As of the DLP of the last periodic benefit risk evaluation report (PBRER, 28 Sep 2022 to 27 Sep 2024) no new information impacting the characterisation of the important identified risk of hepatitis was identified.

Risk Factors and Risk Groups:

Patients with a history of or ongoing moderate or severe hepatic impairment or significant autoimmune disease may be at increased risk of developing immune-mediated hepatitis.

Preventability:

The risk of immune-mediated hepatitis is due to pharmacologic action of cemiplimab and therefore cannot be prevented entirely from occurring in patients exposed to cemiplimab. However, early detection and prompt management including withholding or permanent discontinuation of cemiplimab and use of systemic corticosteroids may reduce the severity when it occurs and may lead to full recovery. Part V provides the details of risk minimisation measures for patients exposed to cemiplimab.

Impact on the Risk-benefit Balance of the Product:

Immune-mediated hepatitis can be fatal, especially if not identified early and managed by treatment modification and/or use of systemic corticosteroid. It is expected that with the implementation of the routine and additional risk minimisation described in this RMP, the number of reported life-threatening or fatal hepatitis events will be very low. Therefore, the impact of this risk on the risk-benefit balance of cemiplimab will be minimal following successful implementation of the risk minimisation plan.

Public Health Impact:

This risk has minimal impact on public health outside the effect on individual patients.

**Immune-mediated Endocrinopathies**

- **Hypothyroidism**
- **Hyperthyroidism**
- **Thyroiditis**
- **Hypophysitis**
- **Adrenal insufficiency**
- **Type 1 Diabetes Mellitus**

Potential Mechanisms:

See potential mechanism above for imARs.

Evidence Source(s) and Strength of Evidence:

In Studies 1423, 1540, 1620, 1624 and 1676, in which patients (N=1281) with advanced solid tumours (a variety of tumour types, including CSCC, BCC, NSCLC and cervical cancer) were treated with cemiplimab, immune-mediated endocrinopathies occurred in patients receiving cemiplimab.

In Study 16113 Part 2 in which patients (N=312) with locally advanced and metastatic NSCLC irrespective of PDL-1 expression who had received no prior systemic treatment for their

advanced disease were treated with cemiplimab in combination with platinum-based doublet chemotherapy (cemiplimab/chemotherapy), immune-mediated endocrinopathies occurred in patients receiving cemiplimab.

**Hypothyroidism**

Characterisation of the Risk with Cemiplimab Monotherapy:

Hypothyroidism occurred in 87 (6.8%) of 1281 patients receiving cemiplimab including 1 (<0.1%) patient with grade 3 hypothyroidism. Three (0.2%) of 1281 patients discontinued cemiplimab due to hypothyroidism. Among the 87 patients with hypothyroidism, the median time to onset was 4.0 months (range: 15 days to 18.9 months) with a median duration of 9.2 months (range: 1 day to 37.1 months). Resolution of hypothyroidism had occurred in 5 (5.7%) of the 87 patients at the time of data cutoff.

Characterisation of the Risk with Cemiplimab in Combination Therapy (cemiplimab/chemotherapy):

Immune-mediated hypothyroidism occurred in 24 (7.7%) of 312 patients receiving cemiplimab, including 1 (0.3%) patient with grade 3 hypothyroidism. Immune-mediated hypothyroidism did not lead to permanent discontinuation of cemiplimab. Among the 24 patients with immune-mediated hypothyroidism, the median time to onset was 5.6 months (range: 2.6 to 14.0 months) and the median duration of hypothyroidism was 5.4 months (range: 0.7 to 12.2 months). Resolution of hypothyroidism had occurred in 3 (12.5%) of the 24 patients at the time of data cutoff.

**Hyperthyroidism**

Characterisation of the Risk with Cemiplimab Monotherapy:

Hyperthyroidism occurred in 39 (3.0%) of 1281 patients receiving cemiplimab including 1 (<0.1%) patient with grade 3 and 11 (0.9%) patients with grade 2 hyperthyroidism. No patient discontinued cemiplimab due to hyperthyroidism. Among the 39 patients with hyperthyroidism, the median time to onset was 1.9 months (range: 20 days to 23.8 months) and the median duration was 1.9 months (range: 9 days to 32.7 months). Resolution of hyperthyroidism had occurred in 22 (56.4%) of the 39 patients at the time of data cutoff.

Characterisation of the Risk with Cemiplimab in Combination Therapy (cemiplimab/chemotherapy):

Immune-mediated hyperthyroidism occurred in 16 (5.1%) of 312 patients receiving cemiplimab, with no grade ≥ 3 hyperthyroidism cases reported. Immune-mediated hyperthyroidism did not lead to permanent discontinuation of cemiplimab. Among the 16 patients with immune-mediated hyperthyroidism, the median time to onset was 4.0 months (range: 1.3 to 15.8 months) and the median duration of hyperthyroidism was 1.2 months (range: 0.7 to 11.9 months). Resolution of hyperthyroidism had occurred in 10 (62.5%) of the 16 patients at the time of data cutoff.

**Thyroiditis**

Characterisation of the Risk with Cemiplimab Monotherapy:

Thyroiditis occurred in 8 (0.6%) of 1281 patients receiving cemiplimab including 4 (0.3%) patients with grade 2 thyroiditis. No patient discontinued cemiplimab due to thyroiditis. Resolution of thyroiditis had occurred in 1 (12.5%) of the 8 patients at the time of data cutoff.

Characterisation of the Risk with Cemiplimab in Combination Therapy (cemiplimab/chemotherapy):

Immune-mediated thyroiditis occurred in 2 (0.6%) of 312 patients receiving cemiplimab, with no grade ≥ 3 cases reported. Immune-mediated thyroiditis did not lead to permanent discontinuation of cemiplimab. Neither of the 2 cases of thyroiditis had resolved at the time of data cutoff.

**Hypophysitis**

Characterisation of the Risk with Cemiplimab Monotherapy:

Hypophysitis occurred in 7 (0.5%) of 1281 patients receiving cemiplimab, including 3 (0.2%) patients with grade 3 hypophysitis. One (<0.1%) of 1281 patients discontinued cemiplimab due to hypophysitis. Among the 7 patients with hypophysitis, the median time to onset was 7.4 months (range: 2.5 months to 10.4 months) with a median duration of 2.7 months (range: 9 days to 34.9 months). Six of the 7 patients (85.7%) were treated with systemic corticosteroids. Hypophysitis resolved in 1 (14.3%) of 7 patients at the time of data cutoff.

Characterisation of the Risk with Cemiplimab in Combination Therapy (cemiplimab/chemotherapy):

To date, no patients reported immune-mediated hypophysitis in Study 16113 Part 2.

**Adrenal Insufficiency**

Characterisation of the Risk with Cemiplimab Monotherapy:

Adrenal insufficiency occurred in 6 (0.5%) of 1281 patients receiving cemiplimab, all grade 3. One (<0.1%) of 1281 patients discontinued cemiplimab due to adrenal insufficiency. Among the 6 patients with adrenal insufficiency, the median time to onset was 7.5 months (range: 4.2 to 18.3 months) and the median duration was 2.9 months (range: 22 days to 6.1 months). Five of the 6 patients (83.3%) were treated with systemic corticosteroids. Adrenal insufficiency had resolved in 1 of the 6 (16.7%) patients at the time of data cutoff.

Characterisation of the Risk with Cemiplimab in Combination Therapy (cemiplimab/chemotherapy):

To date, no patients reported immune-mediated adrenal insufficiency in Study 16113 Part 2.

**Type 1 Diabetes Mellitus**

Characterisation of the Risk with Cemiplimab Monotherapy:

Type 1 diabetes mellitus occurred in 1 (<0.1%) of 1281 patients. This case of type 1 diabetes mellitus was grade 4. No patients discontinued cemiplimab due to type 1 diabetes mellitus. Type 1 diabetes had not resolved at the time of data cutoff.

Characterisation of the Risk with Cemiplimab in Combination Therapy (cemiplimab/chemotherapy):

Immune-mediated type 1 diabetes mellitus occurred in 1 (0.3%) of 312 patients receiving cemiplimab; the event of immune-mediated type 1 diabetes mellitus was grade 2. The event of immune-mediated type 1 diabetes mellitus did not lead to permanent discontinuation of cemiplimab. Time to onset was 7.5 months (range: 7.5 to 7.5 months) and the duration of type 1 diabetes mellitus was 0.8 months (range: 0.8 to 0.8 months). The event of immune-mediated type 1 diabetes mellitus had not resolved at the time of data cutoff.

Post-marketing data: As of the DLP of the last periodic benefit risk evaluation report (PBRER, 28 Sep 2022 to 27 Sep 2024) no new information impacting the characterisation of the important identified risk of endocrinopathies was identified.

Risk Factors and Risk Groups:

Patients with a history of or ongoing significant autoimmune disease may be at increased risk of immune-mediated endocrinopathies.

Preventability:

The risk of immune-mediated endocrinopathies is due to pharmacologic action of cemiplimab and therefore cannot be prevented entirely from occurring in patients exposed to cemiplimab. However, early detection and prompt management including withholding of cemiplimab and/or use of systemic corticosteroids (if appropriate) and/or hormone replacement may reduce the severity and may lead to full recovery. Part V provides the details of risk minimisation measures for patients exposed to cemiplimab.

Impact on the Risk-benefit Balance of the Product:

Immune-mediated endocrinopathies can be severe or life-threatening especially if not identified early and managed by treatment modification, hormone replacement, and/or use of systemic corticosteroids. It is expected that, with the implementation of the routine and additional risk minimisation described in this RMP, the number of reported severe or life-threatening immune-mediated endocrinopathy events will be very low. Therefore, the impact of this risk on the risk-benefit balance of cemiplimab will be minimal following successful implementation of the risk minimisation plan.

Public Health Impact:

This risk has minimal impact on public health outside the effect on individual patients.

**Immune-mediated Skin Adverse Reactions**

Potential Mechanisms:

See potential mechanism above for imARs.

Evidence Source(s) and Strength of Evidence:

Immune-mediated skin adverse reactions, defined as requiring use of corticosteroids with no clear alternative aetiology, including rash, erythema multiforme, pemphigoid, and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) (some cases with fatal outcome) have been observed in patients treated with cemiplimab. Cases of SJS/TEN/stomatitis including fatal TEN occurred following 1 dose of cemiplimab in patients with prior exposure

to idelalisib, who were participating in a clinical trial evaluating cemiplimab in Non-Hodgkins Lymphoma.

In Studies 1423, 1540, 1620, 1624 and 1676, in which patients (N=1281) with advanced solid tumours (a variety of tumour types, including CSCC, BCC, NSCLC and cervical cancer) were treated with cemiplimab, immune-mediated skin adverse reactions occurred in 24 (1.9%) of 1281 patients receiving cemiplimab.

In Study 16113 Part 2 in which patients (N=312) with locally advanced and metastatic NSCLC irrespective of PDL-1 expression who had received no prior systemic treatment for their advanced disease were treated with cemiplimab in combination with platinum-based doublet chemotherapy (cemiplimab/chemotherapy), immune-mediated skin reactions occurred in 1.9% (6/312) of patients.

Characterisation of the Risk with Cemiplimab Monotherapy:

Immune-mediated skin adverse reactions occurred in 24 (1.9%) of 1281 patients receiving cemiplimab including 11 (0.9%) patients with grade 3 immune-mediated skin adverse reactions. Immune-mediated skin adverse reactions led to permanent discontinuation of cemiplimab in 3 (0.2%) of 1281 patients. Among the 24 patients with immune-mediated skin adverse reactions, the median time to onset was 2.0 months (range: 2 days to 17.0 months) and the median duration was 2.9 months (range: 8 days to 38.8 months). Seventeen patients (70.8%) with immune-mediated skin adverse reactions received high-dose corticosteroids for a median of 10 days (range: 1 day to 2.9 months). Resolution of immune-mediated skin adverse reactions had occurred in 17 (70.8%) of 24 patients at the time of data cutoff.

Characterisation of the Risk with Cemiplimab in Combination Therapy (cemiplimab/chemotherapy):

Immune-mediated skin reactions occurred in 6 (1.9%) of 312 patients receiving cemiplimab, including 3 (1.0%) patients with grade 3. Immune-mediated skin reactions led to permanent discontinuation of cemiplimab in 1 (0.3%) of 312 patients. Among the 6 patients with immune-mediated skin reactions, the median time to onset was 1.4 months (range: 0.2 to 6.8 months) and the median duration of immune-mediated skin reactions was 1.3 months (range: 0.1 to 13.6 months). Five of the 6 patients (83.3%) received high-dose corticosteroids (defined as ≥40 mg of prednisone or equivalent per day) for a median of 0.7 months (range: 0.03 to 1.4 months). Resolution of immune-mediated skin reactions had occurred in 4 (66.7%) of the 6 patients at the time of data cutoff.

