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Opdivo (*nivolumab*)

An overview of Opdivo and why it is authorised in the EU

What is Opdivo and what is it used for?

Opdivo is a cancer medicine used to treat the following:

- melanoma, a type of skin cancer;
- a lung cancer called non-small cell lung cancer (NSCLC);
- advanced renal cell carcinoma, a kidney cancer;
- classical Hodgkin lymphoma, a cancer of the lymphocytes (a type of white blood cell);
- squamous cell cancer of the head and neck (SCCHN);
- urothelial cancer, a cancer of the bladder and urinary tract;
- malignant pleural mesothelioma (a cancer of the lining of the lungs);
- a kind of cancer of the colon or rectum (lower part of the gut) that is described as microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR);
- squamous oesophageal cancer (cancer of the oesophagus, the passage from mouth to stomach);
- oesophageal cancer and gastro-oesophageal junction cancer (cancer at the junction between the stomach and the oesophagus) after chemotherapy, radiotherapy and surgery;
- gastric (stomach), gastro-oesophageal junction or oesophageal adenocarcinoma.

The medicine is used in adults; for melanoma it is also used in adolescents from 12 years of age.

Opdivo is mainly used when cancers are advanced, unresectable (cannot be removed by surgery) or metastatic (have spread to other parts of the body), or when other treatments do not work.

For NSCLC that can be removed by surgery but is at high risk of coming back, Opdivo can also be given before surgery (neoadjuvant treatment). For melanoma, oesophageal cancer, gastro-oesophageal junction cancer and urothelial cancer, Opdivo is also used to help prevent the cancer from coming back after patients have had surgery (adjuvant treatment).

Opdivo works on cancer cells that produce a protein called PD-L1. For some cancers, Opdivo can only be used if tests confirm that the cancer cells produce enough PD-L1.

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Opdivo can be used on its own and, for some cancers, it is also used together with other cancer medicines such as cabozantinib, ipilimumab or platinum-based chemotherapy.

Opdivo contains the active substance nivolumab.

How is Opdivo used?

Treatment with Opdivo must be started and supervised by a doctor experienced in treating cancer. The medicine can only be obtained with a prescription.

Opdivo is given as an infusion (drip) into a vein. The dose and how often it is given depends on the condition it is being used for and whether it is used alone or in combination with other cancer medicines. The doctor may delay doses if certain side effects occur or stop treatment altogether for certain severe side effects.

For more information about using Opdivo, see the package leaflet or contact your doctor or pharmacist.

How does Opdivo work?

The active substance in Opdivo, nivolumab, is a monoclonal antibody, a type of protein that has been designed to attach to a receptor called PD-1 found on cells of the immune system called T cells. Cancer cells can produce proteins (PD-L1 and PD-L2) that attach to this receptor and switch off the activity of the T cells, preventing them from attacking the cancer. By attaching to the receptor, nivolumab prevents PD-L1 and PD-L2 from switching off the T cells, thereby increasing the ability of the immune system to kill cancer cells.

What benefits of Opdivo have been shown in studies?

Melanoma

Opdivo used on its own was studied in two main studies in adults with advanced melanoma who had not undergone surgery. The first study, involving 418 previously untreated advanced melanoma patients, found that patients treated with Opdivo lived longer than patients who received the cancer medicine dacarbazine: 73% of patients treated with Opdivo were alive after 12 months compared with 42% of patients given dacarbazine. In the second study, 405 patients with advanced melanoma whose disease had got worse despite previous treatment with a cancer medicine 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 a treatment chosen by their doctor (dacarbazine or a combination of carboplatin and paclitaxel).

