Summary of the risk management plan (RMP) for Opdivo (nivolumab)

This is a summary of the risk management plan (RMP) for Opdivo, which details the measures to be taken in order to ensure that Opdivo 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 Opdivo, which can be found on Opdivo’s EPAR page.

Overview of disease epidemiology

Opdivo is a medicine which contains the active substance nivolumab. It is used to treat melanoma (a type of skin cancer) that has metastasised (spread to other parts of the body) or cannot be surgically removed. The number of people diagnosed with this cancer is increasing worldwide. In 2008, around 69,000 new melanomas occurred in 27 European countries. In about 6 out of 100 newly-diagnosed cases, the melanoma is inoperable or has metastasised. This suggests that newly-diagnosed inoperable or metastatic melanomas in these 27 European countries number over 4,000 per year.

Summary of treatment benefits

Opdivo has been shown to be effective in treating patients with advanced malignant melanoma (melanoma that could not be treated by surgery or had spread throughout the body) in two main studies.

The first study looked at 418 previously untreated advanced melanoma patients who received either Opdivo or a standard cancer medicine (dacarbazine). The study found that patients treated with Opdivo survived longer (on average for over 14 months) than patients who received dacarbazine (around 12 months).

The second study looked at 405 advanced melanoma patients whose disease had got worse despite previous treatment with a standard cancer medicine. Patients were given Opdivo or the investigator’s choice of cancer treatment (dacarbazine or a combination of carboplatin and paclitaxel). In this study, where patients were followed up for at least 6 months, around 32% (38 out of 120) of patients given Opdivo responded to treatment and had a reduction in their tumours compared with about 11% (5 out of 47) of patients given investigator’s choice of treatment.

Unknowns relating to treatment benefits

The benefits of Opdivo on its own or in combination in previously untreated patients or in those who did not respond to previous treatment are still being studied. Studies in children are also being carried out.
### Summary of safety concerns

#### Important identified risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
<th>Preventability</th>
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<tbody>
<tr>
<td>Immune-related pneumonitis (lung inflammation resulting from activity of the immune system)</td>
<td>Opdivo increases the risk of lung inflammation. In clinical trials, between 2 and 3 patients in 100 developed lung inflammation, sometimes fatal. Signs or symptoms may include dry cough and shortness of breath.</td>
<td>In the event of lung inflammation, doctors might consider stopping treatment with Opdivo temporarily or permanently, depending on the severity. Prompt recognition of signs and symptoms and implementation of the recommended management guidelines may 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.</td>
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<td>Immune-related colitis (inflammation of the gut resulting from activity of the immune system)</td>
<td>Nivolumab increases the risk of diarrhoea or colitis. In nivolumab clinical trials, 17 patients in 100 developed diarrhoea or colitis. 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.</td>
<td>In the event of diarrhoea or colitis, doctors might consider stopping treatment with Opdivo temporarily or permanently, depending on the severity. Prompt recognition of signs and symptoms and implementation of the recommended management guidelines may 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.</td>
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<tr>
<td>Immune-related hepatitis (liver inflammation resulting from activity of the immune system)</td>
<td>Nivolumab increases the risk of hepatitis. In nivolumab clinical trials, between 3 and 8 patients in 100 had abnormal liver tests. Signs and symptoms of hepatitis may include eye or skin yellowing (jaundice), pain on the right side of the stomach area and tiredness.</td>
<td>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 Opdivo temporarily or permanently. Prompt review of blood tests, recognition of signs and symptoms and implementation of the recommended management guidelines may prevent serious complications. Patients will be provided with an alert 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.</td>
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<tr>
<td>Immune-related nephritis (kidney inflammation) or kidney problems resulting from activity of the immune system</td>
<td>Nivolumab increases the risk of kidney inflammation. In nivolumab clinical trials, 2 patients in 100 developed kidney inflammation. Signs or symptoms may include production of smaller amounts of urine.</td>
<td>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 Opdivo temporarily or permanently. Prompt recognition of signs and symptoms, prompt review of blood tests and implementation of the recommended management guidelines may 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.</td>
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<td>Immune-related endocrinopathies (problems with hormone producing organs resulting from activity of the immune system)</td>
<td>Nivolumab increases the risk of inflammation of hormone-producing glands (thyroid, adrenal, or pituitary glands) and may affect how these glands work. In nivolumab clinical trials, 9 patients in 100 developed disorders of hormone-producing glands. Signs or symptoms of endocrine gland problems may include headaches, tiredness and weight changes.</td>
<td>Patients should be monitored for signs and symptoms of endocrinopathies. In the event of an endocrinopathy, treatment with Opdivo should be stopped temporarily or permanently. Prompt recognition of signs and symptoms and implementation of the recommended management guidelines may 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.</td>
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<tr>
<td>Immune-related rash</td>
<td>Nivolumab increases the risk of rash. In the clinical trials, between 35 and 41 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.</td>
<td>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 the severity of skin reactions).</td>
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### Important potential risks

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<tr>
<td>Effects on the developing baby</td>
<td>Based on its mechanism of action and data from animal studies, nivolumab may cause fetal harm when administered to a pregnant woman. A study in experimental models revealed damaged to the fetus, which suggested that pregnant women exposed to Opdivo may be at risk of losing their fetus in the third trimester or of giving birth prematurely. Therefore, Opdivo is not recommended in pregnant women, nor in women of childbearing potential not using effective contraception unless the benefit outweighs the potential risks. Effective contraception should be used for at least 5 months following the last dose of Opdivo.</td>
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<td>(embryofetal toxicity)</td>
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<td>Development of antibodies (immune</td>
<td>Theoretically, immunogenicity may lead to infusion reactions or reduced effectiveness. Although low rates of immunogenicity were seen, no impact has</td>
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### Risk