Post-marketing data: As of the DLP of the last periodic benefit risk evaluation report (PBRER, 28 Sep 2022 to 27 Sep 2024), no new information impacting the characterisation of the important identified risk of skin reactions was identified.

Risk Factors and Risk Groups:

Patients with a history of or ongoing significant autoimmune disease may be at increased risk of developing immune-mediated reactions. Patients who were previously exposed to idelalisib may be at increased risk of experiencing severe immune-mediated mucocutaneous adverse reactions.

Preventability:

The risk of immune-mediated skin reactions is due to pharmacologic action of cemiplimab and therefore cannot be prevented entirely from occurring in patients exposed to cemiplimab. However, early detection and prompt management including withholding or permanent discontinuation of cemiplimab and use of systemic corticosteroids may reduce the severity and

may lead to full recovery. Part V provides the details of risk minimisation measures for patients exposed to cemiplimab. A more aggressive schedule of measures is proposed for patients previously treated with idelalisib. Physicians are instructed to weigh the benefit/risk of treating patients with cemiplimab who had previously received idelalisib.

Impact on the Risk-benefit Balance of the Product:

Immune-mediated skin adverse reactions can be fatal, especially if not identified early and managed by treatment modifications and use of systemic corticosteroid. It is expected that with the implementation of the routine and additional risk minimisation described in this RMP, the number of reported life-threatening or fatal skin reactions will be very low. Therefore, the impact of this risk on the risk-benefit balance of cemiplimab will be minimal following implementation of the risk minimisation plan, including disclosure of data in section 4.4 of the SmPC. Idelalisib is only used in the treatment of certain lymphomas, so prior exposure to this drug is only a concern in patients who previously had lymphoma.

Public Health Impact:

This risk has minimal impact on public health outside the effect on individual patients.

**Immune-mediated Nephritis**

Potential Mechanisms:

See potential mechanisms above for imARs.

Evidence Source(s) and Strength of Evidence:

Immune-mediated nephritis, defined as requiring use of corticosteroids with no clear alternative aetiology, have been observed in patients treated with cemiplimab. In Studies 1423, 1540, 1620, 1624 and 1676 in which patients (N=1281) with advanced solid tumours (a variety of tumour types, including CSCC, BCC NSCLC, cervical cancer) were treated with cemiplimab, immune-mediated nephritis occurred in 9 (0.7%) of 1281 patients receiving cemiplimab.

In Study 16113 Part 2 in which patients (N=312) with locally advanced and metastatic NSCLC irrespective of PDL-1 expression who had received no prior systemic treatment for their advanced disease were treated with cemiplimab in combination with platinum-based doublet chemotherapy (cemiplimab/chemotherapy), immune-mediated nephritis occurred in 0.6% (2/312) of patients.

Characterisation of the Risk with Cemiplimab Monotherapy:

Immune-mediated nephritis occurred in 9 (0.7%) of 1281 patients receiving cemiplimab including 1 (<0.1%) patient with grade 5 and 1 (<0.1%) patient with grade 3 immune-mediated nephritis. Immune-mediated nephritis led to permanent discontinuation of cemiplimab in 2 (0.2%) of 1281 patients. Among the 9 patients with immune-mediated nephritis, the median time to onset was 2.1 months (range: 14 days to 12.5 months) and the median duration of nephritis was 1.5 months (range: 9 days to 5.5 months). Six (66.7%) patients with immune-mediated nephritis received high-dose corticosteroids for a median of 18 days (range: 3 days to 1.3 months). Resolution of nephritis had occurred in 7 (77.8%) of the 9 patients at the time of data cutoff.

Characterisation of the Risk with Cemiplimab in Combination Therapy (cemiplimab/chemotherapy):

Immune-mediated nephritis occurred in 2 (0.6%) of 312 patients receiving cemiplimab, with no grade ≥ 3 cases reported. Immune-mediated nephritis did not lead to permanent discontinuation of cemiplimab. Among the 2 patients with immune-mediated nephritis, the median time to onset was 7.6 months (range: 0.8 to 14.5 months) and the median duration of nephritis was 1.0 months (range: 0.7 to 1.2 months). Both patients received high-dose corticosteroids (defined as ≥40 mg of prednisone or equivalent per day) for a median of 0.7 months (range: 0.6 to 0.72 months). Resolution of nephritis had occurred in 1 (50.0%) of the 2 patients at the time of data cutoff.

Post-marketing data: As of the DLP of the last periodic benefit risk evaluation report (PBRER, 28 Sep 2022 to 27 Sep 2024), no new information impacting the characterisation of the important identified risk of nephritis was identified.

Risk Factors and Risk Groups:

Patients with a history of significant autoimmune disease may be at higher risk of developing immune-mediated nephritis.

Preventability:

The risk of immune-mediated nephritis is due to the pharmacologic action of cemiplimab and therefore cannot be prevented entirely from occurring in patients exposed to cemiplimab. However, early detection and prompt management, including withholding or permanent discontinuation of cemiplimab and/or use of systemic corticosteroids, may reduce the severity when it occurs and may lead to full recovery. Part V provides the details of risk minimisation measures for patients exposed to cemiplimab.

Impact on the Risk-benefit Balance of the Product:

Immune-mediated nephritis can be fatal, especially if not identified early and managed by treatment modification and/or use of systemic corticosteroid and supportive care. It is expected that with the successful implementation of the routine and the additional risk minimisation described in this RMP, the number of reported life-threatening or fatal nephritis events will be very low. Therefore, the impact of this risk on the risk-benefit balance of cemiplimab will be minimal following successful implementation of the risk minimisation plan.

Public Health Impact:

This risk has minimal impact on public health outside the effect on individual patients.

**Other Immune-mediated Adverse Reactions**

Potential Mechanisms:

See potential mechanism above for imARs.

Evidence Source(s) and Strength of Evidence:

Other imARs, defined as requiring use of corticosteroids with no clear alternative aetiology, have been observed in patients treated with cemiplimab monotherapy.

In Study 16113 Part 2 in which patients (N=312) with locally advanced and metastatic NSCLC irrespective of PDL-1 expression who had received no prior systemic treatment for their advanced disease were treated with cemiplimab in combination with platinum-based doublet

chemotherapy (cemiplimab/chemotherapy), other imARs, defined as requiring use of corticosteroids with no clear alternative aetiology, were also observed.

Characterisation of the Risk with Cemiplimab Monotherapy:

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% (unless otherwise noted) of 1281 patients with advanced solid malignancies treated with cemiplimab monotherapy in clinical trials. The events were grade 3 or less unless stated otherwise:

Nervous System Disorders: Aseptic meningitis, paraneoplastic encephalomyelitis (grade 5), chronic inflammatory demyelinating polyradiculoneuropathy, encephalitis, myasthenia gravis, peripheral neuropathy[1]

Cardiac Disorders: Myocarditis[2] (grade 5), pericarditis[3]

Immune System Disorders: Immune thrombocytopenia

Musculoskeletal and Connective Tissue Disorders: Arthralgia (1.2%), arthritis[4], muscular weakness, myalgia, myositis[5] (grade 4), polymyalgia rheumatica, Sjogren's syndrome

Skin and Subcutaneous Tissue Disorders: Pruritus

Eye Disorders: Keratitis, Uveitis[6] (grade 4)

Gastrointestinal Disorders: Stomatitis, immune-mediated gastritis

The following additional immune-mediated adverse reactions were observed in patients receiving combination therapy in clinical trials: vasculitis, Guillain-Barre syndrome, central nervous system inflammation, and meningitis (grade 4), each with the frequency of rare (≥ 1/10,000 to < 1/1,000).

Characterisation of the Risk with Cemiplimab in Combination Therapy (cemiplimab/chemotherapy):

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 5% of 312 patients with locally advanced and metastatic NSCLC irrespective of PDL-1 expression who had received no prior systemic treatment for their advanced disease were treated with cemiplimab in combination with platinum-based doublet chemotherapy (cemiplimab/chemotherapy) in Study 16113 Part 2:

Blood Thyroid Stimulating Hormone Increased (4.2%) (< grade 3)

Blood Thyroid Stimulating Hormone Decreased (1.6%) (< grade 3)

Arthritis (≤0.5%) (< grade 3)

Blood Alkaline Phosphatase Increased (≤0.5%) (< grade 3)

[1] includes neuritis, peripheral neuropathy, peripheral sensory neuropathy, and polyneuropathy
[2] includes autoimmune myocarditis, immune-mediated myocarditis, and myocarditis
[3] includes autoimmune pericarditis and pericarditis
[4] includes arthritis, immune-mediated arthritis, and polyarthritis
[5] Includes myositis and dermatomyositis
6 Reported in clinical studies outside the pooled safety database

Risk Factors and Risk Groups:

Patients with a history of significant autoimmune disease may be at higher risk of developing immune-mediated AEs.

Preventability:

The risk of imARs is due to pharmacologic action of cemiplimab and therefore cannot be prevented entirely from occurring in patients exposed to cemiplimab. However, early detection and prompt management including withholding or permanent discontinuation of cemiplimab and use of systemic corticosteroids may reduce the severity and may lead to full recovery. Part V provides the details of risk minimisation measures for patients exposed to cemiplimab.

Impact on the Risk-benefit Balance of the Product:

Immune-mediated adverse reactions can be fatal in some patients, especially if not identified early and managed by treatment modification and use of systemic corticosteroid. It is expected that with the implementation of the routine and additional risk minimisation described in this RMP, the number of reported life-threatening or fatal imARs will be low. Therefore, the impact of this risk on the risk-benefit balance of cemiplimab will be minimal following the implementation of the risk minimisation plan.

Public Health Impact:

This risk has minimal impact on public health outside the effect on individual patients.

**Important Identified Risk: Infusion-related Reactions**

Potential Mechanisms:

A fully human monoclonal antibody is a foreign protein that may contain potential antigens capable of inducing hypersensitivity reactions.

Evidence Source(s) and Strength of Evidence:

In Studies 1423, Study 1540, 1620, 1624 and 1676 infusion-related reactions (IRRs) occurred in patients with CSCC, BCC NSCLC, cervical cancer receiving cemiplimab. These have also been observed in patients exposed to other PD-1 inhibitors. Infusion-related reactions occurred in 94 (7.3%) of 1281 patients treated with cemiplimab.

In Study 16113 Part 2 in which patients (N=312) with locally advanced and metastatic NSCLC irrespective of PDL-1 expression who had received no prior systemic treatment for their advanced disease were treated with cemiplimab in combination with platinum-based doublet chemotherapy (cemiplimab/chemotherapy), IRRs were also observed. Infusion-related reactions (IRRs) occurred in 7 (2.2%) of 312 patients receiving cemiplimab.

Characterisation of the Risk with Cemiplimab Monotherapy:

Infusion-related reactions occurred in 94 (7.3%) of 1281 patients treated with cemiplimab including 2 (0.2%) patients with grade 3 or grade 4 infusion-related reactions. Common symptoms of infusion-related reactions include nausea, pyrexia, and vomiting.

Characterisation of the Risk with Cemiplimab in Combination Therapy (cemiplimab/chemotherapy):

Infusion-related reactions (IRRs) occurred in 7 (2.2%) of 312 patients receiving cemiplimab, with no grade ≥ 3 cases reported. IRRs did not lead to permanent discontinuation of cemiplimab.

Risk Factors and Risk Groups:

Even though all patients are potentially at risk of IRRs, patients with documented allergic reactions or acute hypersensitivity reactions attributed to antibody treatments may be at higher risk of developing severe IRRs.

Preventability:

The risk of IRRs is due to the nature of cemiplimab (a fully human monoclonal antibody) and therefore cannot be prevented entirely from occurring in patients exposed to cemiplimab. However, early detection and prompt management including discontinuation of cemiplimab and use of supportive care (eg, IV fluids and anti-pyretics) or systemic corticosteroids may reduce the severity and may lead to full recovery. Cemiplimab is contraindicated in patients with known hypersensitivity to cemiplimab or any of its excipients. Part V provides the details of risk minimisation measures for patients exposed to cemiplimab.

Impact on the Risk-benefit Balance of the Product:

Infusion related reactions can be life-threatening or fatal, especially if not identified early and managed by treatment discontinuation and timely intervention including use of supportive care (eg, IV fluids and/or anti-pyretics), corticosteroids, or other resuscitative measures. It is expected that with the implementation of the routine and additional risk minimisation described in this RMP, the number of reported life-threatening or fatal IRRs will be very low. Therefore, the impact of this risk on the risk-benefit balance of cemiplimab will be minimal following the implementation of the risk minimisation plan.

Public Health Impact:

This risk has minimal impact on public health outside the effect on individual patients.

**Important Potential Risk: Lack of Effect due to Anti-drug Antibodies**

Potential Mechanism:

Administration of any monoclonal antibody has the potential to elicit formation of ADAs.

Evidence Source(s) and Strength of Evidence:

In nonclinical studies, the prevalence of immunogenicity/ADA was high; however, continuous exposure was maintained for 80% and 50% of animals throughout the 4-week and 26-week toxicology studies, respectively. As cemiplimab is a human antibody, the presence of ADA following cemiplimab administration to cynomolgus monkeys was expected and not considered predictive of the human ADA response to cemiplimab.

