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Summary of the risk management plan (RMP) for Nivolumab BMS (nivolumab)

This is a summary of the risk management plan (RMP) for Nivolumab BMS, which details the measures to be taken in order to ensure that Nivolumab BMS is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Nivolumab BMS, which can be found on Nivolumab BMS's EPAR page.

Overview of disease epidemiology

Nivolumab BMS is a cancer medicine used to treat adults with a type of lung cancer known as squamous cell non-small cell lung cancer. Lung cancer is the most common cancer worldwide. It is the leading cause of cancer deaths in men and the second leading cause of cancer deaths in women. In 2012, there were about 410,000 newly diagnosed lung cancer cases in Europe.

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases and has several subtypes: the squamous cell subtype represents about 20 to 30% of all lung cancer. At diagnosis, 10-15% of NSCLC patients have locally advanced cancer (stage IIIB), and 40% of patients have metastatic cancer (stage IV, when the cancer has spread to other parts of the body).

Summary of treatment benefits

Nivolumab BMS contains the active substance nivolumab and is given by infusion (drip) into a vein. It has been shown to improve patients' survival in one main study involving 272 patients with previously treated squamous NSCLC that was advanced or had spread throughout the body. Treatment with Nivolumab BMS was compared with another cancer medicine, docetaxel, and the main measure of effectiveness was overall survival (how long patients lived). The average survival among 135 patients given Nivolumab BMS was around 9 months, whereas among the 137 patients given docetaxel it was 6 months. Supportive information was also provided from another study indicating that Nivolumab BMS could produce a response in patients whose disease had progressed despite several previous treatments.

Unknowns relating to treatment benefits

Studies to confirm the longer-term effects of Nivolumab BMS in patients with NSCLC are ongoing. The safety and effectiveness of the medicine in patients less than 18 years of age, as well as those with severely reduced liver and kidney function, or with auto-immune diseases (conditions where the immune system attacks the patient's own body) have not been formally studied.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Immune-related pneumonitis (lung inflammation resulting from activity of the immune system)	Nivolumab BMS increases the risk of lung inflammation. In clinical trials, between 5 and 7 patients in 100 developed lung inflammation, sometimes fatal. Signs or symptoms may include dry cough and shortness of breath.	In the event of lung inflammation, treatment with Nivolumab BMS may need to be temporarily or permanently stopped by the doctor, depending on the severity. Prompt recognition of signs and symptoms and implementation of the recommended management guidelines may help prevent serious complications such as respiratory failure. Patients will be provided with an alert card warning them of the risk of lung inflammation and how to recognise the symptoms, and should contact their doctor right away if these occur or worsen.
Immune-related colitis (inflammation of the gut resulting from activity of the immune system)	Nivolumab BMS increases the risk of diarrhoea or colitis. In clinical trials, 16 to 18 patients in 100 developed diarrhoea or colitis with the medicine. Signs and symptoms may include watery, loose or soft stools, an increased number of bowel movements, blood in stools or dark-coloured stools and pain or tenderness in the stomach area.	In the event of diarrhoea or colitis, treatment with Nivolumab BMS may need to be temporarily or permanently stopped by the doctor, depending on the severity. Prompt recognition of signs and symptoms and implementation of the recommended management guidelines may help prevent serious complications such as gut perforation (developing a hole in the wall of the gut) or severe colitis requiring colectomy (surgery to remove a part of the gut). Patients will be provided with an alert card warning them of the risk of gut inflammation and how to recognise the symptoms, and should contact their doctor right away if these occur or worsen.
Immune-related hepatitis (liver inflammation resulting from activity of the immune system)	Nivolumab BMS increases the risk of hepatitis. In clinical trials, 2 to 3 patients in 100 developed abnormal liver test results. Signs and symptoms of hepatitis may include eye or skin yellowing (jaundice), pain on the right side of the stomach area and tiredness.	Patients should be monitored for signs and symptoms of hepatitis such as an increase in blood levels of transaminases and total bilirubin levels. In the event of abnormal liver enzyme tests, doctors might consider stopping treatment with Nivolumab BMS temporarily or permanently. Prompt review of blood tests, recognition of signs and symptoms and implementation of the recommended management guidelines may help prevent serious complications. Patients will be provided with an alert

