See also p 180

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

Inadequate premarketing assessment

NOT ACCEPTABLE

An evaluation just as inadequate as that of *nivolumab* in Hodgkin lymphoma, mainly based on a single, short, non-comparative trial using surrogate endpoints. *Pembrolizumab* has many, sometimes serious, adverse effects.

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).

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Prescrire's literature search up to 6 February 2018

In response to our request for information, Merck Sharp & Dohme provided us with no documentation.

1- Prescrire Editorial Staff "Nivolumab and Hodgkin lymphoma. Barely evaluated" *Prescrire Int* 2018; **27** (191): 63-65.
2- European Commission "SPC-Keytruda" 8 December 2017: 73 pages.
3- EMA - CHMP "Public assessment report for Keytruda. EMEA/H/C/003820/II/0014" 23 March 2017: 102 pages.
4- Prescrire Editorial Staff "Pembrolizumab and metastatic or inoperable melanoma. A nivolumab me-too" *Prescrire Int* 2017; **26** (182): 118-119.
5- EMA - CHMP "Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s) for pembrolizumab. EMEA/H/C/PSUSA/00010403/201609" 21 April 2017: 2 pages.

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