In patients with solid tumours, cemiplimab was administered as monotherapy or in combination with radiotherapy and/or chemotherapy in the FIH Study 1423; cemiplimab was administered as monotherapy in Study 1540 [CSCC], Study 1620 [BCC], Study 1624 [NSCLC] and Study 1676 [cervical cancer]; cemiplimab was administered with chemotherapy in Study 16113 Part 2 [NSCLC]).

In clinical studies of cemiplimab, no lack of efficacy due to neutralizing ADA was identified.

Characterisation of the Risk with Cemiplimab Monotherapy and in Combination Therapy (cemiplimab/chemotherapy):

The incidence of treatment-emergent immunogenicity was low (2.2%) in all patients (n = 823) receiving cemiplimab at any dose and regimen and was low (2.3%) in all patients (n = 385) receiving cemiplimab 350 mg Q3W.

Anti-drug antibodies titers were all low with the exception of one patient who exhibited moderate ADA titers. Of the patients who developed treatment-emergent antibodies to cemiplimab, none developed neutralizing antibodies (NAbs). In the small number of patients with treatment-emergent ADA response, there was no evidence of altered PK profile with anti-cemiplimab antibody development.

Approximately 2.1% of 1116 patients developed treatment emergent antibodies to cemiplimab. Of the patients who developed treatment emergent antibodies to cemiplimab, none developed NAbs. None of the patients with CSCC developed treatment emergent antibodies. Approximately 0.3% of all patients receiving cemiplimab 3 mg/kg Q2W had persistent antibody responses defined as having at least two consecutive positive post-baseline samples separated by at least 16 weeks. Antibody titers were low to moderate. In the few patients who developed anti-cemiplimab antibodies, there was no evidence of altered PK profile.

Anti-drug antibodies are usually non-serious; In the few patients who developed anti-cemiplimab antibodies, there was no evidence of altered PK profile or altered efficacy.

Cemiplimab has known low immunogenicity. There are no known cases where ADA have impacted the patients.

Risk Factors and Risk Groups:

Even though all patients are potentially at risk of infusion-related reactions, patients with documented allergic reactions or acute hypersensitivity reactions attributed to antibody treatments may be at higher risk of developing severe infusion-related reactions and were excluded from the development programme for cemiplimab.

Preventability:

The risk of immunogenicity is due to the formation of ADAs and NAbs and these ADA may or may not be neutralizing. Neutralizing antibodies cannot be prevented.

Impact on the Risk-benefit Balance of the Product:

The impact on the risk-benefit balance remains unknown. Development of ADA and NAbs may reduce efficacy of cemiplimab and may increase the risk of AEs.

Public Health Impact:

The potential for public health impact is minimal.

# Part II: Module SVIII - Summary of the Safety Concerns

**Table Part II.SVIII. 1 Summary of Safety Concerns**

| **Summary of Safety Concerns** | |
|---|---|
| **Important Identified Risks** | imARs (pneumonitis, colitis, hepatitis, endocrinopathies, immune-mediated skin adverse reactions, nephritis, and other imARs)<br>IRRs |
| **Important Potential Risks** | Lack of effect due to anti-drug antibodies |

# PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

## III.1 Routine Pharmacovigilance Activities

**Table Part III. 1 Routine Pharmacovigilance Activities**

| Identified or Potential Risks and Missing Information for Further Investigation | Proposed Pharmacovigilance Activities | Objectives |
|---|---|---|
| **Important Identified Risk: Immune-mediated Adverse Reactions** (immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, immune-mediated skin reactions, nephritis, and other imARs) | Routine pharmacovigilance | To monitor, identify, evaluate, and characterise reports of imARs in patients exposed to cemiplimab |
| | Use of specific follow-up questionnaire for spontaneous postmarketing reports of imARs | To obtain all necessary and consistent information on spontaneous imARs that will ensure further characterisation of such imARs |
| **Important Identified Risk: Infusion-related Reactions** | Routine pharmacovigilance | To monitor, identify, evaluate, and characterise AE reports of IRRs in patients exposed to cemiplimab |
| | Use of specific follow-up questionnaire for spontaneous post-authorisation reports of IRRs | To obtain all necessary and consistent information that will ensure further characterisation of IRRs |
| **Important Potential Risk: Lack of Effect due to Anti-drug Antibodies** | Routine pharmacovigilance | To monitor, identify, evaluate, and characterise AE reports involving lack of effect due to ADA |

**Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:**

**Specific Adverse Reaction Follow-up Questionnaires for Important Identified Risks of imARs and IRRs**

The follow-up questionnaires (Annex 4) will be used to obtain consistent medically relevant information that will ensure further analysis, evaluation, and characterisation of imARs and IRRs during post-approval period.

## III.2 Additional Pharmacovigilance Activities

All studies from RMP part III have been completed. There are no additional pharmacovigilance activities planned for this product.

# PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

None

# PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

## V.1. Routine Risk Minimisation Measures

**Table Part V. 1 Description of Routine Risk Minimisation Measures by Safety Concern**

| Safety concern | Routine Risk Minimisation Activities |
|---|---|
| **Important Identified Risk: Immune-mediated Adverse Reactions (**immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, immune-mediated skin reactions, nephritis, and other imARs) | Routine risk communication messages:<br>SmPC sections 4.4 and 4.8<br>PL section 2 and section 4<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>SmPC sections 4.2 and 4.4<br>PL sections 2 and 3<br>Other routine risk minimisation measures beyond the Product Information:<br>Legal status:<br>Cemiplimab is subject to restricted medical prescription, and treatment must be initiated and supervised by physicians experienced in the treatment of cancer. |
| **Important Identified Risk: Infusion-related Reactions** | Routine communication messages:<br>SmPC sections 4.4 and 4.8<br>PL sections 2 and 4<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>SmPC sections 4.2, 4.3, and 4.4.<br>PL sections 2 and 3<br>Other routine risk minimisation measures beyond the Product Information:<br>Legal status:<br>Cemiplimab is restricted to a medical prescription and treatment must be initiated and supervised by physicians experienced in the treatment of cancer. |
| **Important Potential Risks:**<br>**Lack of Effect due to Anti-drug Antibodies** | Routine communication messages:<br>SmPC section 4.8<br>Other routine risk minimisation measures beyond the Product Information:<br>Legal status:<br>Cemiplimab is subject to restricted medical prescription and treatment must be initiated and supervised by physicians experienced in the treatment of cancer. |

## V.2. Additional Risk Minimisation Measures

### Additional Risk Minimisation 1: Patient Card

### Table Part V. 2 Patient Card

| **Additional Risk Minimisation 1: Patient Card** | |
|---|---|
| **Important Identified Risk: Immune-mediated Adverse Reactions (**immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, immune-mediated skin reactions, nephritis, and other imARs)<br>**Important Identified Risk: Infusion-related Reactions** | |
| **Objectives:** | To educate patients about the important risks (ie, imARs and IRRs), how to recognise the early symptoms, and what to do when they notice any of those symptoms.<br>To ensure that special information regarding the patient's current therapy with cemiplimab and its important risks (ie, imARs and IRRs) is held by the patient at all times and reaches the relevant healthcare professional as appropriate. |
| **Rationale for the additional risk minimisation activity:** | imARs and IRRs are important identified risks for cemiplimab and other anti-PD-1 monoclonal antibodies. Early symptoms of imARs and IRRs are usually mild to moderate; however, if not recognised early and managed appropriately, they can be life-threatening or fatal. This additional risk minimisation is required to ensure early recognition and appropriate management of imARs and IRRs to ensure that the benefit-risk profile of cemiplimab remains positive. |
| **Target audience and planned distribution path:** | Patients will receive information about the early symptoms of imARs and IRRs and about the need to report any of these immediately to their physician or relevant healthcare provider.<br>Patients will be given the Patient Card and instructed on the need to carry this card at all times and to show it to a physician at all times whenever they are treated by a medical professional.<br>The key elements of the Patient Card are included in Annex 6. |
| **Plans to evaluate the effectiveness of the interventions and criteria for success:** | The effectiveness of this additional risk minimisation will be measured indirectly by routine pharmacovigilance activities. It is anticipated that successful implementation of this additional risk minimisation will lead to early identification and successful management of most imARs and IRRs. Therefore, the rate of life-threatening and fatal imARs and IRRs will be very low. Cases of imARs and IRRs will be analysed and characterised with each PSUR. |

### Removal of Additional Risk Minimisation Activities

On 31 March 2023, EMA's Pharmacovigilance Risk Assessment Committee (PRAC) requested that at the next regulatory procedure affecting the RMP, the MAH remove the Patient Guide which contained similar information to the Patient Card. (Procedure No: EMEA/H/C/PSUSA/00010780/202209).

## V.3 Summary of Risk Minimisation Measures

**Table Part V. 3 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**

| Safety Concern | Risk Minimisation Activities | Proposed Pharmacovigilance Activities |
|---|---|---|
| **Important Identified Risk: Immune-mediated Adverse Reactions**<br>Immune-mediated adverse reactions (immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, immune- mediated skin reactions, nephritis, and other imARs) | Routine risk communication messages:<br>SmPC sections 4.4 and 4.8<br>PL sections 2 and 4<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>See SmPC sections 4.2 and 4.4<br>See PL sections 2 and 3<br>Other routine risk minimisation measures beyond the Product Information:<br>Legal status:<br>Cemiplimab is supplied subject to restricted medical prescription, and treatment must be initiated and supervised by physicians experienced in the treatment of cancer.<br>Additional risk minimisation measures:<br>Patient Card | Routine pharmacovigilance<br>Use of specific follow-up questionnaire for spontaneous postmarketing reports of imARs |
| **Important Identified Risk: Infusion-related Reactions** | Routine communication messages:<br>SmPC sections 4.4 and 4.8<br>PL sections 2 and 4<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>SmPC sections 4.2, 4.3, and 4.4.<br>PL sections 2 and 3<br>Other routine risk minimisation measures beyond the Product Information:<br>Legal status:<br>Cemiplimab is supplied subject to restricted medical prescription and treatment must be initiated and supervised by physicians experienced in the treatment of cancer.<br>Additional risk minimisation measures:<br>Patient Card | Routine pharmacovigilance<br>Use of specific follow-up questionnaire for spontaneous post-authorisation reports of infusion-related reactions |
| **Important Potential Risk: Lack of Effect due to Anti-drug Antibodies** | Other routine risk minimisation measures beyond the Product Information:<br>Legal status:<br>Cemiplimab is subject to restricted medical prescription and treatment must be initiated and supervised by physicians experienced in the treatment of cancer. | Routine pharmacovigilance |

# PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

## Summary of Risk Management Plan for LIBTAYO® (cemiplimab)

This is a summary of the RMP for cemiplimab. The RMP details important risks of cemiplimab, how these risks can be minimised, and how more information will be obtained about cemiplimab risks and uncertainties (missing information).

Cemiplimab summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how cemiplimab should be used.

This summary of the RMP for cemiplimab should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR). *To be adapted locally.*

Important new concerns or changes to the current ones will be included in updates of cemiplimab RMP.

### I. The Medicine and What it is Used For

Cemiplimab is authorised as monotherapy indicated for the treatment of adult patients with:

(1) Cutaneous Squamous Cell Carcinoma

LIBTAYO as monotherapy is indicated for the treatment of adult patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation.

Proposed Indication: LIBTAYO as monotherapy is indicated for the adjuvant treatment of adult patients with CSCC at high risk of recurrence after surgery and radiation (see section 5.1 for selection criteria).

(2) Basal Cell Carcinoma

LIBTAYO as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic basal cell carcinoma (laBCC or mBCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI).

(3) Non-Small Cell Lung Cancer

LIBTAYO as monotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:

- locally advanced NSCLC who are not candidates for definitive chemoradiation, or
- metastatic NSCLC.

LIBTAYO in combination with platinum-based chemotherapy is indicated for the first-line treatment of adult patients with NSCLC expressing PD-L1 (in ≥ 1% of tumour cells) with no EGFR, ALK or ROS1 aberrations, who have:

- locally advanced NSCLC who are not candidates for definitive chemoradiation or
- metastatic NSCLC.

(4) Cervical Cancer

LIBTAYO as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.

## II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute routine risk minimisation measures.

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

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

If important information that may affect the safe use of cemiplimab is not yet available, it is listed under 'missing information' below.

### II.A List of Important Risks and Missing Information

Important risks of cemiplimab 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 cemiplimab. 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).