Risk	What is known	Preventability
		card warning them of the risk of hepatitis and how to recognise the symptoms, and should contact their doctor right away if these occur or worsen.
Immune-related nephritis or renal dysfunction (kidney inflammation or kidney problems resulting from activity of the immune system)	Nivolumab BMS increases the risk of kidney inflammation. In clinical trials, between 5 and 12 patients in 100 developed kidney inflammation. Signs or symptoms may include passing less urine.	Patients should be monitored for signs and symptoms of kidney problems. In the event of nephritis or kidney dysfunction, doctors might consider stopping treatment with Nivolumab BMS temporarily or permanently. Prompt recognition of signs and symptoms, prompt review of blood tests and implementation of the recommended management guidelines may help prevent serious complications. Patients will be provided with an alert card warning them of the risk of kidney problems and how to recognise the symptoms, and should contact their doctor right away if these occur or worsen.
Immune-related endocrinopathies (problems with hormone-producing organs resulting from activity of the immune system)	Nivolumab BMS increases the risk of inflammation of hormone-producing organs (endocrine glands such as thyroid, adrenal, or pituitary glands) and may affect how these glands work. In clinical trials, 7 to 9 patients in 100 developed disorders of hormone-producing glands. Signs or symptoms of endocrine gland problems may include headaches, tiredness, and weight changes.	Patients should be monitored for signs and symptoms of endocrinopathies. In the event of an endocrinopathy, treatment with Nivolumab BMS should be stopped temporarily or permanently. Prompt recognition of signs and symptoms and implementation of the recommended management guidelines may help prevent serious complications such as adrenal crisis. Patients will be provided with an alert card warning them of the risk of endocrine gland problems and how to recognise the symptoms, and should contact their doctor right away if these occur or worsen.
Immune-related rash	Nivolumab BMS increases the risk of rash. In clinical trials, between 18 and 23 patients in 100 developed rash. Signs or symptoms of severe skin reaction may include skin rash with or without itching, peeling of the skin, and dry skin.	Early detection and timely treatment are key to recovery and to prevent severe complications. Patients will be provided with an alert card warning them of the risk of skin problems and how to recognise the symptoms, and should contact their doctor right away if these occur or worsen. Physicians may start treatment with corticosteroids (in order to prevent more severe complications and reduce

Risk	What is known	Preventability
		the symptoms). If skin reactions occur, doctors may manage them with corticosteroids; treatment with Nivolumab BMS may be stopped temporarily or permanently depending on the severity.
Other immune-related adverse reactions	Selected other immune-related reactions, which are uncommon but considered important identified risks, include uveitis (inflammation of the middle layer of the eye), pancreatitis (inflammation of the pancreas), demyelination (loss of the protective insulating sheath around the nerves), Guillain-Barré syndrome (an immune system disorder that causes nerve inflammation and can result in pain, numbness, muscle weakness and difficulty walking), and myasthenic syndrome (another disorder resulting in muscle weakness). These immune-related reactions can be serious and life-threatening.	For suspected immune-related reactions, appropriate testing should be carried out to see if they may be related to treatment. The medicine should be stopped either temporarily or permanently, depending on the severity of the reaction, and appropriate treatment such as corticosteroids (anti-inflammatory medicines) should be given. Nivolumab BMS must be permanently stopped if any severe immune-related adverse reaction comes back and for any life-threatening immune-related adverse reaction.
Severe infusion reactions	Severe reactions to infusion (drip) into a vein affect less than one patient in 100 given Nivolumab BMS. However, life-threatening reactions may occur. Signs or symptoms may include throat or chest tightness, wheezing, skin rash or hives, dizziness, or lightheadedness.	Patients should not be given Nivolumab BMS if they have a history of allergic reactions to nivolumab or any other ingredients of the medicine. Patients should seek medical attention immediately if they start feeling unwell during or soon after the infusion of Nivolumab BMS.

Important potential risks

Risk	What is known
Effects on the developing baby (embryofetal toxicity)	Based on mechanism of action and data from animal studies, Nivolumab BMS may cause fetal harm when administered to a pregnant woman. Initial laboratory studies suggested that pregnant women exposed to Nivolumab BMS may be at risk of losing their fetus in the third trimester or of premature birth with an increased risk of death of the baby after birth.
Development of antibodies (immune response) against the medicine (immunogenicity)	Low rates of immunogenicity have been observed and no impact has been observed on safety or effectiveness even when patients were given a further dose after a long break. Theoretically, immunogenicity may lead to infusion reactions or reduced effectiveness.

