28 February 2020
EMA/92336/2020
EMEA/H/C/WS/1372

Withdrawal of application to change the marketing authorisation for Opdivo (nivolumab) and Yervoy (ipilimumab)

Bristol-Myers Squibb Pharma EEIG withdrew its application for the use of Opdivo and Yervoy in the treatment of metastatic non-small cell lung cancer that has not been treated previously.

The company withdrew the application on 30 January 2020.

What are Opdivo and Yervoy and what are they used for?

Opdivo and Yervoy are cancer medicines. They contain the active substances nivolumab and ipilimumab, respectively.

Opdivo has been authorised in the EU since June 2015. It is already used on its own to treat non-small cell lung cancer in patients who have previously been treated with other cancer medicines. It is also used to treat the following other cancers: melanoma (a skin cancer), renal cell carcinoma (a kidney cancer), Hodgkin's lymphoma (a blood cancer), squamous cell cancer of the head and neck, and urothelial (bladder) cancer.

Yervoy has been authorised in the EU since July 2011. It is used to treat melanoma and renal cell carcinoma.

Further information on current uses of Opdivo and Yervoy can be found on the Agency's website: ema.europa.eu/medicines/human/EPAR/opdivo and ema.europa.eu/medicines/human/EPAR/yervoy.

What change had the company applied for?

The company applied for an extension of indication to add the use of Opdivo and Yervoy together in patients with previously untreated non-small cell lung cancer that has spread to other parts of the body (metastatic) and where the cancer does not have mutations (changes) in genes called EGFR and ALK.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

How do Opdivo and Yervoy work?

In metastatic non-small cell lung cancer, Opdivo and Yervoy are expected to work in the same way as they do in their existing uses.

The active substances in these medicines, nivolumab and ipilimumab, are monoclonal antibodies, a type of protein that has been designed to recognise and attach to specific targets in the body.

Nivolumab attaches to a receptor (target) called PD-1, which is 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.

Ipilimumab attaches to and blocks the activity of CTLA-4, a protein that controls the activity of T cells. By blocking CTLA-4, ipilimumab activates T cells, which kill the tumour cells.

What did the company present to support its application?

The company presented the results of a study involving 1,739 patients with previously untreated metastatic non-small cell lung cancer. The study compared treatment with the combination of Opdivo and Yervoy, treatment with a combination of two platinum-based cancer medicines, and treatment with the two platinum-based medicines and Opdivo. The study looked at how long patients lived and how long patients lived before the disease worsened.

How far into the evaluation was the application when it was withdrawn?

The application was withdrawn after the European Medicines Agency had evaluated the initial information from the company and had prepared questions for the company. After the Agency had assessed the company's responses to the questions, there were still some unresolved issues.

What did the Agency recommend at that time?

Based on the review of the information and the company's response to the Agency's questions, at the time of the withdrawal, the Agency had some concerns and its provisional opinion was that treatment with Opdivo and Yervoy together could not have been authorised for the treatment of non-small cell lung cancer that has not been treated previously.

During the study, the way it was set up changed substantially several times and there were concerns about how the company handled the data. In addition, there were inconsistencies in the study results for different groups of patients. Therefore, at the time of the withdrawal, the Agency's opinion was that it was not possible to come to reliable conclusions on effectiveness and, as a result, the Agency could not conclude that the benefits of Opdivo and Yervoy together in the treatment of non-small cell lung cancer outweighed the risks.

What were the reasons given by the company for withdrawing the application?

In its letter notifying the Agency of the withdrawal of application, the company stated that the withdrawal was based on the fact that the Agency could not conclude that there was a positive benefit-risk balance for the medicines in the treatment of non-small cell lung cancer that has not been treated previously.

Does this withdrawal affect patients in clinical trials?

The company informed the Agency that there are no consequences for patients in clinical trials using Opdivo and Yervoy.

If you are in a clinical trial and need more information about your treatment, speak with your clinical trial doctor.

What is happening with Opdivo and Yervoy for the treatment of other diseases?

There are no consequences on the use of either medicine in their authorised uses.