List of important risks and missing information:

**Important Identified Risks:**

- Immune-mediated adverse reactions (imARs) such as immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, immune-mediated skin reactions, nephritis, and other imARs
- Infusion-related reactions (IRRs)

**Important Potential Risks:**

Lack of effect due to anti-drug antibodies (ADAs)

## II.B Summary of Important Risks

| **Important Identified Risk: Immune-mediated Adverse Reactions** | |
|---|---|
| **Evidence for Linking the Risk to the Medicine** | Cemiplimab Monotherapy:<br>A total of 249 (20.8%) patients exposed to cemiplimab monotherapy in clinical trials experienced at least 1 imAE, including fatal or grade 5 (0.3%), life-threatening or grade 4 (0.6%), severe or grade 3 (5.6%), and moderate or grade 2 (11.2%). Fifty-six (4.7%) patients discontinued treatment due to imAEs.<br>Cemiplimab in Combination Therapy (cemiplimab/chemotherapy):<br>A total of 59 (18.9%) patients exposed to cemiplimab in combination therapy in clinical trials and included in the RMP experienced at least 1 imAE. Grade ≥3 imAEs were reported in 9 (2.9%) patients, including one patient (0.3%) with grade 5. Three (1.0%) patients discontinued treatment due to imAEs. |
| **Risk Factors and Risk Groups** | Patients with a history of or ongoing autoimmune disease may be at higher risk of developing imAEs and were excluded from the development programme for cemiplimab. Patients who were previously exposed to idelalisib may be at increased risk of experiencing severe immune-mediated mucocutaneous adverse reactions. |
| **Risk Minimisation Measures** | Routine risk communication messages:<br>SmPC sections 4.4 and 4.8<br>PL sections 2 and 4<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>SmPC sections 4.2 and 4.4<br>PL sections 2 and 3<br>Other routine risk minimisation measures beyond the Product Information:<br>Legal status:<br>Cemiplimab is subject to restricted medical prescription, and treatment must be initiated and supervised by physicians experienced in the treatment of cancer.<br>Additional risk minimisation measures:<br>Patient Card |

| **Important Identified Risk: Infusion-related Reactions** | |
|---|---|
| **Evidence for Linking the Risk to the Medicine** | Cemiplimab Monotherapy:<br><br>In Study 1423, Study 1540, Study 1620, Study 1624 and Study 1676, IRRs occurred in patients receiving cemiplimab. These have also been observed in patients exposed to other PD-1 inhibitors.<br><br>Infusion-related reactions occurred in 7.3% (87/1198) of patients receiving cemiplimab including 1 (<0.1%) patient with grade 3 IRRs. Infusion-related reactions led to permanent discontinuation of cemiplimab in 1 (<0.1%) patient. The most common symptoms of infusion-related reaction were nausea, pyrexia, and vomiting. All patients recovered from infusion-related reaction.<br><br>Cemiplimab in Combination Therapy (cemiplimab/chemotherapy):<br><br>Infusion-related reactions occurred in 2.2% (7/312) of patients receiving cemiplimab in combination therapy in clinical trials, all < grade 3. No IRRs led to permanent discontinuation of cemiplimab. The most common symptoms of infusion-related reaction were vomiting and pruritus. All patients recovered from infusion-related reaction. |
| **Risk Factors and Risk Groups** | Even though all patients are potentially at risk of IRRs, patients with documented allergic reactions or acute hypersensitivity reactions attributed to antibody treatments may be at higher risk of developing severe IRRs and were excluded from the development programme for cemiplimab. |
| **Risk Minimisation Measures** | Routine communication messages:<br><br>SmPC sections 4.4 and 4.8<br><br>PL sections 2 and 4<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br><br>SmPC sections 4.2, 4.3, and 4.4.<br><br>PL sections 2 and 3<br><br>Other routine risk minimisation measures beyond the Product Information:<br><br>Legal status:<br><br>Cemiplimab is subject to restricted medical prescription and treatment must be initiated and supervised by physicians experienced in the treatment of cancer.<br><br>Additional risk minimisation measures:<br><br>Patient Card |
| **Additional pharmacovigilance activities** | None |

| **Important Potential Risks: Lack of Effect due to Anti-drug Antibodies** | |
|---|---|
| **Evidence for Linking the Risk to the Medicine** | In nonclinical studies, the prevalence of immunogenicity/ADA was high; however, continuous exposure was maintained for 80% and 50% of animals throughout the 4-week and 26-week toxicology studies, respectively. As cemiplimab is a human antibody, the presence of ADA following cemiplimab administration to cynomolgus monkeys was expected and not considered predictive of the human ADA response to cemiplimab.<br><br>In the overall population of patients with solid tumours, immunogenicity was assessed in all patients with solid tumours, including patients with NSCLC in Study 16113 Part 2, after cemiplimab administration as monotherapy (Studies 1423, 1540, 1620, 1624 and 1676) or in combination with radiotherapy and/or chemotherapy (Study 1423) or with chemotherapy (Study 16113 Part 2).<br>The incidence of treatment-emergent ADA in all patients with solid tumours in the ADA analysis set (n=1310) was low (approximately 2.5%), including the subset of patients who received cemiplimab 350 mg Q3W. The ADA titers were generally low (< 1,000). Overall, only 3 patients (0.3%) had a persistent ADA response. No patients were positive for neutralizing antibodies (NAbs).<br><br>The presence of treatment-emergent ADA did not appear to have a clinically meaningful effect on cemiplimab concentrations (Study 1423 Final CSR Appendix 5 [CP Report] Section 4.4, Study 1540 Interim CSR Appendix 5 [CP Report] Section 4.4, Study 1620 Interim CSR Appendix 5 [CP Report] Section 4.3, Study 1624 Primary Analysis CSR Appendix 16.1.15 [CP Report] Section 4.3, Study 1676 Primary Analysis CSR Appendix 16.1.15 [CP Report] Section 4.3 and Study 16113 Part 2 Primary Analysis CSR Appendix 16.1.15 [CP Report] Section 4.3). |
| **Risk Factors and Risk Groups** | Risk factors are unknown. Any patient who receives cemiplimab has a potential risk of developing ADAs. |
| **Risk Minimisation Measures** | Other routine risk minimisation measures beyond the Product Information:<br><br>Legal status:<br><br>Cemiplimab is subject to restricted medical prescription and treatment must be initiated and supervised by physicians experienced in the treatment of cancer. |

## II.C Post-authorisation Development Plan

### II.C.1 Studies which are Conditions of the Marketing Authorisation

Not applicable.

### II.C.2 Other Studies in Post-authorisation Development Plan

Not Applicable

# PART VII: ANNEXES

# Annex 1 – EudraVigilance Interface

# Annex 2 – Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme

| Study Number | Indication | Study Title | Phase | Study Status | CD Total Number of Planned Patients | Final CSR |
|---|---|---|---|---|---|---|
| R2810-ONC-1540 | CSCC | R2810-ONC-1540: A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programmed Cell Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma | 2 | Completed | 433 | Final CSR released on 19/08/2024 |
| R2810-ONC-1620 | BCC | A Phase 2 study of REGN2810, a fully human monoclonal antibody to Programmed Death-1 in patients with advanced BCC who experienced progression of disease on HHI pathway therapy or were intolerant of prior HHI therapy. | 2 | Completed | 138 | Submission of Final study report: 03/06/2024 |

# Annex 3 - Protocols for Proposed, On-going and Completed Studies in the Pharmacovigilance Plan

**Part A:** Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable

**Part B:** Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable

**Part C:** Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority

Not applicable

## Annex 4 - Specific Adverse Drug Reaction follow-up Forms

**Cemiplimab**
**Immune Related Adverse Events**
**(also known as Immune Mediated Reactions)**

**Targeted Follow-up Form (coversheet)**

- **In the 'Suspect Product(s) Information' section of Individual Safety Information (ISI) Documentation Form and in the 'Suspect Medication/Medical Device (MD)/Vaccine (V)' section of Unsolicited Individual Safety Information (ISI) Report Form, ensure to collect:**

  - Cemiplimab cycle number when the immune related event first occurs

- **In the 'Adverse Event Information (Describe Event)' section of ISI Documentation Form and in the 'Description of the Case' section of Unsolicited ISI Report Form, ensure to collect:**

  - Events details: please describe the intensity (mild, moderate, severe), add final clinical diagnoses consistent with the immune related event if available (for example: hypothyroidism, rash, or other)
  - Did the patient receive treatment with corticosteroids or other immunosuppressive agent for the immune adverse experience?
    - If yes, please list name of corticosteroid or immunosuppressive agent, dose, dates of treatment.
    - If yes, please provide detail if patient improved with corticotherapy and describe in detail.
  - If alternative causes (non-immune mediated) for the reported event were evaluated and excluded (including disease progression). If yes, please describe.

- **In the 'Adverse Event Information (Describe Event)' section of ISI Documentation Form and in the 'Complementary Investigations' section of Unsolicited ISI Report Form, ensure to describe:**

  - Diagnostic Testing: please provide pertinent diagnostic test, date, and results (e.g., ultrasound, CT, MRI, biopsies, laboratory test results, etc.) for the reported event.

- **In the 'Medical History/Risk Factors' section of ISI Documentation Form and in the 'Ongoing Illness/Medical History/Risk Factors' section of Unsolicited ISI Report Form, ensure to collect:**

  - Medical history that is relevant to the immune reaction
  - Cancer History/Treatment: please describe the patient's cancer history (i.e., previous malignancies, indication for cemiplimab use, onset date of current cancer diagnosis)
    - Specify primary tumour site
    - Metastatic sites? Please list.
  - Please also include other cancer treatments received with dates. Please list other cancer treatments (i.e., radiation, chemotherapy) and include therapy dates, sites, doses as applicable
  - Did the patient receive prior treatment with other checkpoint inhibitors: idelalisib, pembrolizumab, ipilimumab, nivolumab, avelumab, durvalumab, atezolizumab or other immune checkpoint inhibitor treatment?
    - If yes, please indicate treatment name(s), indication(s), start and end dates of treatment
    - *For patients with prior idelalisib, pembrolizumab, ipilimumab, nivolumab, avelumab, durvalumab, atezolizumab or other immune checkpoint inhibitor treatment:*
      - If patient had experienced any adverse events while on this/these prior treatments. If yes, please describe (i.e., event term, onset dates, severity, treatment(s) given for event and outcome)

*If appropriate, please attach lab/diagnostic studies, hospital summary and/or autopsy report.*

**Cemiplimab**
**Infusion Related Reactions**

**Targeted Follow-up Form (coversheet)**

- **In the 'Suspect Product(s) Information' section of Individual Safety Information (ISI) Documentation Form and in the 'Suspect Medication/Medical Device (MD)/Vaccine (V)' section of Unsolicited Individual Safety Information (ISI) Report Form, ensure to indicate:**

  - Cycle of cemiplimab when first infusion reaction occurs
  - Dose of cemiplimab
  - Time of event(s) after initiation of infusion

- **In the 'Adverse Event Information (Describe Event)' section of ISI Documentation Form and in the 'Description of the Case' section of Unsolicited ISI Report Form, ensure to collect:**

  - Event details: please describe the reaction in full detail, including event terms, intensity (mild, moderate, severe), seriousness, dates (time) and chronology of events and provide absolute time points relative to infusion or completion of infusion.
  - Please confirm if the patient experienced a systemic reaction or the reaction was localized (please describe). If relevant, list cardiovascular symptoms – *If known, please include blood pressure, heart rate and/or arterial blood gas (baseline & progression during reaction),* gastrointestinal and respiratory symptoms, skin symptoms, other symptoms, and possible contributing factors
  - How was the patient treated (please specify all that apply)?
    - Infusion rate slowed
    - Intravenous fluids
    - Vasopressors
    - Oxygen
    - Bronchodilators
    - Antihistamines
    - Acetaminophen
    - Corticosteroid: topical or systemic administration
    - Other (specify)
  - Did the patient recover from the events?
  - Was cemiplimab re-introduced? If yes, specify dates and if there were any precautions taken and how did the patient respond to cemiplimab?

- **In the 'Adverse Event Information (Describe Event)' section of ISI Documentation Form and in the 'Complementary Investigations' section of Unsolicited ISI Report Form, ensure to indicate:**

  - Lab/diagnosis data**:** if relevant please provide baseline, highest, last on drug and newest values (test-date-results)
  - If any additional evaluations were made, please provide parameters such as:
    - Blood parameters (e.g., full blood count, tryptase, C-reactive protein)
    - Liver parameters (e.g., GOT, GPT, GGT)
    - Kidney parameters (e.g., creatinine, methylhistamine)
    - Another specific tests (e.g., immune complex analysis, complement analysis)

- **In the 'Medical History/Risk Factors' section of ISI Documentation Form and in the 'Ongoing Illness/Medical History/Risk Factors' section of Unsolicited ISI Report Form, ensure to indicate:**

  - If the patient has a history of infusion related reactions to a monoclonal antibody or any other medication?
    If yes, please specify medication, onset, type of reaction and outcome
  - Cancer History/Treatment: please describe the patient's cancer history (i.e., previous malignancies, indication for cemiplimab use, onset date of current cancer diagnosis)
    - Specify primary tumour site
    - Metastatic sites? Please list.
    - Please list other cancer treatments (i.e., radiation, chemotherapy) and include therapy dates, sites, doses as applicable.

