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Keytruda (*pembrolizumab*)

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

What is Keytruda and what is it used for?

Keytruda is a cancer medicine used to treat:

- melanoma, a skin cancer,
- non-small cell lung cancer (NSCLC), a type of lung cancer,
- classical Hodgkin lymphoma, a cancer of the white blood cells,
- urothelial cancer, a cancer of the bladder and urinary tract,
- a cancer affecting the head and neck known as head and neck squamous cell carcinoma (HNSCC),
- renal cell carcinoma (a type of kidney cancer),
- oesophageal cancer (cancer of the gullet or food pipe), including a type of cancer at the junction between the oesophagus and the stomach,
- a kind of breast cancer called triple-negative breast cancer,
- endometrial carcinoma (a cancer of the lining of the womb),
- cervical cancer (a cancer of the cervix),
- the following cancers described as microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) located in:
  - colorectal cancer (a cancer of the colon or rectum, the lower part of the gut),
  - endometrial carcinoma (a cancer of the lining of the womb),
  - gastric cancer (a cancer of the stomach), small intestine cancer, biliary cancer (a cancer of the bile ducts or gallbladder).

Keytruda is mainly used in adults for cancers that are advanced, have spread or returned, are not responding to other treatments or cannot be removed by surgery. Keytruda is also used in children aged 3 years and older with classical Hodgkin lymphoma, and in adolescents aged 12 years and older

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with melanoma. In some cancers, it is only given to patients whose tumours produce certain levels of a protein known as PD-L1 or are determined to be as MSI-H or dMMR.

Keytruda is also used to help prevent the cancer from coming back after patients had surgery to remove melanoma or renal cell carcinoma (adjuvant therapy).

For oesophageal cancer, cervical cancer and triple-negative breast cancer, Keytruda is used in combination with chemotherapy or other cancer medicines. In some patients with triple-negative breast cancer Keytruda can be given before (neoadjuvant treatment) and after (adjuvant treatment) surgery. It can be used on its own or in combination with other cancer medicines for NSCLC, HNSCC, endometrial carcinoma and renal cell carcinoma. For the other cancers, Keytruda is only used on its own.

Keytruda contains the active substance pembrolizumab.

How is Keytruda used?

Keytruda is given as an infusion (drip) into a vein. The dose in adults is either 200 mg every three weeks or 400 mg every six weeks. The dose of Keytruda in children and adolescents is 2 mg per kg of body weight, up to a maximum of 200 mg.

The doctor may delay doses if certain side effects occur or stop treatment altogether if side effects are severe. Tests to check levels of PD-L1 or MSI-H/dMMR tumour status are needed in some cases before starting treatment.

The medicine can only be obtained with a prescription and treatment must be started and supervised by a doctor experienced in the treatment of cancer. For more information about using Keytruda, see the package leaflet or contact your doctor or pharmacist.

How does Keytruda work?

The active substance in Keytruda, pembrolizumab, is a monoclonal antibody, a protein that has been designed to recognise and block a receptor ('target') called PD-1. Some cancers can make a protein (PD-L1) that combines with PD-1 to switch off the activity of certain cells of the immune system (the body's natural defences), preventing them from attacking the cancer. By blocking PD-1, pembrolizumab stops the cancer switching off these immune cells, thereby increasing the immune system's ability to kill the cancer cells.

What benefits of Keytruda have been shown in studies?

Melanoma (skin cancer)

Keytruda can delay worsening of melanoma and improve survival. Results from a study of 540 previously treated patients with melanoma showed that 2 years after start of treatment, the disease had not worsened in 16% of patients treated with Keytruda compared with less than 1% of patients treated with chemotherapy.

A second study looked at 834 patients with melanoma who received either Keytruda or another medicine, ipilimumab. Patients treated with Keytruda lived for up to 5.6 months without their disease getting worse compared with 2.8 months with ipilimumab. Also, up to 74% of patients treated with Keytruda lived for at least 12 months after the start of their treatment compared with 59% of patients on ipilimumab.

A third study in 1,019 patients who had had surgery and who were at high risk for their cancer coming back compared Keytruda to placebo (a dummy treatment). After one and a half years, 72% of patients who had Keytruda were still disease-free compared with 54% of patients who had placebo.

Another study compared Keytruda to placebo in 976 patients who had not received previous treatments and had surgery to remove their cancer. After 14.3 months of treatment, 11% of patients treated with Keytruda had a recurrence of their cancer or had died, compared with about 17% of those treated with placebo.

Because melanoma in adolescents is similar to the disease in adults, Keytruda is expected to be as effective in adolescents as it is in adults. The data from adults therefore apply to adolescents as well.

Non-small cell lung cancer (NSCLC)

Keytruda is also effective in delaying worsening of the disease and improving survival in patients with NSCLC that tested positive for the PD-L1 protein.

In a study looking at around 1,000 previously treated patients, patients lived longer with Keytruda given alone (around 11 months) than with another cancer medicine called docetaxel (around 8 months) and the period during which the disease did not get worse was around 4 months with both treatments. Keytruda was more effective in patients who tested strongly for PD-L1, with these patients living for 15 months on average, 5 months of which without their disease worsening.