Missing information

Risk	What is known
Use in children	The effect of Nivolumab BMS in patients below 18 years old is not known. Nivolumab BMS should not be used in children below 18 years of age.
Severely reduced liver or kidney function (severe hepatic and/or renal impairment)	The effect of Nivolumab BMS in patients with severe hepatic or renal impairment has not been studied.
Patients with autoimmune disease (conditions where the immune system attacks the patient's own body)	No formal clinical study has been conducted with Nivolumab BMS in patients with autoimmune disease.
Patients already receiving systemic immunosuppressants (medicines that suppress the immune system) before starting Nivolumab BMS	No formal study has been conducted.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Nivolumab BMS can be found on Nivolumab BMS's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Nivolumab BMS's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

Immune-related side effects

Risk minimisation measure: Healthcare Professional and Patient Educational material
Objective and rationale: Nivolumab BMS can increase the risks of immune-related pneumonitis, colitis,

Risk minimisation measure: Healthcare Professional and Patient Educational material
hepatitis, nephritis or renal dysfunction, endocrinopathies, rash, and other immune-related adverse reactions. Early recognition and appropriate management are important to prevent more severe complications and ensure the benefits of the medicine continue to outweigh the risks. Additional educational materials are intended to ensure that healthcare professionals and patients are aware of these risks and their appropriate management guidelines.
Description: 1. Adverse Reaction Management Guide for healthcare professionals, reminding them of the important identified risks related to the immune system, how to recognise these risks, and their appropriate management. 2. An Alert Card for patients, warning them of the risks and how to recognise symptoms, and reminding them of the importance of contacting their doctor promptly should these occur or worsen.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	**Objectives**	**Safety concerns / efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
CA209057: An Open-label Randomized Phase III Trial of BMS-936558 (Nivolumab BMS) versus Docetaxel in Previously Treated Metastatic NSQ NSCLC	To compare overall survival.	Efficacy in previously treated advanced non-squamous cell NSCLC	Started	Interim CSR submission Q3 2015 / Final CSR submission Q3 2016
CA209234: Pattern of Use, Safety, and Effectiveness of Nivolumab BMS in Routine Oncology Practice.	To assess use pattern, effectiveness and safety of Nivolumab BMS, and management of important identified risks of Nivolumab BMS in patients with lung cancer or melanoma in routine oncology practice.	Postmarketing use safety profile, management and outcome of immune-related pneumonitis, colitis, hepatitis, nephritis or renal dysfunction, endocrinopathies, rash, other immune-related adverse reactions (uveitis, pancreatitis,	Planned	Final CSR submission: Q4 2024

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
		demyelination, Guillain-Barre syndrome, and myasthenic syndrome), and severe infusion reactions		
CA209037 and CA209066 analyses in patients with advanced melanoma	To continue the exploration of the optimal cut-off for PD-L1 positivity based on current assay method used to further elucidate its value as predictive of nivolumab efficacy.	Efficacy in advanced melanoma	Started	30-Sep-2015
CA209038 and CA209066 analyses	To further investigate the value biomarkers other than PD-L1 expression status at tumour cell membrane level by immunohistochemistry as predictive of nivolumab efficacy.	Efficacy in advanced melanoma	Started	30-Sep-2017
CA209009, CA209038 and CA209064 analyses	To further investigate at post-approval the relation between PD-L1 and PD-L2 expression in Phase 1 studies.	Relationship between PD-L1 and PD-L2 expression	Started	31-Mar-2017
CA209066 analyses	To further investigate the associative analyses between PD-L1 and PD-L2 expression.	Relationship between PD-L1 and PD-L2 expression	Started	31-Dec-2017
CA209009, CA209038 and	To further investigate at	Assessment of PD-L1 status	Started	30-Sep-2017

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
CA209064	post-approval the possible change in PD-L1 status of the tumour during treatment and/or tumour progression.			
CA209017: An Open-label Randomized Phase III Trial of BMS-936558 (Nivolumab) versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-small Cell Lung Cancer (NSCLC)	To compare overall survival.	Efficacy in previously treated advanced squamous cell NSCLC	Started	Updated data: 31-Dec-2015

Studies which are a condition of the marketing authorisation

The updated data from study CA209017 and the analyses from studies CA209009, CA209037, CA209038, CA209064 and CA209066 are conditions of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 07-2015.