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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;
- non-epithelioid malignant pleural mesothelioma, a cancer of the lining of the lungs;
- classical Hodgkin lymphoma, a cancer of the white blood cells;
- urothelial cancer, a cancer of the bladder and urinary tract;
- head and neck squamous cell carcinoma (HNSCC), a cancer affecting the head and neck;
- renal cell carcinoma, a type of kidney cancer;
- oesophageal cancer, a cancer of the oesophagus (gullet or food pipe);
- gastric and gastro-oesophageal junction adenocarcinoma, types of cancer of the stomach and junction between the oesophagus and the stomach, respectively;
- triple-negative breast cancer, a type of breast cancer;
- endometrial carcinoma, a cancer of the lining of the womb;
- cervical cancer, a cancer of the cervix;
- biliary tract cancer, a cancer of the bile ducts (the tubes that carry bile from the liver and gallbladder to the gut or the gallbladder);
- the following cancers when described as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR):
  - colorectal cancer, a cancer of the colon or rectum (the lower part of the gut);
  - endometrial carcinoma;

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- gastric cancer, small intestine cancer or biliary cancer.

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 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 MSI-H or dMMR.

Keytruda is also used to help prevent the cancer from coming back after patients had surgery (adjuvant treatment) to remove melanoma, NSCLC or renal cell carcinoma. In some patients with triple-negative breast cancer, NSCLC or HNSCC, Keytruda can be given before (neoadjuvant treatment) and after (adjuvant treatment) surgery.

Depending on the cancer being treated, Keytruda can be used on its own or in combination with other cancer medicines such as lenvatinib, axitinib or enfortumab vedotin, chemotherapy alone or combined with the cancer medicines trastuzumab or bevacizumab, or chemotherapy combined with radiotherapy.

Keytruda contains the active substance pembrolizumab.

How is Keytruda used?

Keytruda can only be obtained with a prescription and treatment must be started and supervised by a doctor experienced in the treatment of cancer.

Keytruda is given as an infusion (drip) into a vein over 30 minutes, every three or six weeks. When used in adults, it is also available as an injection under the skin in the abdomen (belly) or thigh; it is given by a healthcare professional as a 1-minute injection every 3 weeks or as a 2-minute injection every 6 weeks. Patients can switch between formulations (infusion or injection under the skin) at their next scheduled dose.

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

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. 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.

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 disease did not get worse for 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 study of 305 patients with NSCLC 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 for patients receiving platinum-based chemotherapy.

Keytruda is also effective in combination treatment of a type of NSCLC known as 'non-squamous'. 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.

In a study involving over 1,000 patients with NSCLC who had their cancer surgically removed and had received chemotherapy after surgery, patients treated with Keytruda for up to one year lived an average of 54 months without the disease coming back, compared with 41 months for patients who received placebo.

A further study involved close to 800 patients with NSCLC that had not spread and could be removed by surgery. They received either Keytruda with platinum-containing chemotherapy before surgery

followed by Keytruda alone after surgery, or placebo with platinum-containing chemotherapy before surgery followed by placebo alone after surgery. Patients who received Keytruda lived an average of 47 months before the disease got worse or came back, or the patient died. This compares with 18 months for patients who received placebo. Patients who received placebo lived an average of 52 months; this time could not be calculated in patients who received Keytruda due to the low number of patients who died during the follow-up period.

Non-epithelioid malignant pleural mesothelioma

A main study investigated Keytruda in 440 adults with malignant pleural mesothelioma that had not been treated before, was advanced or metastatic and could not be removed by surgery. In a group of 95 patients with non-epithelioid malignant pleural mesothelioma, those who received Keytruda with chemotherapy (cisplatin and pemetrexed) lived for an average of 12.3 months compared with 8.2 months for those who received chemotherapy alone. In addition, patients in the Keytruda group lived for an average of 7.1 months without their disease getting worse, compared with 4.5 months for those who received chemotherapy alone.

Hodgkin lymphoma

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

In a main study of 210 adults, 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 a 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 involving 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.

A further study involving 886 patients with advanced or metastatic urothelial cancer that had not yet been treated with systemic (affecting the whole body) therapy compared the benefits of Keytruda in combination with enfortumab vedotin with those of platinum-based chemotherapy and gemcitabine (other cancer medicines). Patients treated with Keytruda plus enfortumab vedotin lived on average for around 13 months without the disease getting worse and for an average of 32 months overall. Patients treated with platinum-based chemotherapy and gemcitabine lived for an average of around 6 months without the disease getting worse and for an average of around 16 months overall.

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 involving 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 the HNSCC has 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, the 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.

Another study involved 714 patients with locally advanced HNSCC (Stage III-IVA; when the cancer has grown significantly and may have spread nearby) that can be removed by surgery. Most patients had cancer cells that produced a certain level of PD-L1.

A first group of patients received Keytruda before surgery, followed by, within 6 weeks after surgery, Keytruda in combination with either radiation and chemotherapy for patients who had signs that cancer cells were still present after surgery or had spread, or radiation alone for those not presenting these signs. A second group of patients did not receive treatment before surgery; within 6 weeks after surgery, they received either radiation and chemotherapy or radiation alone, as patients in the first group, but without Keytruda.

Patients in the first group lived an average of 60 months before their disease got worse or came back, or the patient died, compared with 30 months on average for patients in the second group.

