pembrolizumab (KEYTRUDA°) in urothelial carcinoma

POSSIBLY HELPFUL

In a non-blinded comparative randomised trial after failure of platinum-containing chemotherapy, *pembrolizumab* prolonged survival by about 3 months compared with taxane- or *vinflunine*-containing chemotherapy. Its adverse effects were different and less frequent.

KEYTRUDA° - *pembrolizumab* powder for concentrate for solution, or concentrate for solution for intravenous infusion

- **immunostimulant; anti-PD-1**
- **New indication:** "*as monotherapy* (...) *for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy* [or] *who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10*". [EU centralised procedure]

For patients with locally advanced or metastatic urothelial carcinoma, platinum-based chemotherapy is often proposed as first-line treatment. When it fails, there is no consensus on treatment. Taxanes such as *docetaxel* and *paclitaxel* are second-line options. The vinca alkaloid *vinflunine* has an unfavourable harm-benefit balance (1,2). *Nivolumab* and *atezolizumab* are immunostimulatory monoclonal antibodies targeting the PD-1 receptor pathway. They have been authorised in the European Union for this situation, although they have not been shown to prolong survival (1,3).

Pembrolizumab (Keytruda°, Merck Sharp & Dohme) is another immunostimulatory anti-PD-1 monoclonal antibody that is already authorised for various cancers in the European Union. It has now also been authorised for use in patients with locally advanced or metastatic urothelial carcinoma, after failure of platinum-based chemotherapy or when *cisplatin*-containing chemotherapy cannot be used.

Clinical evaluation after failure of platinum-based chemotherapy is based on a single non-blinded randomised trial in 542 patients. Patients were randomised to receive either *pembrolizumab* or the investigator's choice of chemotherapy regimen: *docetaxel*, *paclitaxel* or *vinflunine* (2). After a median follow-up of about 14 months, median survival was longer in the *pembrolizumab* group: 10.3 months versus 7.4 months in the chemotherapy group (p = 0.002) (2,3). Analysis of survival curves shows that mortality was higher in the *pembrolizumab* group during the first 2 months of treatment, after which the curves crossed, and mortality was subsequently higher in the chemotherapy group (2).

The authorisation of *pembrolizumab* as first-line therapy when *cisplatin*-containing chemotherapy cannot be used is based on a single non-comparative trial, thus it cannot be demonstrated whether it constitutes an advance over existing options (2). A trial underway as of June 2018 includes a comparison of *pembrolizumab* monotherapy versus platinum-containing chemotherapy as first-line treatment. Preliminary analysis of the data showed that mortality was higher in the *pembrolizumab* monotherapy group among patients whose tumour cells and immune cells weakly expressed the ligand of the PD-1 receptor (PD-L1). In response to this finding, the European Medicines Agency (EMA) recommended restricting the indication for first-line *pembrolizumab* to patients in whom PD-L1 is expressed by at least 10% of tumour cells and immune cells (4,5). This restriction was added to the European summary of product characteristics in June 2018 (6).

In the comparative trial after failure of platinum-containing chemotherapy, adverse effects were less frequent in the *pembrolizumab* group (61% versus 90% in the chemotherapy group). This was also the case for serious adverse effects: about 10% in the *pembrolizumab* group versus 22% (2). As foreseeable, given its mechanism, immunological adverse effects were more frequent in the *pembrolizumab* group. Gastrointestinal, haematological and neurological disorders and alopecia were more frequent in the chemotherapy group (2).

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Literature search up to 3 July 2018

In response to our request for information, MSD provided us with no documentation on its product.

1- Prescrire Rédaction "atézolizumab (Tecentriq°) et carcinome urothélial" *Rev Prescrire* 2018; **38** (418): 575-576.
2- EMA - CHMP "Public assessment report for Keytruda. EMEA/H/C/003820/II/0023/G" 20 July 2017: 146 pages.
3- HAS - Commission de la Transparence "Projet d'avis-Opdivo" 25 October 2017 + "Avis-Keytruda" 21 February 2018: 49 pages.
4- EMA "EMA restricts use of Keytruda and Tecentriq in bladder cancer" 1 June 2018: 3 pages.
5- "Study of pembrolizumab with or without platinum-based combination chemotherapy versus chemotherapy alone in urothelial carcinoma (MK-3475-361/Keynote-361). NCT02853305". clinicaltrials.gov accessed 19 June 2018: 7 pages.
6- European Commission "SPC-Keytruda" 6 July 2018: 75 pages.

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