A third study in 906 adults with stage IIIB, IIIC or IV melanoma who had surgery and who were at high risk of the cancer coming back compared Opdivo with ipilimumab. Patients treated with Opdivo lived on average 31 months before the cancer came back, or a new melanoma occurred or they died, compared with 24 months for patients treated with ipilimumab. A fourth study in 790 adults with stage IIB or IIC melanoma who had surgery compared Opdivo with placebo (a dummy treatment). After an average follow-up of 24 months, 19% of patients who took Opdivo had a recurrence of their cancer or a new melanoma or had died, compared with 32% of patients given placebo.

A fifth study in 945 previously untreated adults with advanced melanoma investigated Opdivo in combination with ipilimumab, Opdivo used alone or ipilimumab used alone. Patients given Opdivo plus ipilimumab lived for 11.5 months without their disease getting worse compared with 6.9 months for patients given only Opdivo and 2.9 months for patients given only ipilimumab. More patients were

alive after 2 years with Opdivo and ipilimumab treatment (64%) than with Opdivo alone (59%) or ipilimumab alone (45%). The study included patients whose cancer cells produced high levels of PD-L1 as well as patients whose cancer cells produced low levels of PD-L1. Improvements in the time patients lived without their disease getting worse when treated with Opdivo plus ipilimumab relative to Opdivo used on its own were only seen for patients whose cancer cells produced low levels of PD-L1.

As melanoma in adolescents is similar to the disease in adults, the data from adults apply to adolescents as well.

Data from adults, adolescents and children also showed that in the treatment of advanced melanoma and as adjuvant treatment of melanoma in adolescents aged 12 years and older, Opdivo behaves in a similar way to that seen in adults.

NSCLC

For a type of NSCLC known as non-squamous cancer, one main study involved 582 adults whose disease had got worse despite previous treatments. The average time patients lived with Opdivo was 12.2 months, compared with 9.4 months with docetaxel (another cancer medicine).

For another type of NSCLC known as squamous cancer, a study involving 272 adults showed that patients given Opdivo lived for 9.2 months after starting treatment, compared with 6.0 months in patients given docetaxel. Supportive information from another study indicated that Opdivo led to a response in patients with squamous NSCLC whose disease had worsened despite several previous treatments.

For metastatic NSCLC, a study involving 719 adults who had not previously been treated showed that patients given Opdivo in combination with ipilimumab and another cancer medicine lived on average for 14 months after starting treatment compared with 11 months in patients given other cancer medicines.

Another study involved 358 adults with NSCLC that had not spread and could be removed by surgery. Of the patients whose cancer produced PD-L1 and was at risk of coming back after surgery, 32% (26 out of 81) of patients who received Opdivo in combination with platinum-based chemotherapy before surgery had no detectable tumour in the lung tissue removed during surgery compared with 2% (2 out of 86) of those given platinum-based chemotherapy alone. In addition, patients who received chemotherapy alone lived an average of 21 months before the disease got worse or came back, or the patient died; for patients who received Opdivo with chemotherapy, this period could not be calculated because too few patients had experienced one of these events during an average follow up of 41 months.

Advanced renal cell carcinoma

Opdivo was compared with everolimus (another cancer medicine) in one main study involving 821 patients with advanced renal cell carcinoma whose disease had worsened despite previous treatment. Patients given Opdivo lived for 25.0 months, compared with 19.6 months for patients given everolimus.

Another main study involving 1,096 adults with previously untreated advanced renal cell carcinoma compared treatment with Opdivo and ipilimumab versus treatment with another cancer medicine, sunitinib. After 24 months, 66.5% of patients at moderate or high risk of their cancer getting worse given the combination were alive compared with 52.9% in the sunitinib group. In addition, 41.6% of patients (177 out of 423) responded to the treatment with the combination compared with 26.5% (112

out of 416) of those receiving sunitinib. The time patients lived before their disease got worse was 11.6 months with the combination compared with 8.4 with sunitinib.

A third main study compared treatment with Opdivo plus cabozantinib with sunitinib treatment alone in 651 patients with previously untreated advanced renal cell carcinoma or renal cell carcinoma that had spread. In this study, patients treated with Opdivo plus cabozantinib lived on average for around 17 months without their cancer getting worse while those treated with sunitinib lived for around 8 months without their cancer worsening.