In a second lung cancer study of 305 patients whose tumours tested strongly for PD-L1 and who had not been treated before, patients on Keytruda lived for around 10 months without their disease getting worse compared with 6 months in patients receiving platinum-based chemotherapy.

Keytruda is also effective in combination treatment of a type of NSCLC known as 'non-squamous' cancer, based on the type of cancer cells involved. In a study of 616 patients with non-squamous NSCLC that had spread, 69% of patients taking Keytruda with pemetrexed and platinum chemotherapy were alive at 11 months, compared with less than half of patients who had only pemetrexed and platinum chemotherapy. In addition, patients who had Keytruda treatment lived on average for 8.8 months without the disease getting worse compared with 4.9 months for patients who were not given Keytruda.

In a further study of 559 patients with 'squamous' NSCLC that had spread, patients given Keytruda with carboplatin and paclitaxel or nab-paclitaxel lived on average for 15.9 months compared with 11.3 months for patients given placebo with carboplatin and paclitaxel or nab-paclitaxel. Patients in the Keytruda group lived on average for around 6 months without their disease getting worse compared with 4.8 months for patients in the placebo group.

Hodgkin lymphoma

Keytruda partially or completely clears cancer cells in classical Hodgkin lymphoma that has not improved or had returned after previous treatment.

In a main study of 210 adult patients, Keytruda produced a complete or partial remission (clearing) of the cancer in 71% of the patients; a complete remission occurred in 28% of them, meaning they no longer had any signs of cancer. The average time that patients lived without their disease getting worse again was around 14 months.

Another main study of 304 adults showed that Keytruda was also effective in patients who had tried stem cell transplant and those who had had two other treatments and were unable to have a stem cell transplant. In this study, patients who received Keytruda lived on average for 13 months without their

disease getting worse compared with around 8 months for those treated with brentuximab vedotin. Data from a study in children indicate that the medicine could also be effective in that age group.

Urothelial cancer

Keytruda improves survival of patients with urothelial cancer. A study looked at 542 patients previously treated with platinum-based medicines who received either Keytruda or another cancer medicine chosen by the doctor (paclitaxel, docetaxel or vinflunine). Patients treated with Keytruda lived on average around 10 months compared with around 7 months with the other cancer medicines. Keytruda did not delay worsening of the disease compared with the other cancer medicines (time to disease worsening was 2 and 3 months respectively).

In a second study of 370 patients who could not be treated with cisplatin-containing medicines, Keytruda produced a complete or partial remission (clearing) of the cancer in 108 patients (29%); a complete remission occurred in 30 (8%) of them, meaning they no longer had any signs of cancer.

Head and neck cancer

Keytruda is also effective in improving survival of patients with head and neck squamous cell carcinoma (HNSCC) that has spread or come back. In a study of 495 patients, patients treated with Keytruda who had high levels of PD-L1 lived on average for 11.6 months while those taking standard cancer treatments lived for 6.6 months.

Another study in 882 patients with HNSCC showed that Keytruda alone or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy is effective at prolonging patients' lives when HNSCC tests positive for a certain level of PD-L1. Patients taking the Keytruda combination lived on average for 13.6 months compared with 10.4 months for patients taking other standard treatments. In addition, patients taking Keytruda alone lived on average 12.3 months compared with 10.3 months for patients taking other standard treatments.

In this study, disease did not get worse for 5.1 months on average in patients taking Keytruda combination, 3.2 months in patients taking Keytruda alone and 5.0 months in patients taking other standard treatments.

Kidney cancer

In a study of 861 patients with renal cell carcinoma, patients given Keytruda in combination with an already authorised medicine for renal cell carcinoma, axitinib, lived for around 15 months without their disease getting worse, compared with 11 months for patients who received treatment with another renal cell carcinoma medicine, sunitinib, which was used as a control treatment. Keytruda is also effective in improving survival of patients with renal cell cancer. At 18 months, 81% of the patients given the combination were alive, compared with 71% in the sunitinib group.

Another study, involving 1,069 patients, with renal cell carcinoma compared the effects of Keytruda or everolimus in combination with lenvatinib with the effects of sunitinib. In this study, patients in the Keytruda plus lenvatinib group lived for around 24 months without their disease getting worse, while those in the sunitinib group lived for 9 months without their disease worsening.

A third study looked at the effect of Keytruda after surgery in 994 patients who had a higher risk of their cancer coming back. After one year, the probability of being alive without the disease coming back was 86% for patients receiving Keytruda treatment compared with 76% for patients receiving placebo. After two years, the figures were 77% for those had Keytruda and 68% for those who had placebo.

Oesophageal cancer

A main study of 749 patients with oesophageal cancer that was advanced or had spread compared Keytruda plus chemotherapy with placebo plus chemotherapy.

Keytruda treatment mainly benefited patients whose cancer produced high levels of PD-L1. Among these patients, those who received Keytruda lived on average for around 14 months while those who had placebo lived for 9 months. In addition, those in the Keytruda group lived for 8 months without the disease getting worse, compared with 6 months for those in the placebo group.