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<td>response) against the medicine (Immunogenicity)</td>
<td>been observed on safety or efficacy, even following prolonged dose interruptions and re-administration of the medicine.</td>
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<tr>
<td>Cardiac arrhythmias (heart rhythm problems)</td>
<td>In a study with previously untreated patients who were not eligible for surgery due to spread of their melanoma the incidence of cardiac arrhythmia with Opdivo was lower than with dacarbazine. However, in another study comparing nivolumab with cancer medicines called anti-CTLA4 medicines or BRAF inhibitors, the incidence of arrhythmias was higher in those given nivolumab.</td>
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### Missing information

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<tr>
<td>Use in children</td>
<td>The effect of Opdivo in patients below 18 years old is not known. Opdivo should not be used in children below 18 years of age.</td>
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<tr>
<td>Severely reduced liver and/or kidney function (severe liver and/or renal impairment)</td>
<td>The effect of Opdivo in patients with severely reduced liver or kidney function has not been studied. Opdivo must be given with caution in patients with moderately or severely reduced liver function.</td>
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<tr>
<td>Patients with autoimmune diseases</td>
<td>No formal study with Opdivo has been conducted in patients with autoimmune diseases.</td>
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<tr>
<td>Patients already receiving systemic immunosuppressants (medicines that suppress the immune system) before starting nivolumab</td>
<td>No formal study has been conducted.</td>
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### 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 Opdivo can be found on [Opdivo’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 Opdivo’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 pneumonitis, colitis, hepatitis, nephritis or renal dysfunction, endocrinopathies, rash, and other immune-related adverse reactions**

<table>
<thead>
<tr>
<th>Risk minimisation measure: Healthcare professional and patient educational material.</th>
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<tr>
<td><strong>Objective and rationale:</strong> To ensure that healthcare professionals and patients are aware of these risks and their appropriate management measures.</td>
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<td><strong>Description:</strong> The following educational materials will be provided to physicians and patients who are expected to use Opdivo:</td>
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<td>• adverse reaction management guide, for healthcare professionals, reminding them of the important identified risks related to the immune system, how to recognise these conditions, and their appropriate management.</td>
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<tr>
<td>• 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.</td>
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<td>These communication tools will provide the opportunity for reinforcing key messages about early recognition and appropriate management of important identified risks to maintain a favourable benefit-risk of Opdivo.</td>
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**Planned post-authorisation development plan**

**List of studies in post-authorisation development plan**

<table>
<thead>
<tr>
<th>Study/activity (including study number)</th>
<th>Objectives</th>
<th>Safety concerns /efficacy issue addressed</th>
<th>Status</th>
<th>Planned date for submission of (interim and) final results</th>
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<tr>
<td>CA209067: Phase 3, randomized, double-blind study in subjects treated with nivolumab monotherapy, ipilimumab monotherapy, and nivolumab combined with ipilimumab.</td>
<td>To compare overall survival.</td>
<td>Clinical efficacy in subjects with previously untreated, unresectable (non-operative) or metastatic (spread) melanoma.</td>
<td>Started</td>
<td>Interim CSR submission: 3Q2015 / Final CSR submission: 1Q2017.</td>
</tr>
<tr>
<td>CA209069: Phase 2, randomized double blind study in subjects treated with nivolumab combined with ipilimumab vs</td>
<td>To compare objective response rate.</td>
<td>Clinical efficacy in subjects with tumours that have a wild type (WT) BRAF gene (also known as non-mutated, the most common form of the gene), who have previously untreated</td>
<td>Started</td>
<td>Final CSR submission: 3Q2015.</td>
</tr>
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<tr>
<td>ipilimumab monotherapy.</td>
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<td>unresectable or metastatic melanoma.</td>
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<tr>
<td>CA209066: a Phase 3, randomized, double-blind study of nivolumab vs dacarbazine in subjects with BRAF wild type, previously untreated, unresectable or metastatic melanoma.</td>
<td>To compare overall survival, progression-free survival, and objective response rate.</td>
<td>Clinical efficacy in subjects with tumours that have non-mutated BRAF previously untreated unresectable or metastatic melanoma.</td>
<td>Started</td>
<td>The final clinical study report should be submitted by 30th June 2016.</td>
</tr>
<tr>
<td>CA209037: a Phase 3, randomized, open-label study of nivolumab vs investigator's choice in advanced (unresectable or metastatic) melanoma patients progressing post anti-CTLA-4 therapy.</td>
<td>To compare objective response rate, overall survival, and progression-free survival.</td>
<td>Clinical efficacy in subjects with advanced (unresectable or metastatic) melanoma.</td>
<td>Started</td>
<td>The updated data/study report should be submitted by 31st December 2015.</td>
</tr>
<tr>
<td>CA209234: Pattern of Use, Safety, and Effectiveness of Nivolumab in Routine Oncology Practice.</td>
<td>To assess use pattern, effectiveness, and safety of nivolumab, and management of important identified risks of nivolumab in patients with lung cancer or melanoma in routine oncology practice.</td>
<td>Postmarketing use, safety profile, management and outcome of immune-related pneumonitis, colitis, hepatitis, nephritis or renal dysfunction, endocrinopathies, rash, and other immune-related adverse reactions (uveitis, pancreatitis, demyelination, Guillain-Barré syndrome, and</td>
<td>Planned</td>
<td>Final CSR submission: 4Q2024.</td>
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<td>myasthenic syndrome), and infusion reactions.</td>
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**Studies which are a condition of the marketing authorisation**

None of the above studies are conditions of the marketing authorization.

**Summary of changes to the risk management plan over time**

Not applicable.

This summary was last updated in 05-2015.