Classical Hodgkin lymphoma

Opdivo was studied in one main study and a supportive study involving a total of 95 adults with classical Hodgkin lymphoma whose disease had not responded or had returned after autologous stem cell transplantation and treatment with the cancer medicine brentuximab vedotin. Opdivo was used on its own and not compared with any other medicine. After treatment, cancer cells were partially or completely cleared in around 66% of patients (63 out of 95).

Advanced SCCHN

Opdivo was investigated in one main study involving 361 adults with SCCHN whose cancer had worsened despite previous treatment with platinum medicines. Opdivo was used on its own and was compared with another cancer medicine (cetuximab, methotrexate or docetaxel) chosen by the treating doctor. Patients given Opdivo lived on average for 7.5 months, compared with 5.1 months in patients given other treatments.

Urothelial cancer

Opdivo was investigated in one main study involving 270 adults with urothelial cancer whose cancer got worse or returned despite previous treatment with platinum medicines. Opdivo was used on its own and not compared with any other medicine. In the study, 20% of patients (54 out of 270) responded to treatment with a reduction in the size of their tumour.

Another main study involving 709 patients at high risk of their urothelial cancer coming back after their cancer had been removed completely by surgery showed that Opdivo was effective at preventing the disease from returning in patients whose cancer produced PD-L1 protein. Patients in this group who were given placebo lived on average 8.4 months before their disease came back; for those treated with Opdivo, the period could not be calculated because the disease had not come back in many patients during an average follow up of 22 months.

Malignant pleural mesothelioma

A main study involving 605 patients with malignant pleural mesothelioma that could not be removed by surgery looked at how long patients lived when they received Opdivo with ipilimumab or when they received pemetrexed- and platinum-based chemotherapy. In this study, patients who received Opdivo lived on average for 18 months while patients who had chemotherapy lived for an average of 14 months.

Advanced colorectal cancer

A main study involving 119 patients with MSI-H or dMMR colon or rectal cancer examined the effect of treatment with a combination of Opdivo and ipilimumab. Around 65% of patients responded to treatment and had a reduction in tumour size.

Advanced squamous oesophageal cancer

A main study involved 419 adults with advanced or metastatic squamous oesophageal cancer whose disease had worsened or returned after treatment with fluoropyrimidine- and platinum-based chemotherapy or patients for whom these medicines were not suitable. In this study, patients treated with Opdivo lived for an average of 11 months compared with patients treated with docetaxel or paclitaxel who lived on average for 8 months.

Another main study involved 970 adults with previously untreated squamous oesophageal cancer that could not be removed by surgery, had come back or had spread. The study looked at either Opdivo plus ipilimumab or Opdivo plus chemotherapy compared with chemotherapy alone.

Patients whose cancer produced PD-L1 protein and who were treated with Opdivo plus ipilimumab lived on average for 13.7 months compared with 9.1 months for those treated with chemotherapy. There was no difference between the two treatments in the time patients lived without their disease worsening.

Patients whose cancer produced PD-L1 and who were treated with Opdivo plus chemotherapy lived on average for 15.4 months compared with 9.1 months for patients treated with chemotherapy alone. In addition, the time patients lived before their disease got worse was 6.9 months with Opdivo plus chemotherapy compared with 4.4 months for chemotherapy alone.

Localised (early) oesophageal cancer and gastro-oesophageal junction cancer

A main study of 794 patients looked at the effect of Opdivo in patients with localised oesophageal cancer and gastro-oesophageal junction cancer. All patients still had some cancer cells left in the body after chemotherapy, radiotherapy and surgery and were at high risk of the cancer coming back.

In this study, patients who received Opdivo lived on average for 22 months without their cancer coming back compared to 11 months for patients given placebo.

Advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma

In a main study that included 955 adults with previously untreated advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours have high levels of PD-L1 (defined as a combined positive score ≥5), Opdivo in combination with chemotherapy was compared with chemotherapy alone. Patients who received Opdivo and chemotherapy lived on average 8 months without their disease getting worse and 14 months overall. This compares with 6 months and 11 months respectively for patients who received chemotherapy only.

What are the risks associated with Opdivo?

For the full list of side effects and restrictions with Opdivo, see the package leaflet.

The most common side effects with Opdivo on its own (which may affect more than 1 in 10 people) include tiredness, pain in muscles and bones, diarrhoea, rash, cough, nausea (feeling sick), itching, decreased appetite, pain in the joints, constipation, difficulty breathing, pain in the abdomen, nose and throat infection, fever, headache, anaemia (low red blood cell counts) and vomiting. The safety profile in adolescents is comparable to that seen in adults.

Opdivo is also commonly associated with side effects related to the activity of the immune system on body organs. Most will go away with appropriate treatment or on stopping Opdivo.

Additional side effects may occur when Opdivo is used with other cancer medicines.

Why is Opdivo authorised?

The European Medicines Agency considered that Opdivo has been shown to benefit patients with certain advanced cancers (melanoma, NSCLC, renal cell carcinoma, malignant pleural mesothelioma, cancer of the colon or rectum as well as certain types of gastric and oesophageal cancers). Opdivo is also effective in preventing the cancer from coming back after surgery in patients with melanoma, oesophageal cancer, cancers at the junction of the oesophagus and the stomach, and urothelial cancer.

The medicine has also been shown to be effective in treating NSCLC before surgery, when the cancer produces PD-L1 and is at high risk of coming back.

Melanoma in adolescents is similar to the disease in adults and Opdivo behaves in a similar way in adults and adolescents. Therefore, when used in adolescents to treat advanced melanoma or to prevent melanoma from coming back after surgery, Opdivo is expected to provide similar benefits to those seen in adults.

Patients with urothelial cancer responded to treatment with Opdivo after other medical treatments had failed. For patients with classical Hodgkin lymphoma, although studies involved only a small number of patients, high response rates were seen in these patients, in whom other treatments had failed and who had few other treatment options.

Side effects with Opdivo are considered manageable with appropriate measures and are outweighed by the benefits. The Agency therefore decided that Opdivo's benefits are greater than its risks and recommended that it can be authorised for use in the EU.

What measures are being taken to ensure the safe and effective use of Opdivo?

The company will provide an alert card for patients with information on the risks of the medicine, as well as instructions on when to contact their doctor if they have symptoms of immune-related side effects. The company will also provide further data on the long-term benefits of Opdivo and carry out studies to identify which patients are most likely to benefit from treatment with the medicine.

As it is not clear how much ipilimumab contributes to the benefits when given in combination with Opdivo in patients with advanced renal cell carcinoma, the company must conduct a study to determine contribution of ipilimumab and if the risks associated with ipilimumab can be further minimised.

The company must also provide further data on the effectiveness of Opdivo from an ongoing study in patients with oesophageal or gastro-oesophageal junction cancer, from an ongoing study in patients with urothelial cancer, and from an ongoing study in adults and adolescents aged 12 years and older with stage IIB or IIC melanoma. They must also provide further data on the effectiveness of Opdivo from an ongoing study in patients with NSCLC when the medicine is used before surgery.

Recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of Opdivo have also been included in the summary of product characteristics and the package leaflet.

As for all medicines, data on the use of Opdivo are continuously monitored. Side effects reported with Opdivo are carefully evaluated and any necessary action taken to protect patients.

Other information about Opdivo

Opdivo received a marketing authorisation valid throughout the EU on 19 June 2015.

Further information on Opdivo can be found on the Agency's website: ema.europa.eu/medicines/human/EPAR/opdivo.

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