Triple-negative breast cancer

A main study of 1,174 patients with high-risk early stage triple negative breast cancer compared the effects of giving Keytruda before (neoadjuvant treatment) and after (adjuvant treatment) surgery with the effects of giving placebo before and after surgery. All patients in the study, whose cancer was locally advanced and at risk of coming back, also had chemotherapy before surgery. The result was that 64% of patients given Keytruda neoadjuvant treatment had no signs of invasive cancer in the breast tissue removed during surgery compared with 55% of patients treated with placebo. In addition, after 24 months the probability of being alive without the disease coming back was 88% for patients who had Keytruda as neoadjuvant and adjuvant treatment, compared with 81% for those treated with placebo.

Another main study compared Keytruda plus chemotherapy with placebo and chemotherapy in 847 patients with previously untreated triple-negative breast cancer that could not be removed surgically or had spread. Among patients with high levels of PD-L1, those in the Keytruda group lived for almost 10 months without their disease getting worse, while those in the placebo group lived for 5 months without the disease worsening. When the study looked at survival (how long they lived), those in the Keytruda group lived longer: 23 months compared with 16 months.

Endometrial carcinoma

A study of 827 patients with endometrial carcinoma compared Keytruda plus lenvatinib with chemotherapy treatments (doxorubicin or paclitaxel). Patients in the Keytruda group lived for around 7 months without their disease getting worse, while patients in the chemotherapy group lived for almost 4 months without their disease worsening. In addition, when the study looked at survival (how long they lived), patients in the Keytruda group lived on average for around 18 months compared with 11 months for patients in the chemotherapy group.

Cervical cancer

Keytruda given with other cancer treatments is also effective in patients with cervical cancer that came back after previous treatment or has spread and tested positive for PDL-1 protein.

Patients who received Keytruda, together with chemotherapy, with or without another cancer medicine called bevacizumab, lived on average 10.4 months without their disease getting worse (273 patients) compared with 8.2 months for those who received only chemotherapy, with or without bevacizumab (275 patients). In addition, early data from the study show patients who received Keytruda living longer that those who did not.

MSI-H or dMMR cancers

A main study compared Keytruda with standard treatment, including chemotherapy, in 307 patients with MSI-H or dMMR colorectal cancer that had spread and who did not receive any previous treatment

for their cancer. Patients who received Keytruda lived for around 17 months without the disease getting worse compared with 8 months for patients who received standard treatments.

Two additional studies looked at the effect of Keytruda in patients with other MSI-H or dMMR cancers that had spread and came back after previous treatments. Among the patients participating in the study, 124 had a colorectal cancer, 83 had endometrial carcinoma, 51 had a gastric cancer, 27 had a cancer of the small intestine and 22 had a biliary cancer.

The proportion of patients whose cancer responded to Keytruda treatment was about 34% in patients with colorectal cancer, 51% in patients with endometrial carcinoma, 37% in patients with gastric cancer, 56% in patients with a small intestine cancer and 41% in those with biliary cancer.

What are the risks associated with Keytruda?

The side effects of Keytruda are mostly related to the activity of the immune system, which may cause inflammation of body organs and tissues and can be serious, although most side effects resolve with appropriate treatment or on stopping Keytruda. The most common side effects of Keytruda given alone (which may affect more than 1 in 5 people) are tiredness, nausea (feeling sick) and diarrhoea. The most serious adverse reactions were immune reactions and severe reactions related to the infusion.

Additional side effects may occur when Keytruda is used with other cancer medicines. For the full list of side effects and restrictions with Keytruda, see the package leaflet.

Why is Keytruda authorised in the EU?

Keytruda is effective at improving survival or delaying the worsening of disease in patients with advanced cancers or cancers that have spread or come back or cannot be removed surgically. In some patients, tumours have to produce a certain level of PD-L1 or have to be determined as MSH-I or dMMR for the medicine to be effective.

Keytruda is also effective in preventing melanoma and kidney cancer from coming back in patients who have had surgery, and improves the outcome in patients with triple negative breast cancer given Keytruda before and after surgery.

The side effects with this medicine are manageable and are similar to those of various other cancer treatments.

The European Medicines Agency decided that Keytruda's benefits are greater than its risks and it can be authorised for use in the EU.

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

The company that markets Keytruda will provide patients with an information pack and alert card to inform them about the risks of potential immune-related side effects and give instructions on when to contact their doctor if they experience symptoms.

In addition, the company will provide the final results of studies with Keytruda to confirm the long-term benefits of the medicine. The company will also provide study results to confirm the efficacy of Keytruda against melanoma in adults and adolescents aged 12 years and older, and against certain MSI-H or dMMR cancers (gastric cancer, biliary cancer and cancer of the small intestine). Moreover, the company will carry out analyses to better understand which patients are likely to benefit most from treatment with Keytruda.

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

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

Other information about Keytruda

Keytruda received a marketing authorisation valid throughout the EU on 17 July 2015.

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

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