- **In the 'Concomitant Medicines (e.g. drugs, devices, vaccines)' section of ISI Documentation Form and in the 'Concomitant Medication/Medical device/Vaccine' section of Unsolicited ISI Report Form, ensure to include:**

  - Use of any premedication taken (including name, dosage, dosage regimen, frequency, indication etc.)

# Unsolicited Individual Safety Information (ISI) Report Form

*Grey fields are for Regeneron use only*

## 1 ADMINISTRATIVE SECTION FOR AFFILIATE/PARTNER ONLY

Company contact date: / / Local PV receipt date: / /

Country of Occurrence:

Social Media case: Yes ☐ No ☐ If Yes: Name of the social media:

☐ INITIAL ☐ FOLLOW-UP Global Safety Database ID:

Local Reference ID: Local PTC ID: Global PTC ID:

## 2 PATIENT

Title, Name (first, middle, last)/Initials: ..... Gender: F ☐ M ☐ Unk ☐

Address, city, postal code, state:

Country: Phone:

Email address:

Date of Birth (DD/MM/YYYY): / / . Age or Age Group (at time of the reaction): .....

Height: cm/feet & inches Weight: kg/lb Registry ID #: Click here to enter text.

## 3 REPORTER

First Name: Last Name:

Occupation: .....

Address:

Zip / Postal Code:

Country:

Individual Safety Information Documentation Form
Version Number: 9.0
Effective date: 11-Jan-2021

## 3 REPORTER

Phone:

Fax:

E-mail address:

If the primary reporter is a consumer, is contact information provided for a HealthCare Professional? *Yes ☐ No ☐ NA ☐

If your country requires patient consent to contact the HCP, has the patient given their consent? *Yes ☐ **No ☐ NA ☐

*If YES, attempts should be made to contact the HCP **If NO, do not contact the HCP and document the exchange

Was FU request sent to reporter? Yes ☐ No ☐ NA ☐

The reporter will not have any further information ☐

The reporter does not wish to be contacted by the Pharmacovigilance Department ☐

## 4 SUSPECT MEDICATION / MEDICAL DEVICE (MD) / VACCINE (V)

| Brand Name /INN | Indication | Dosage/ Unit/ Frequency/ Amount | Batch Number (Mandatory. If not available, enter NA/ if not obtainable at all enter NO) | Start Date (DD/MM /YYYY) | Stop Date or duration (DD/MM/YYYY) | Route of Administration | Company product (Yes/No) | Primary/Booster (V) | Site of Injection (V) | Side (V) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | ..... | | ..... | ..... | ..... |
| | | | | | | ..... | | ..... | ..... | ..... |
| | | | | | | ..... | | ..... | ..... | ..... |
| | | | | | | ..... | | ..... | ..... | ..... |
| | | | | | | ..... | | ..... | ..... | ..... |
| | | | | | | ..... | | ..... | ..... | ..... |

*Is medical device available for evaluation (MD)?* ☐Yes ☐No
*Did the problem occur with initial use or during re-use of the medical device (MD)?* ☐Yes ☐No

*For company suspect product inappropriately used as per local Marketing Authorization:*
*Is it intentional?* ☐Yes ☐No ☐Unk *at the initiative of* ☐HCP ☐Consumer ☐Unk *for a therapeutic purpose?* ☐Yes ☐No ☐Unk

*Comments (Complementary information: presentation, syringe, single dose, multidose, storage conditions)*:

## 5 CONCOMITANT MEDICATION / MEDICAL DEVICE / VACCINE

| Brand Name /INN | Indication | Dosage/ Unit/ Frequency/ Amount | Batch Number | Start Date (DD/MM/ YYYY) | Stop Date or duration (DD/MM/ YYYY) | Route of Administration | Company product (Yes/No) | Primary/ Booster (V) | Site of Injection (V) | Side (V) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | ..... | | ..... | ..... | ..... |
| | | | | | | ..... | | ..... | ..... | ..... |
| | | | | | | ..... | | ..... | ..... | ..... |
| | | | | | | ..... | | ..... | ..... | ..... |
| | | | | | | ..... | | ..... | ..... | ..... |
| | | | | | | ..... | | ..... | ..... | ..... |
| | | | | | | ..... | | ..... | ..... | ..... |
| | | | | | | ..... | | ..... | ..... | ..... |

*Comments (Complementary information: presentation, syringe, single dose, multidose, storage conditions)*:

## 6 REACTION DESCRIPTION

| Reaction | Date of Onset (DD/MM/YYYY) | Stop Date or Duration (DD/MM/YYYY) | Outcome | Corrective Treatment | Action Taken | Did reaction abate after product was stopped? | Did reaction recur after product was started again? | Kind of Reaction (V) | Lack of efficacy / failure (V) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | ..... | |
| | | | | | | | | ..... | |
| | | | | | | | | ..... | |
| | | | | | | | | ..... | |
| | | | | | | | | ..... | |

**7 DESCRIPTION OF THE CASE** *(signs & symptoms, possible causes, progression, treatments, relevant medical history, investigations, severity ….)*

**8 ONGOING ILLNESS / MEDICAL HISTORY / RISK FACTORS**

Personal *(if relevant for the reaction described in this form)*:

Family *(if relevant for the reaction described in this form)*:

**9 HISTORY OF ADVERSE REACTION TO PREVIOUS ADMINISTRATION OF VACCINE (V)**

| Product Name / Therapeutic Class | Date of Occurrence (DD/MM/YYYY) | Reaction | Duration |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

*Comments*:

**10 COMPLEMENTARY INVESTIGATIONS Type / Results *(indicate unit / attach photocopies if relevant. If patient died, please specify if autopsy was performed and what was result)***

**11 SERIOUSNESS**

☐ **Non-Serious** ☐ **Serious (select at least one criteria below)**

☐ Death *Date of Death:* *Autopsy performed*: Yes ☐ No ☐ Unk ☐

☐ Life threatening

☐ Medically Significant (as per HCP)

☐ Hospitalization or prolongation of hospitalization *Duration of hospitalization:*

☐ Persistent or significant disability or incapacity

☐ Suspected transmission of infectious agent

☐ Congenital anomaly, birth defect

Was this reaction reported to Regulatory Authority? Yes ☐ No ☐

**NAME & SIGNATURE :**

**Individual Safety Information Documentation Form**

*Grey fields are for Regeneron use only*

**ADMINISTRATIVE SECTION FOR AFFILIATE/PARTNER ONLY**

**Person completing this form:**

Name, Title:_____ Telephone Number: _____

Services Provider Name: _____

☐ Initial ☐ Follow-up

Name of Program: _____ Name of Collecting Organization: _____

Study ID: _____ Center ID: _____ Patient ID: _____

Local Reference ID: _____ Global PV Database ID: _____

Local PTC ID (if applicable): _____ Global PTC ID (if applicable): _____

Date AE was First Reported to Services Provider: _____

Local PV receipt date: _____

**Patient Information** *(Complete any known information and as per local data privacy regulations):*

Patient First, Middle and Last Names / Initials (not to be collected for case report from clinical studies): _____

Sex: _____

Date of Birth (For clinical study, Year of birth to be collected only): _____

Age or Age Group: _____

**Suspect Product(s) Information** (*Complete any known information):*

| Product Name (INN, Brand) | Company product (Yes/No) | Was AE Related to Product? | Indication / Taken For | Dose/ Unit | Frequency | Route | Start Date | Stop Date / Ongoing? | Action Taken | Batch Number (Mandatory. If not available, enter NA/ if not obtainable at all enter NO) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | |
| | Click here to enter text. | | | | | | | | | |
| | Click here to enter text. | | | | | | | | | |

**Adverse Event Information** *Complete any known information. (If more than one AE reported, complete additional AE pages):*

Date AE started: _____ Date AE stopped/Duration: _____

**Describe event** (*Provide clinical details below, including other reasons that may explain the occurrence of the AE, relevant test results and necessary treatment. If more than one event is reported, complete additional AE pages*):

| |
|---|
| |

**Outcome of Event:** _____ **If fatal outcome:** Date of Death: _____

Cause of death: _____

Autopsy results: _____

Did AE lead to hospitalization or to prolonged hospitalization? _____

Did AE result in immediate risk of death? _____

Did AE result in persistent or significant disability or incapacity? _____

Is the AE a congenital anomaly/birth defect? _____

Is there suspected transmission of an infectious agent via the product? _____

**Concomitant Medicines (e.g. drugs, devices, vaccines) taken when AE occurred, but which are not suspected** (*Complete any known information):*

| Product Name (INN/Brand) | Indication / Taken For | Dose/ Unit | Frequency | Route | Start Date | Stop Date/Ongoing? |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |
| | | | | | | |

**Medical History/Risk Factors** *(Describe additional relevant information, e.g. medical or surgical history, past drug history, ongoing illness, risk factors such as allergies, alcohol use, drug abuse, etc.)*:

| |
|---|
| |

**Reporter Information** (*Who told you about this adverse event?):*

Name: _____ Address (postal code, city, state): _____

Country: _____

Department/Institution: _____

Phone: _____ Email: _____

Is the reporter a Health Care professional? _____

**Treating Physician Information (if not the reporter):**

Name: _____ Address: _____

Phone: _____ Email: _____

The reporter will not have any further information ☐

The reporter does not wish to be contacted by the Pharmacovigilance-Department ☐

**Name and Signature:**

_____

Signature:

**ADVERSE EVENT 2**

**Suspect Product Information** (*Complete any known information):*

| Product Name (INN, Brand) | Company product (Yes/No) | Was AE Related to Product? | Indication / Taken For | Dose/ Unit | Frequency | Route | Start Date | Stop Date / Ongoing? | Action Taken | Batch Number (Mandatory. If not available, enter NA/ if not obtainable at all enter NO |
|---|---|---|---|---|---|---|---|---|---|---|
| | Click here to enter text. | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |

Date AE started: _____ Date AE stopped/Duration: _____

**Describe event and any necessary treatment** (*Provide clinical details for each of the adverse events listed below*)**:**

| |
|---|
| |

**Outcome of Event:** _____ **If fatal outcome:** Date of Death: _____

Cause of death: _____

Autopsy results: _____

Did AE lead to hospitalization or to prolonged hospitalization? _____

Did AE result in immediate risk of death? _____

Did AE result in persistent or significant disability or incapacity? _____

Is the AE a congenital anomaly/birth defect? _____

Is there suspected transmission of an infectious agent via the product? _____

**ADVERSE EVENT 3**

**Suspect Product Information** (*Complete any known information):*

| Product Name (INN, Brand) | Company product (Yes/No) | Was AE Related to Product? | Indication / Taken For | Dose/ Unit | Frequency | Route | Start Date | Stop Date / Ongoing? | Action Taken | Batch Number (Mandatory. If not available, enter NA/ if not obtainable at al enter NO |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |

Date adverse event started: _____ Date adverse event stopped/Duration: _____

**Describe event and any necessary treatment** (*Provide clinical details for each of the adverse events listed below*):

| |
|---|
| |

**Outcome of Event:** _____ **If fatal outcome:** Date of Death: _____

Cause of death: _____

Autopsy results: _____

Did AE lead to hospitalization or to prolonged hospitalization? _____

Did AE result in immediate risk of death? _____

Did AE result in persistent or significant disability or incapacity? _____

Is the AE a congenital anomaly/birth defect? _____

Is there suspected transmission of an infectious agent via the product? _____

## Annex 5 - Protocols for Proposed and On-going Studies in RMP Part IV

No applicable.

# Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if Applicable)

Risk Minimisation Activity: Patient Educational materials (Patient Card)

The Marketing Authorisation Applicant (MAA) shall ensure that all physicians who are expected to prescribe cemiplimab are provided with Patient Cards.

Overview of Implementation

- The MAA will ensure distribution of the educational materials; the format and content of the educational material will be agreed with the National Competent Authorities.

Patient Card

Key elements:

The key elements of the patient educational material should contain the following:

- Description of the main signs or symptoms of the imARs (pneumonitis, colitis, hepatitis, endocrinopathies, immune-mediated skin adverse reactions, nephritis, other imARs and IRRs) and the importance of notifying their treating physician immediately if symptoms occur
- The importance of not attempting to self-treat any symptoms without consulting their healthcare professional first
- The importance of carrying the Patient Card at all times and to show it at all medical visits to healthcare professionals other than the prescriber (eg, emergency healthcare professionals)
- Reminder that all known or suspected adverse drug reactions (ADRs) can also be reported to local regulatory authorities
- The contact details of their Libtayo prescriber

The Card reminds patients about key symptoms that need to be reported immediately to the physician/nurse. It also contains prompts to enter contact details of the physician and to alert other physicians that the patient is treated with LIBTAYO®.

## Annex 7 - Other Supporting Data (Including Referenced Material)

Adegoke O, Kulasingam S, Virnig B. Cervical cancer trends in the United States: a 35-year population-based analysis. J Womens Health (Larchmt). 2012;21(10):1031-7.

