pembrolizumab (KEYTRUDA®) in Hodgkin lymphoma with no further treatment options

Inadequate premarketing assessment

KEYTRUDA® - pembrolizumab powder for concentrate for solution for intravenous infusion, and concentrate for solution for intravenous infusion

• 50 mg of pembrolizumab powder, to be dissolved to obtain a 25 mg/ml solution, then diluted in an IV infusion bag
• 100 mg of pembrolizumab as a 25 mg/ml solution, to be diluted in an IV infusion bag

■ Immunostimulant; PD-1 inhibitor
■ New indication: "relapsed or refractory Hodgkin lymphoma after failure of autologous stem cell transplant and brentuximab vedotin, as monotherapy in adult patients". [EU centralised procedure]

In patients with relapsed or refractory Hodgkin lymphoma who have already received an autologous haemopoietic stem cell transplant, no drugs, including brentuximab vedotin, have been shown to prolong survival. After failure of autologous transplantation and brentuximab vedotin, the harm-benefit balance of the immunostimulatory anti-PD-1 antibody nivolumab is unfavourable as of early 2018, because its effect on clinical endpoints has barely been evaluated and due to its many and severe adverse effects (1).

Another immunostimulatory anti-PD-1 antibody, pembrolizumab (Keytruda®, Merck Sharp & Dohme), has been authorised in the European Union for patients with Hodgkin lymphoma after failure of an autologous haemopoietic stem cell transplant and brentuximab vedotin; or after failure of brentuximab vedotin alone when autologous haemopoietic stem cell transplantation is not an option (2).

The clinical evaluation for pembrolizumab in this situation, at a dose of 200 mg every 3 weeks, is focused on a single non-comparative trial in 210 adults. After a median follow-up of 10 months, 4 patients had died. As pembrolizumab was not compared with appropriate symptomatic care and the follow-up was so short, it is impossible to determine whether this drug prolongs survival. 22% of the patients exhibited a "complete" response, based on radiological assessment (2,3). The duration of the complete responses was not specified in the documents identified by our literature search.

The known adverse effects of pembrolizumab are often of immunological origin: rash, including Stevens-Johnson syndrome and toxic epidermal necrolysis, endocrine disorders (thyroid disease, hypophysitis, diabetes), hepatitis, pneumonitis, diarrhoea, colitis, neurological disorders (including encephalitis and Guillain-Barré syndrome), nephritis, uveitis, myositis, transplant rejection; and also sarcoidosis and severe infusion reactions (2,4,5). In a pooled analysis of the trial referred to above, in 210 patients, and a non-comparative trial of a different dose of pembrolizumab in 31 patients with Hodgkin lymphoma, a severe pembrolizumab-related adverse effect was reported in 12% of patients (3).

A total of 23 patients in these two non-comparative trials underwent allogeneic haemopoietic stem cell transplantation after receiving pembrolizumab (3). Seven of them had a complication, including six with graft-versus-host disease. One case was fatal (2,3). It is probable that pembrolizumab had a role in these reactions due to its immunostimulatory action. Nivolumab is thought to carry the same risk (1).