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. Keytruda is also effective in improving survival of patients with renal cell carcinoma. 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 kidney 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 who 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.

Gastric and gastro-oesophageal junction adenocarcinoma

A main study was carried out in 698 patients with HER2-positive advanced gastric or gastro-oesophageal junction adenocarcinoma who had not been treated before and whose cancer could not be removed by surgery. HER2-positive means that the cancer cells produce a protein called HER2 on their surface. The study compared Keytruda with placebo in patients who were also receiving another cancer medicine called trastuzumab and chemotherapy. Keytruda treatment only showed benefits in patients whose cancer produced a certain level of PD-L1. Among these patients, those who received Keytruda lived on average 11 months without their disease getting worse and about 21 months overall, compared with about 7 months and 16 months, respectively, for those who received placebo.

Another main study was carried out in 1,579 patients with HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma who had not previously received systemic therapy for metastatic disease. Patients received either Keytruda or placebo, together with chemotherapy medicines chosen by the doctor (5-FU plus cisplatin or capecitabine plus oxaliplatin). Keytruda treatment showed greater benefits in patients whose cancer produced a certain level of PD-L1. Among these patients, those who were treated with Keytruda lived for 13 months on average, compared with 11.4 months for those who received placebo.

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 both 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 results showed that 64% of patients given Keytruda as neoadjuvant treatment had no signs of invasive cancer in the breast tissue removed during surgery compared with 55% of patients given 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.

A further study involved 810 patients with advanced or recurrent endometrial carcinoma which was either mismatch repair deficient (dMMR; meaning that the cancer cells lack certain proteins that correct mistakes made when DNA in dividing cells is copied) or mismatch repair proficient (pMMR; meaning that the cancer cells do not have this repair problem). Patients either had not previously received chemotherapy or had received chemotherapy after cancer surgery at least 12 months before the study. During the study, patients received either Keytruda with paclitaxel and carboplatin, or placebo with paclitaxel and carboplatin. In the pMMR group, patients given Keytruda lived an average of 13 months without their disease getting worse compared with about 9 months for patients given placebo. In the dMMR group, patients who received placebo lived an average of 8 months without their disease getting worse; this duration could not be calculated for patients who received Keytruda as not enough people had experienced worsening of the disease to allow the average time to be calculated. However, results showed that, at the time of the analysis, 26% (29 out of 110) of dMMR patients had experienced worsening of their disease with Keytruda compared with 54% (60 out of 112) of patients who received placebo.

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 that patients who received Keytruda live longer than those who did not.

A further study involved 1,060 patients with locally advanced cervical cancer who had not previously received any surgery to completely remove the cancer, radiation, or systemic therapy for cervical cancer; 601 of whom had their cancer classified as FIGO 2014 Stage III-IVA (this means the cancer has started to spread to nearby structures like the vagina, bladder or end gut). Patients received either Keytruda with chemoradiotherapy (cisplatin and external radiotherapy followed by brachytherapy, a type of internal radiation therapy) followed by Keytruda alone, or placebo with chemoradiotherapy. The treatment lasted for up to approximately 2 years. In patients with FIGO 2014 stage III-IVA cancer, not enough people had experienced worsening of the disease to allow the average time they lived without their disease getting worse and the time they lived overall to be calculated in either the Keytruda or the placebo group. However, results showed that 15% of patients (43 out of 296) who received Keytruda with chemoradiotherapy had died compared with 24% (73 out of 305) of patients in the placebo group. In addition, 27% (79 out of 296) of patients had experienced worsening of their disease with Keytruda compared with 41% (125 out of 305) of patients who received placebo.

Biliary tract cancer

In a study in 1,069 patients with locally advanced unresectable or metastatic biliary tract cancer who had not received systemic therapy for their advanced disease before, patients received either Keytruda or placebo, together with gemcitabine and cisplatin. Patients treated with Keytruda lived for 12.7 months on average, compared with 10.9 months for those who received placebo.

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 had not received 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 come back after previous treatments. Among the patients in the study, 124 had colorectal cancer, 83 had endometrial carcinoma, 51 had gastric cancer, 27 had cancer of the small intestine and 22 had 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 small intestine cancer and 41% in those with biliary cancer.

What are the risks associated with Keytruda?

For the complete list of side effects and restrictions with Keytruda, see the package leaflet.

The side effects with 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 with Keytruda given alone (which may affect more than 1 in 5 people) include tiredness, nausea (feeling sick) and diarrhoea. The most serious adverse reactions were immune reactions and severe reactions related to the infusion.

In addition, when Keytruda is given as an injection under the skin, reaction at the site of injection may occur.

Additional side effects may occur when Keytruda is used with other cancer medicines, chemotherapy or chemoradiotherapy.

Why is Keytruda authorised in the EU?

Keytruda is effective at improving the 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 being MSI-H or dMMR for the medicine to be effective.

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

The benefits of Keytruda when added to chemotherapy were also shown to outweigh the risks in adults with non-epithelioid malignant pleural mesothelioma.

The side effects of Keytruda 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 alert card to inform them about the risks of potential immune-related side effects and to give instructions on when to contact their doctor if they experience symptoms.

In addition, the company must provide the results of studies with Keytruda to confirm its benefits, including in the long-term, in the treatment of melanoma in adults and adolescents aged 12 years and older, as well as in the treatment of Hodgkin lymphoma and NSCLC in adults.

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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