Amengual J, Montaño J, Franch P, Ramos M. [Survival by cervical cancer stage and factors collected by the Cancer Registry in Mallorca (Spain)]. Gac Sanit. 2020;34(6):589-94.

American Cancer Society. Key statistics for lung cancer 2020 [cited 2020 10 June]. Available from: https://www.cancer.org/cancer/lung-cancer/about/key-statistics.html#:~:text=The%20American%20Cancer%20Society's%20estimates,men%20and%2063%2C220%20in%20women

Arbyn M, Dillner J. Review of current knowledge on HPV vaccination: an appendix to the European Guidelines for Quality Assurance in Cervical Cancer Screening. J Clin Virol. 2007;38(3):189-97.

Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. The Lancet Global health. 2020;8(2):e191-e203.

Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. J Photochem Photobiol B. 2001;63(1-3):8-18.

Asgari MM, Moffet HH, Ray GT, Quesenberry CP. Trends in Basal Cell Carcinoma Incidence and Identification of High-Risk Subgroups, 1998-2012. JAMA dermatology. 2015;151(9):976-81.

Benard VB, Watson M, Saraiya M, Harewood R, Townsend JS, Stroup AM, et al. Cervical cancer survival in the United States by race and stage (2001-2009): Findings from the CONCORD-2 study. Cancer. 2017;123 Suppl 24(Suppl 24):5119-37.

Besse B, Adjei A, Baas P, Meldgaard P, Nicolson M, Paz-Ares L, et al. 2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease. Annals of oncology : official journal of the European Society for Medical Oncology. 2014;25(8):1475-84.

Birch-Johansen F, Jensen A, Mortensen L, Olesen AB, Kjær SK. Trends in the incidence of nonmelanoma skin cancer in Denmark 1978-2007: Rapid incidence increase among young Danish women. International journal of cancer. 2010;127(9):2190-8.

Blue ED, Freeman SC, Lobl MB, Clarey DD, Fredrick RL, Wysong A, et al. Cutaneous Squamous Cell Carcinoma Arising in Immunosuppressed Patients: A Systematic Review of Tumor Profiling Studies. JID Innov. 2022;2(4):100126.

Bookman MA, Blessing JA, Hanjani P, Herzog TJ, Andersen WA. Topotecan in squamous cell carcinoma of the cervix: A Phase II study of the Gynecologic Oncology Group. Gynecologic oncology. 2000;77(3):446-9.

Brantsch KD, Meisner C, Schonfisch B, Trilling B, Wehner-Caroli J, Rocken M, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. The Lancet Oncology. 2008;9(8):713-20.

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018;68(6):394-424.

Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. The Lancet Oncology. 2012;13(8):790-801.

Brewer JD, Colegio OR, Phillips PK, Roenigk RK, Jacobs MA, Van de Beek D, et al. Incidence of and risk factors for skin cancer after heart transplant. Archives of dermatology. 2009;145(12):1391-6.

Brotherston D, Poon I. SBRT Treatment of Multiple Recurrent Auricular Squamous Cell Carcinomas Following Surgical and Conventional Radiation Treatment Failure. Cureus. 2015;7(9):e325.

Burton KA, Ashack KA, Khachemoune A. Cutaneous Squamous Cell Carcinoma: A Review of High-Risk and Metastatic Disease. American journal of clinical dermatology. 2016;17(5):491-508.

Carsin AE, Sharp L, Comber H. Geographical, urban/rural and socioeconomic variations in nonmelanoma skin cancer incidence: a population-based study in Ireland. The British journal of dermatology. 2011;164(4):822-9.

Carter JB, Johnson MM, Chua TL, Karia PS, Schmults CD. Outcomes of primary cutaneous squamous cell carcinoma with perineural invasion: an 11-year cohort study. JAMA dermatology. 2013;149(1):35-41.

Cerner Enviza. Epi Database® 2021 [cited 2021 26 Oct]. Available from: www.epidb.com

Chung HC, Ros W, Delord JP, Perets R, Italiano A, Shapira-Frommer R, et al. Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results From the Phase II KEYNOTE-158 Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2019;37(17):1470-8.

Clingan P, Ladwa R, Brungs D, Harris DL, McGrath M, Arnold S, et al. Efficacy and safety of cosibelimab, an anti-PD-L1 antibody, in metastatic cutaneous squamous cell carcinoma. Journal for immunotherapy of cancer. 2023;11(10).

Cohen EEW, Soulieres D, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. Lancet (London, England). 2019;393(10167):156-67.

Crosbie EJ, Einstein MH, Franceschi S, Kitchener HC. Human papillomavirus and cervical cancer. Lancet (London, England). 2013;382(9895):889-99.

Czarnecki D, Staples M, Mar A, Giles G, Meehan C. Metastases from squamous cell carcinoma of the skin in southern Australia. Dermatology (Basel, Switzerland). 1994;189(1):52-4.

D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Identifying patients at risk for significant versus clinically insignificant postoperative prostate-specific antigen failure. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005;23(22):4975-9.

Danial C, Sarin KY, Oro AE, Chang AL. An Investigator-Initiated Open-Label Trial of Sonidegib in Advanced Basal Cell Carcinoma Patients Resistant to Vismodegib. Clinical cancer research : an official journal of the American Association for Cancer Research. 2016;22(6):1325-9.

de Groot PM, Wu CC, Carter BW, Munden RF. The epidemiology of lung cancer. Translational lung cancer research. 2018;7(3):220-33.

Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. Clinics in chest medicine. 2011;32(4):605-44.

Diepgen TL, Mahler V. The epidemiology of skin cancer. The British journal of dermatology. 2002;146 Suppl 61:1-6.

Duma N, Santana-Davila R, Molina JR. Non-Small Cell Lung Cancer: Epidemiology, Screening, Diagnosis, and Treatment. Mayo Clinic proceedings. 2019;94(8):1623-40.

Ebrahimi A, Gupta R, Luk P, Low TH, McDowell L, Magarey MJR, et al. Number of nodal metastases and the American Joint Committee on cancer staging of head and neck cutaneous squamous cell carcinoma: A multicenter study. Oral oncology. 2020;111:104855.

Eigentler TK, Leiter U, Häfner HM, Garbe C, Röcken M, Breuninger H. Survival of Patients with Cutaneous Squamous Cell Carcinoma: Results of a Prospective Cohort Study. The Journal of investigative dermatology. 2017;137(11):2309-15.

Eskander RN, Tewari KS. Chemotherapy in the treatment of metastatic, persistent, and recurrent cervical cancer. Curr Opin Obstet Gynecol. 2014;26(4):314-21.

Ettinger DS, Wood DE, Akerley W, Bazhenova LA, Borghaei H, Camidge DR, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 4.2016. Journal of the National Comprehensive Cancer Network : JNCCN. 2016;14(3):255-64.

Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global Cancer Observatory: Cancer Today Lyon, France: International Agency for Research on Cancer; 2018 [cited 2020 15 Jul]. Available from: https://gco.iarc.fr/today

Fonseca-Moutinho JA. Smoking and cervical cancer. ISRN Obstet Gynecol. 2011;2011:847684.

Ganti AK, Klein AB, Cotarla I, Seal B, Chou E. Update of Incidence, Prevalence, Survival, and Initial Treatment in Patients With Non-Small Cell Lung Cancer in the US. JAMA oncology. 2021.

Goldenberg G, Karagiannis T, Palmer JB, Lotya J, O'Neill C, Kisa R, et al. Incidence and prevalence of basal cell carcinoma (BCC) and locally advanced BCC (LABCC) in a large commercially insured population in the United States: A retrospective cohort study. Journal of the American Academy of Dermatology. 2016;75(5):957-66.e2.

Granger EE, Ran NA, Groover MK, Koyfman SA, Vidimos AT, Wysong A, et al. Most cutaneous squamous cell carcinoma recurrences occur in the first 3 years after diagnosis: A multicenter retrospective cohort study. Journal of the American Academy of Dermatology. 2024;91(5):957-60.

Grob JJ, Gonzalez R, Basset-Seguin N, Vornicova O, Schachter J, Joshi A, et al. Pembrolizumab Monotherapy for Recurrent or Metastatic Cutaneous Squamous Cell Carcinoma: A Single-Arm Phase II Trial (KEYNOTE-629). Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2020;38(25):2916-25.

Guleria I, Khosroshahi A, Ansari MJ, Habicht A, Azuma M, Yagita H, et al. A critical role for the programmed death ligand 1 in fetomaternal tolerance. The Journal of experimental medicine. 2005;202(2):231-7.

Guo A, Liu X, Li H, Cheng W, Song Y. The Global, Regional, National Burden of Cutaneous Squamous Cell Carcinoma (1990–2019) and Predictions to 2035. European Journal of Cancer Care. 2023;2023(1):5484597.

Halder RM, Bang KM. Skin cancer in blacks in the United States. Dermatol Clin. 1988;6(3):397-405.

Hanna GJ, Ruiz ES, LeBoeuf NR, Thakuria M, Schmults CD, Decaprio JA, et al. Real-world outcomes treating patients with advanced cutaneous squamous cell carcinoma with immune checkpoint inhibitors (CPI). Br J Cancer. 2020;123(10):1535-42.

Hartevelt MM, Bavinck JN, Kootte AM, Vermeer BJ, Vandenbroucke JP. Incidence of skin cancer after renal transplantation in The Netherlands. Transplantation. 1990;49(3):506-9.

Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Review, 1975-2016, based on November 2018 SEER data submission Bethesda, MD: National Cancer Institute; 2019 [updated 9 Apr 2020; cited Accessed 2020]. Available from: https://seer.cancer.gov/csr/1975_2016/

Huang S, Jiang J, Wong HS, Zhu P, Ji X, Wang D. Global burden and prediction study of cutaneous squamous cell carcinoma from 1990 to 2030: A systematic analysis and comparison with China. J Glob Health. 2024;14:04093.

Hughes BGM, Guminski A, Bowyer S, Migden MR, Schmults CD, Khushalani NI, et al. A phase 2 open-label study of cemiplimab in patients with advanced cutaneous squamous cell carcinoma (EMPOWER-CSCC-1): Final long-term analysis of groups 1, 2, and 3, and primary

analysis of fixed-dose treatment group 6. Journal of the American Academy of Dermatology. 2025;92(1):68-77.

Huo D, Anderson D, Palmer JR, Herbst AL. Incidence rates and risks of diethylstilbestrol-related clear-cell adenocarcinoma of the vagina and cervix: Update after 40-year follow-up. Gynecologic oncology. 2017;146(3):566-71.

Iachina M, Jakobsen E, Møller H, Lüchtenborg M, Mellemgaard A, Krasnik M, et al. The effect of different comorbidities on survival of non-small cells lung cancer patients. Lung. 2015;193(2):291-7.

Islami F, Fedewa SA, Jemal A. Trends in cervical cancer incidence rates by age, race/ethnicity, histological subtype, and stage at diagnosis in the United States. Prev Med. 2019;123:316-23.

Jabbour S, et al. Pembrolizumab Plus Platinum Chemotherapy and Radiotherapy for Unresectable, Locally Advanced, Stage 3 NSCLC: KEYNOTE-799. Int J Radiat Oncol Biol Phys. 2021;111(3S):S9-S10.

Jensen P, Hansen S, Møller B, Leivestad T, Pfeffer P, Geiran O, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. Journal of the American Academy of Dermatology. 1999;40(2 Pt 1):177-86.

Joseph MG, Zulueta WP, Kennedy PJ. Squamous cell carcinoma of the skin of the trunk and limbs: the incidence of metastases and their outcome. Aust N Z J Surg. 1992;62(9):697-701.

Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. The New England journal of medicine. 2015;372(8):711-23.

Karia PS, Morgan FC, Califano JA, Schmults CD. Comparison of Tumor Classifications for Cutaneous Squamous Cell Carcinoma of the Head and Neck in the 7th vs 8th Edition of the AJCC Cancer Staging Manual. JAMA dermatology. 2018;154(2):175-81.

Kim JYS, Kozlow JH, Mittal B, Moyer J, Olenecki T, Rodgers P. Guidelines of care for the management of cutaneous squamous cell carcinoma. Journal of the American Academy of Dermatology. 2018;78(3):560-78.

Kitagawa R, Katsumata N, Shibata T, Kamura T, Kasamatsu T, Nakanishi T, et al. Paclitaxel Plus Carboplatin Versus Paclitaxel Plus Cisplatin in Metastatic or Recurrent Cervical Cancer: The Open-Label Randomized Phase III Trial JCOG0505. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(19):2129-35.

Kocher F, Hilbe W, Seeber A, Pircher A, Schmid T, Greil R, et al. Longitudinal analysis of 2293 NSCLC patients: a comprehensive study from the TYROL registry. Lung cancer (Amsterdam, Netherlands). 2015;87(2):193-200.

Koh D, Wang H, Lee J, Chia KS, Lee HP, Goh CL. Basal cell carcinoma, squamous cell carcinoma and melanoma of the skin: analysis of the Singapore Cancer Registry data 1968-97. The British journal of dermatology. 2003;148(6):1161-6.

Kosmas C, Mylonakis N, Tsakonas G, Vorgias G, Karvounis N, Tsavaris N, et al. Evaluation of the paclitaxel-ifosfamide-cisplatin (TIP) combination in relapsed and/or metastatic cervical cancer. Br J Cancer. 2009;101(7):1059-65.

Lai B, Shen Y, Guminski A, Shumack S, Mulligan SP. Metastatic squamous cell carcinoma in chronic lymphocytic leukaemia in a haematology-dermatology multidisciplinary clinic. Australas J Dermatol. 2023;64(2):291-5.

Lampros TD, Cobanoglu A, Parker F, Ratkovec R, Norman DJ, Hershberger R. Squamous and basal cell carcinoma in heart transplant recipients. J Heart Lung Transplant. 1998;17(6):586-91.

Lang R, Welponer T, Richtig E, Wolf I, Hoeller C, Hafner C, et al. Nivolumab for locally advanced and metastatic cutaneous squamous cell carcinoma (NIVOSQUACS study)-Phase II data covering impact of concomitant haematological malignancies. Journal of the European Academy of Dermatology and Venereology : JEADV. 2023;37(9):1799-810.

Lear JT, Tan BB, Smith AG, Bowers W, Jones PW, Heagerty AH, et al. Risk factors for basal cell carcinoma in the UK: case-control study in 806 patients. Journal of the Royal Society of Medicine. 1997;90(7):371-4.

Legge F, Chiantera V, Macchia G, Fagotti A, Fanfani F, Ercoli A, et al. Clinical outcome of recurrent locally advanced cervical cancer (LACC) submitted to primary multimodality therapies. Gynecologic oncology. 2015;138(1):83-8.

Leiter U, Keim U, Eigentler T, Katalinic A, Holleczek B, Martus P, et al. Incidence, Mortality, and Trends of Nonmelanoma Skin Cancer in Germany. The Journal of investigative dermatology. 2017;137(9):1860-7.

Lergenmuller S, Rueegg CS, Perrier F, Robsahm TE, Green AC, Lund E, et al. Lifetime Sunburn Trajectories and Associated Risks of Cutaneous Melanoma and Squamous Cell Carcinoma Among a Cohort of Norwegian Women. JAMA dermatology. 2022;158(12):1367-77.

Li H, Wu X, Cheng X. Advances in diagnosis and treatment of metastatic cervical cancer. J Gynecol Oncol. 2016;27(4):e43.

Lin C, Tripcony L, Keller J, Poulsen M, Martin J, Jackson J, et al. Perineural infiltration of cutaneous squamous cell carcinoma and basal cell carcinoma without clinical features. Int J Radiat Oncol Biol Phys. 2012;82(1):334-40.

Lin SH, Lin Y, Yao L, Kalhor N, Carter BW, Altan M, et al. Phase II Trial of Concurrent Atezolizumab With Chemoradiation for Unresectable NSCLC. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2020;15(2):248-57.

Liu BY, O'Malley J, Mori M, Fagnan LJ, Lieberman D, Morris CD, et al. The association of type and number of chronic diseases with breast, cervical, and colorectal cancer screening. J Am Board Fam Med. 2014;27(5):669-81.

Liu J, Ebrahimi A, Low TH, Gao K, Palme CE, Sydney C, et al. Predictive value of the 8th edition American Joint Commission Cancer (AJCC) nodal staging system for patients with cutaneous squamous cell carcinoma of the head and neck. J Surg Oncol. 2018;117(4):765-72.

Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. The British journal of dermatology. 2012;166(5):1069-80.

Long HJ, 3rd, Bundy BN, Grendys EC, Jr., Benda JA, McMeekin DS, Sorosky J, et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005;23(21):4626-33.

Lortet-Tieulent J, Renteria E, Sharp L, Weiderpass E, Comber H, Baas P, et al. Convergence of decreasing male and increasing female incidence rates in major tobacco-related cancers in Europe in 1988-2010. European journal of cancer (Oxford, England : 1990). 2015;51(9):1144-63.

Lorusso D, Ferrandina G, Pignata S, Ludovisi M, Vigano R, Scalone S, et al. Evaluation of pemetrexed (Alimta, LY231514) as second-line chemotherapy in persistent or recurrent carcinoma of the cervix: the CERVIX 1 study of the MITO (Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies) Group. Annals of oncology : official journal of the European Society for Medical Oncology. 2010;21(1):61-6.

Louie KS, de Sanjose S, Diaz M, Castellsagué X, Herrero R, Meijer CJ, et al. Early age at first sexual intercourse and early pregnancy are risk factors for cervical cancer in developing countries. Br J Cancer. 2009;100(7):1191-7.

Lounas M, Ylitalo L, Salmi T, Jernman J, Palve J, Luukkaala T, et al. Recent Changes in the Incidence and Characteristics of Cutaneous Squamous Cell Carcinomas in Finland from 2006 to 2020: A Retrospective Cohort Study. Acta dermato-venereologica. 2024;104:adv39891.

Madan V, Lear JT, Szeimies RM. Non-melanoma skin cancer. Lancet (London, England). 2010;375(9715):673-85.

Marth C, Landoni F, Mahner S, McCormack M, Gonzalez-Martin A, Colombo N. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2017;28(suppl_4):iv72-iv83.

Maubec E, Petrow P, Scheer-Senyarich I, Duvillard P, Lacroix L, Gelly J, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(25):3419-26.

McCusker M, Basset-Seguin N, Dummer R, Lewis K, Schadendorf D, Sekulic A, et al. Metastatic basal cell carcinoma: prognosis dependent on anatomic site and spread of disease. European journal of cancer (Oxford, England : 1990). 2014;50(4):774-83.

Migden MR, Chang ALS, Dirix L, Stratigos AJ, Lear JT. Emerging trends in the treatment of advanced basal cell carcinoma. Cancer treatment reviews. 2018;64:1-10.

Migden MR, Guminski A, Gutzmer R, Dirix L, Lewis KD, Combemale P, et al. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial. The Lancet Oncology. 2015;16(6):716-28.

Miller DS, Blessing JA, Bodurka DC, Bonebrake AJ, Schorge JO. Evaluation of pemetrexed (Alimta, LY231514) as second line chemotherapy in persistent or recurrent carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecologic oncology. 2008;110(1):65-70.

Modesitt SC, van Nagell JR, Jr. The impact of obesity on the incidence and treatment of gynecologic cancers: a review. Obstet Gynecol Surv. 2005;60(10):683-92.

Mohan SV, Chang AL. Advanced Basal Cell Carcinoma: Epidemiology and Therapeutic Innovations. Current dermatology reports. 2014;3(1):40-5.

Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda J, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2004;22(15):3113-9.

Moreno V, Bosch FX, Muñoz N, Meijer CJ, Shah KV, Walboomers JM, et al. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. Lancet (London, England). 2002;359(9312):1085-92.

Muderspach LI, Blessing JA, Levenback C, Moore JL, Jr. A Phase II study of topotecan in patients with squamous cell carcinoma of the cervix: a gynecologic oncology group study. Gynecologic oncology. 2001;81(2):213-5.

Muggia FM, Blessing JA, Method M, Miller DS, Johnson GA, Lee RB, et al. Evaluation of vinorelbine in persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecologic oncology. 2004;92(2):639-43.

Muggia FM, Blessing JA, Waggoner S, Berek JS, Monk BJ, Sorosky J, et al. Evaluation of vinorelbine in persistent or recurrent nonsquamous carcinoma of the cervix: a Gynecologic Oncology Group Study. Gynecologic oncology. 2005;96(1):108-11.

Muñoz N, Franceschi S, Bosetti C, Moreno V, Herrero R, Smith JS, et al. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. Lancet (London, England). 2002;359(9312):1093-101.

Muzic JG, Schmitt AR, Wright AC, Alniemi DT, Zubair AS, Olazagasti Lourido JM, et al. Incidence and Trends of Basal Cell Carcinoma and Cutaneous Squamous Cell Carcinoma: A Population-Based Study in Olmsted County, Minnesota, 2000 to 2010. Mayo Clinic proceedings. 2017;92(6):890-8.

Naidoo J, Page DB, Li BT, Connell LC, Schindler K, Lacouture ME, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Annals of oncology : official journal of the European Society for Medical Oncology. 2015;26(12):2375-91.

National Cancer Institute. Non-Small Cell Lung Cancer Treatment (PDQ®)–Health Professional Version 2019 [updated 7 May 2020; cited 2020 10 June]. Available from: www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology-Non-small cell lung cancer v6 2021 [cited 2021 26 Oct]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

Nguyen-Nielsen M, Wang L, Pedersen L, Olesen AB, Hou J, Mackey H, et al. The incidence of metastatic basal cell carcinoma (mBCC) in Denmark, 1997-2010. European journal of dermatology : EJD. 2015;25(5):463-8.

Oishi S, Kudaka W, Toita T, Ariga T, Nakamoto T, Wakayama A, et al. Prognostic Factors and Treatment Outcome for Patients with Stage IVB Cervical Cancer. Anticancer Res. 2016;36(7):3471-5.

Olsen CM, Pandeya N, Ragaini BS, Neale RE, Whiteman DC. International patterns and trends in the incidence of melanoma and cutaneous squamous cell carcinoma, 1989-2020. The British journal of dermatology. 2024;190(4):492-500.

Osmani L, Askin F, Gabrielson E, Li QK. Current WHO guidelines and the critical role of immunohistochemical markers in the subclassification of non-small cell lung carcinoma (NSCLC): Moving from targeted therapy to immunotherapy. Semin Cancer Biol. 2018;52(Pt 1):103-9.

Penson RT, Huang HQ, Wenzel LB, Monk BJ, Stockman S, Long HJ, 3rd, et al. Bevacizumab for advanced cervical cancer: patient-reported outcomes of a randomised, phase 3 trial (NRG Oncology-Gynecologic Oncology Group protocol 240). The Lancet Oncology. 2015;16(3):301-11.

Peters S, Felip E, Dafni U, Belka C, Guckenberger M, Irigoyen A, et al. Safety evaluation of nivolumab added concurrently to radiotherapy in a standard first line chemo-radiotherapy regimen in stage III non-small cell lung cancer-The ETOP NICOLAS trial. Lung cancer (Amsterdam, Netherlands). 2019;133:83-7.

Pham KN, Cullen J, Hurwitz LM, Wolff EM, Levie KE, Odem-Davis K, et al. Prospective Quality of Life in Men Choosing Active Surveillance Compared to Those Biopsied but not Diagnosed with Prostate Cancer. J Urol. 2016;196(2):392-8.

Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2018;29(Suppl 4):iv192-iv237.

Porceddu SV, Bressel M, Poulsen MG, Stoneley A, Veness MJ, Kenny LM, et al. Postoperative Concurrent Chemoradiotherapy Versus Postoperative Radiotherapy in High-Risk Cutaneous Squamous Cell Carcinoma of the Head and Neck: The Randomized Phase III TROG 05.01 Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(13):1275-83.

Poulalhon N, Dalle S, Balme B, Thomas L. Fast-growing cutaneous squamous cell carcinoma in a patient treated with vismodegib. Dermatology (Basel, Switzerland). 2015;230(2):101-4.

Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: Incidence, risk factors, diagnosis, and staging. Journal of the American Academy of Dermatology. 2018;78(2):237-47.

Queirolo P, Cinquini M, Argenziano G, Bassetto F, Bossi P, Boutros A, et al. Guidelines for the diagnosis and treatment of cutaneous squamous cell carcinoma: a GRADE approach for evidence evaluation and recommendations by the Italian Association of Medical Oncology. ESMO Open. 2024;9(5):103005.

Reck M, Popat S, Reinmuth N, De Ruysscher D, Kerr KM, Peters S. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2014;25 Suppl 3:iii27-39.

Ridge CA, McErlean AM, Ginsberg MS. Epidemiology of lung cancer. Seminars in interventional radiology. 2013;30(2):93-8.

Robsahm TE, Helsing P, Veierod MB. Cutaneous squamous cell carcinoma in Norway 1963-2011: increasing incidence and stable mortality. Cancer medicine. 2015;4(3):472-80.

Rogers HW, Weinstock MA, Harris AR, Hinckley MR, Feldman SR, Fleischer AB, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. Archives of dermatology. 2010;146(3):283-7.

Rose PG, Ali S, Watkins E, Thigpen JT, Deppe G, Clarke-Pearson DL, et al. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(19):2804-10.

Salzmann M, Leiter U, Loquai C, Zimmer L, Ugurel S, Gutzmer R, et al. Programmed cell death protein 1 inhibitors in advanced cutaneous squamous cell carcinoma: real-world data of a retrospective, multicenter study. European journal of cancer (Oxford, England : 1990). 2020;138:125-32.

Schiffman M, Wentzensen N, Wacholder S, Kinney W, Gage JC, Castle PE. Human papillomavirus testing in the prevention of cervical cancer. Journal of the National Cancer Institute. 2011;103(5):368-83.

Schilder RJ, Blessing J, Cohn DE. Evaluation of gemcitabine in previously treated patients with non-squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecologic oncology. 2005;96(1):103-7.

Schmults CD, Karia PS, Carter JB, Han J, Qureshi AA. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma: a 10-year, single-institution cohort study. JAMA dermatology. 2013;149(5):541-7.

SEER*Explorer: An interactive website for SEER cancer statistics. Surveillance Research Program, National Cancer Institute; [cited 2021 29 jun]. Available from: https://seer.cancer.gov/explorer/

Sekulic A, Migden MR, Lewis K, Hainsworth JD, Solomon JA, Yoo S, et al. Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12-month update of efficacy and safety of vismodegib in advanced BCC. Journal of the American Academy of Dermatology. 2015;72(6):1021-6.e8.

Sekulic A, Migden MR, Oro AE, Dirix L, Lewis KD, Hainsworth JD, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. The New England journal of medicine. 2012;366(23):2171-9.

Sekulic A, Von Hoff D. Hedgehog Pathway Inhibition. Cell. 2016;164(5):831.

Shankar G, Pendley C, Stein KE. A risk-based bioanalytical strategy for the assessment of antibody immune responses against biological drugs. Nature biotechnology. 2007;25(5):555-61.

Shin DM, Glisson BS, Khuri FR, Clifford JL, Clayman G, Benner SE, et al. Phase II and biologic study of interferon alfa, retinoic acid, and cisplatin in advanced squamous skin cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2002;20(2):364-70.

Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA: a cancer journal for clinicians. 2021;71(1):7-33.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA: a cancer journal for clinicians. 2016;66(1):7-30.

Simard EP, Naishadham D, Saslow D, Jemal A. Age-specific trends in black-white disparities in cervical cancer incidence in the United States: 1975-2009. Gynecologic oncology. 2012;127(3):611-5.

Simms KT, Steinberg J, Caruana M, Smith MA, Lew JB, Soerjomataram I, et al. Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020-99: a modelling study. The Lancet Oncology. 2019;20(3):394-407.

Soleymani T, Brodland DG, Arzeno J, Sharon DJ, Zitelli JA. Clinical outcomes of high-risk cutaneous squamous cell carcinomas treated with Mohs surgery alone: An analysis of local recurrence, regional nodal metastases, progression-free survival, and disease-specific death. Journal of the American Academy of Dermatology. 2023;88(1):109-17.

Stang A, Khil L, Kajüter H, Pandeya N, Schmults CD, Ruiz ES, et al. Incidence and mortality for cutaneous squamous cell carcinoma: comparison across three continents. Journal of the European Academy of Dermatology and Venereology : JEADV. 2019;33 Suppl 8(Suppl 8):6-10.

Stenbygaard LE, Sørensen JB, Olsen JE. Metastatic pattern at autopsy in non-resectable adenocarcinoma of the lung--a study from a cohort of 259 consecutive patients treated with chemotherapy. Acta oncologica (Stockholm, Sweden). 1997;36(3):301-6.

Stevens JS, Murad F, Smile TD, O'Connor DM, Ilori E, Koyfman S, et al. Validation of the 2022 National Comprehensive Cancer Network Risk Stratification for Cutaneous Squamous Cell Carcinoma. JAMA dermatology. 2023;159(7):728-35.

Stevens VW, Stenehjem DD, Patterson OV, Kamauu AWC, Yim YM, Morlock RJ, et al. Characterization and survival of patients with metastatic basal cell carcinoma in the Department of Veterans Affairs: a retrospective electronic health record review. Archives of dermatological research. 2018;310(6):505-13.

Stratigos A, Garbe C, Lebbe C, Malvehy J, del Marmol V, Pehamberger H, et al. Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. European journal of cancer (Oxford, England : 1990). 2015;51(14):1989-2007.

Stratigos AJ, Garbe C, Dessinioti C, Lebbe C, van Akkooi A, Bataille V, et al. European consensus-based interdisciplinary guideline for invasive cutaneous squamous cell carcinoma. Part 1: Diagnostics and prevention-Update 2023. European journal of cancer (Oxford, England : 1990). 2023;193:113251.

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a cancer journal for clinicians. 2021;71(3):209-49.

Taarnhøj GA, Christensen IJ, Lajer H, Fuglsang K, Jeppesen MM, Kahr HS, et al. Risk of recurrence, prognosis, and follow-up for Danish women with cervical cancer in 2005-2013: A national cohort study. Cancer. 2018;124(5):943-51.

Takeuchi S, Dobashi K, Fujimoto S, Tanaka K, Suzuki M, Terashima Y, et al. [A late phase II study of CPT-11 on uterine cervical cancer and ovarian cancer. Research Groups of CPT-11 in Gynecologic Cancers]. Gan to kagaku ryoho Cancer & chemotherapy. 1991;18(10):1681-9.

Tejera-Vaquerizo A, Descalzo-Gallego MA, Otero-Rivas MM, Posada-García C, Rodríguez-Pazos L, Pastushenko I, et al. Skin Cancer Incidence and Mortality in Spain: A Systematic Review and Meta-Analysis. Actas dermo-sifiliograficas. 2016;107(4):318-28.

Tewari KS, Monk BJ. New strategies in advanced cervical cancer: from angiogenesis blockade to immunotherapy. Clinical cancer research : an official journal of the American Association for Cancer Research. 2014a;20(21):5349-58.

Tewari KS, Sill MW, Long HJ, Penson RT, Huang H, Ramondetta LM, et al. Improved Survival with Bevacizumab in Advanced Cervical Cancer. New England Journal of Medicine. 2014b;370(8):734-43.

Tewari KS, Sill MW, Monk BJ, Penson RT, Long HJ, 3rd, Poveda A, et al. Prospective Validation of Pooled Prognostic Factors in Women with Advanced Cervical Cancer Treated with Chemotherapy with/without Bevacizumab: NRG Oncology/GOG Study. Clinical cancer

research : an official journal of the American Association for Cancer Research. 2015;21(24):5480-7.

Tokez S, Wakkee M, Louwman M, Noels E, Nijsten T, Hollestein L. Assessment of Cutaneous Squamous Cell Carcinoma (cSCC) In situ Incidence and the Risk of Developing Invasive cSCC in Patients With Prior cSCC In situ vs the General Population in the Netherlands, 1989-2017. JAMA dermatology. 2020;156(9):973-81.

Vaccarella S, Herrero R, Snijders PJ, Dai M, Thomas JO, Hieu NT, et al. Smoking and human papillomavirus infection: pooled analysis of the International Agency for Research on Cancer HPV Prevalence Surveys. Int J Epidemiol. 2008;37(3):536-46.

van Brummelen EM, Ros W, Wolbink G, Beijnen JH, Schellens JH. Antidrug Antibody Formation in Oncology: Clinical Relevance and Challenges. Oncologist. 2016;21(10):1260-8.

Venables ZC, Autier P, Nijsten T, Wong KF, Langan SM, Rous B, et al. Nationwide Incidence of Metastatic Cutaneous Squamous Cell Carcinoma in England. JAMA dermatology. 2019a;155(3):298-306.

Venables ZC, Nijsten T, Wong KF, Autier P, Broggio J, Deas A, et al. Epidemiology of basal and cutaneous squamous cell carcinoma in the U.K. 2013-15: a cohort study. The British journal of dermatology. 2019b;181(3):474-82.

Verkerk K, Geurts BS, Zeverijn LJ, van der Noort V, Verheul HMW, Haanen J, et al. Cemiplimab in locally advanced or metastatic cutaneous squamous cell carcinoma: prospective real-world data from the DRUG Access Protocol. Lancet Reg Health Eur. 2024;39:100875.

Verloop J, van Leeuwen FE, Helmerhorst TJM, de Kok I, van Erp EJM, van Boven HH, et al. Risk of cervical intra-epithelial neoplasia and invasive cancer of the cervix in DES daughters. Gynecologic oncology. 2017;144(2):305-11.

Verschraegen CF, Levy T, Kudelka AP, Llerena E, Ende K, Freedman RS, et al. Phase II study of irinotecan in prior chemotherapy-treated squamous cell carcinoma of the cervix. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1997;15(2):625-31.

Wang SS, Sherman ME, Hildesheim A, Lacey JV, Jr., Devesa S. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976-2000. Cancer. 2004;100(5):1035-44.

Wehner MR, Shive ML, Chren MM, Han J, Qureshi AA, Linos E. Indoor tanning and non-melanoma skin cancer: systematic review and meta-analysis. BMJ (Clinical research ed). 2012;345:e5909.

Wong CS, Strange RC, Lear JT. Basal cell carcinoma. BMJ (Clinical research ed). 2003;327(7418):794-8.

Wu S, Han J, Li WQ, Li T, Qureshi AA. Basal-cell carcinoma incidence and associated risk factors in U.S. women and men. American journal of epidemiology. 2013;178(6):890-7.

Xi LF, Koutsky LA, Castle PE, Edelstein ZR, Meyers C, Ho J, et al. Relationship between cigarette smoking and human papilloma virus types 16 and 18 DNA load. Cancer Epidemiol Biomarkers Prev. 2009;18(12):3490-6.

Xu MJ, Lazar AA, Garsa AA, Arron ST, Ryan WR, El-Sayed IH, et al. Major prognostic factors for recurrence and survival independent of the American Joint Committee on Cancer eighth edition staging system in patients with cutaneous squamous cell carcinoma treated with multimodality therapy. Head & neck. 2018;40(7):1406-14.

Zanetti R, Rosso S, Martinez C, Navarro C, Schraub S, Sancho-Garnier H, et al. The multicentre south European study 'Helios'. I: Skin characteristics and sunburns in basal cell and squamous cell carcinomas of the skin. Br J Cancer. 1996;73(11):1440-6.

Zarogoulidis K, Zarogoulidis P, Darwiche K, Boutsikou E, Machairiotis N, Tsakiridis K, et al. Treatment of non-small cell lung cancer (NSCLC). Journal of thoracic disease. 2013;5 Suppl 4(Suppl 4):S389-96.

ICH (2012). Addendum to ICH S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals: S6(R1).

# Annex 8 – Summary of Changes to the Risk Management Plan over Time

| Version | Approval date<br>Procedure | Change |
|---|---|---|
| 1.0 | Approved with Procedure: Initial marketing authorisation<br>Date of Approval (CHMP opinion date): 26 April 2019 | |
| 2.0 | | Part II Module SI: Epidemiology Information added for 2 new indications (BCC and NSCLC)<br>Part II Module SIII: Updated with clinical trial exposure data for studies R2810-ONC-620 and R2810-ONC-1624<br>Part II Module SIV: Updated with excluded populations for R2810-ONC-1620 and R2810-ONC-1624<br>Part II Module SV: Updated with post-authorisation exposure data by region<br>Part II Module SVII: Frequencies updated based on pooled data<br>Part III: R2810-ONC-1540 Group 6 status updated<br>Part IV: R2810-ONC-1540 Group 6 status updated<br>Added R2810-ONC-1620 mBCC PAES<br>Part VI: Updated to reflect changes elsewhere<br>Part VII: Literature references updated and Protocol R2810-ONC-1540 Amendment 7 (CSCC) attached<br>Summary of changes to RMP added to reflect changes elsewhere |
| 3.0 | | Part I: Product Overview updated to reflect changes elsewhere<br>Part II Module SI: Epidemiology information added for the new indication of CC)<br>Part II Module SIII: Updated with clinical trial exposure data for studies R2810-ONC-1620 and R2810-ONC-1676 |

| Version | Approval date<br>Procedure | Change |
|---|---|---|
| | | Part II Module SIV: Updated with excluded populations for R2810-ONC-1676<br>Part II Module SV: Updated with post-authorisation exposure data by region<br>Part II Module SVII: Risk frequencies updated based on pooled data<br>Part VI: Updated to reflect changes elsewhere<br>Part VII: Literature references updated<br>Summary of changes to RMP added |
| 4.0 | | Part I: updated to reflect changes elsewhere<br>Part II Module SI: Updated with epidemiology data for NSCLC combination cemiplimab/chemotherapy<br>Part II Module SIII: Updated with clinical trial exposure data for Study 1540 and Study 16113 Part 2.<br>Part II Module SIV: Updated with data for Study 16113 Part 2.<br>Part II Module SV: Updated with post-authorisation exposure data by region<br>Part II Module SVII: Risk frequencies updated based on pooled data<br>Part III: Updated to reflect completion of additional PV activities<br>Part IV: Updated to reflect completion of a post-authorisation efficacy study<br>Part VI: Updated to reflect changes elsewhere<br>Part VII: Annex 4 updated with new versions of follow-up questionnaires -format changes only, no change to key messages |