

**Urgent Clinical
Commissioning Policy
Statement:
Pembrolizumab for
drug-resistant
gestational
trophoblastic neoplasia**

NHS England Reference: 170027P



1 Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of this policy statement, we have:

- given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

In the interests of delivering an urgent commissioning position, a rapid initial equality impact assessment has been carried out.

2 Background

Gestational Trophoblastic Neoplasia (GTN) is a rare group of pregnancy related cancers that derive from the placenta. In the UK about 150 new cases are diagnosed each year and most will be cured with one or two single chemotherapeutic agents (Seckl et al 2010). About 40 patients each year will not respond and will require multi-agent chemotherapy; between 1-3 patients each year will have disease that is not eradicated by single or multi-agent chemotherapy and will need high dose chemotherapy with autologous peripheral stem cell support as a tandem procedure. This treatment is associated with significant toxicity with a 3% death rate and 100% risk of grade 4 myelotoxicities. It requires 3-4 weeks of in-patient care with each round of high dose treatment and costs about £70,000 per patient. The first published UK data in 11 patients showed that about 20% of patients are likely to be long term survivors with this approach (El-Helw et al 2005).

Pembrolizumab is given intravenously every 3 weeks to treat patients with several types of cancer including melanoma and lung cancer for which there is NICE guidance for use (NICE 2015, NICE 2017). Pembrolizumab works by allowing the body's immune cells that have recognised cancer cells as foreign but are not yet active to become fully active and kill the cancer cells. Cancers that derive from the placenta, collectively called gestational trophoblastic neoplasia (GTN), may be recognised as 'foreign' by immune cells because about half of the genetic material in these cancers comes from the male partner. However, in pregnancy, immune cells are prevented from destroying the placenta because of immune cell suppression by a placental molecule called PD-L1 that binds to an immune cell receptor called PD-1. This mechanism also applies to cancers derived from the placenta, protecting the cancer from attack by the immune system. Pembrolizumab blocks the binding of PD-L1 to PD-1,

and hence may enable full activation of the immune cells to destroy both normal placental/fetal tissue and cancer arising from the placenta.

Pembrolizumab may be given in a hospital day/case outpatient setting. From the evidence, it is considered less toxic than high dose chemotherapy.

Pembrolizumab is not currently commissioned for gestational trophoblastic neoplasia.

3 Evidence Summary

NHS England has considered the evidence submitted as part of the preliminary policy proposal. This has been assessed as requiring an urgent clinical commissioning policy statement. This statement includes the clinical criteria for initiating and for discontinuing this treatment. The statement is informed by up to three of the most clinically important publications, identified using a literature search strategy defined by the clinical lead. These publications are summarised below.

Publication 1 (Huang et al 2017)

Huang et al (2017) provide a case report of a patient with a widely metastatic choriocarcinoma who achieved complete serological remission after treatment with pembrolizumab following two unsuccessful standard treatment regimes. This is a case report in a single patient but provides evidence for the effectiveness of pembrolizumab in a patient with an otherwise fatal prognosis. Follow up was limited to 6 weeks after normalisation of blood markers and genetic proof that the cancer was gestational was not presented.

Publication 2 (Ghorani et al 2017)

Ghorani et al describe 4 patients with genetically proven GTN who received treatment with pembrolizumab. All had disease that failed multiple prior lines of therapy including two who had already received high dose chemotherapy and two who were not fit enough for high dose chemotherapy. Both of the patients with disease that failed high dose treatment and one of the patients not fit enough for high dose treatment entered remission on pembrolizumab despite having advanced multi-drug resistant disease. One patient with disease that failed two prior lines of multi-agent chemotherapy and surgery also failed to respond to pembrolizumab. Molecular comparison of the tumours from the 3 responding versus one non-responding patient revealed that all expressed PD-L1 and none expressed classical HLA class 1 or 2 major histocompatibility (MHC) molecules. However, all 3 patients with disease that responded to treatment demonstrated tumour infiltrating lymphocytes and good expression of human Leukocyte antigen G (HLA G) whilst the non-responder had no infiltrating lymphocytes and very weak HLA G expression (HLA G is expressed in the placenta and may play a role in immune tolerance in pregnancy). Further work in responding versus non-responding cases should shed light on whether these markers might be useful predictors of response to pembrolizumab in GTN. Importantly, all patients who responded had 5 consolidation courses of pembrolizumab once the serum pregnancy hormone (human chorionic

gonadotrophin (hCG)) was normal. All patients remain in remission at 25, 13 and 5 months following discontinuation of pembrolizumab. This small case series demonstrates that pembrolizumab can induce prolonged remissions in patients with GTN otherwise expected to have a fatal outcome.

4 Commissioning Position

Rationale for a clinical commissioning policy statement

Pembrolizumab to treat multi-agent chemotherapy resistant gestational trophoblastic neoplasia is of a level of significant clinical importance that an immediate clinical commissioning policy statement has been adopted. The time taken to develop a full clinical commissioning policy proposition for relative prioritisation and implementation would not meet the immediate need for patients, clinicians and the NHS to have clarity about whether an intervention is or is not routinely commissioned.

An urgent clinical commissioning policy statement has been developed because there are encouraging results from recent studies in a very small number of patients. These studies suggest that pembrolizumab is effective, at least in the short term, for a proportion of patients with:

- disease that failed to respond to high dose chemotherapy with autologous peripheral stem cell support and would otherwise be expected to die from their disease; and,
- disease that failed to respond to multi-agent chemotherapy for whom the last active treatment option would otherwise be high dose chemotherapy with autologous peripheral stem cell support.

There is no evidence to support the commissioning of pembrolizumab earlier in the treatment pathway. There is not yet enough evidence for a full commissioning policy.

Clinical commissioning position

Based on a limited scoping of the evidence, NHS England has concluded that there is sufficient evidence to support the routine commissioning of pembrolizumab for gestational trophoblastic neoplasia meeting the clinical criteria listed.

Clinical commissioning criteria

Pembrolizumab is commissioned for GTN patients as third line treatment following standard regimes for GTN patients assessed as high risk (gestational trophoblastic neoplasia International Federation of Obstetrics and Gynaecology (FIGO) staging score of seven or more as described in Seckl 2010).

Patients must first have received:

- First line treatment: EMA-CO: etoposide, methotrexate and dactinomycin (EMA) alternating every week with cyclophosphamide and vincristine or etoposide and cisplatin (EP) alternating weekly with EMA; and
- Second line treatment: etoposide with cisplatin (EP) alternating every week with EMA but omitting the second day of etoposide and dactinomycin or use of paclitaxel and etoposide (TE) alternating every two weeks with paclitaxel and cisplatin (TP).

Patients are then eligible to receive pembrolizumab as third line treatment.

Pembrolizumab will also be commissioned for patients with poor risk placental site trophoblastic tumours or epithelioid trophoblastic tumours (described in Seckl 2010) and may have received the first and second line treatments described above and are then being considered for high dose chemotherapy. Pembrolizumab can then either be used before high dose chemotherapy (HDC) (Ghorani et al Lancet 2017) or following failure of HDC.

Only one course of pembrolizumab will be commissioned for any one patient as there is no evidence to support re-treatment with pembrolizumab or treatment both before and after HDC with autologous peripheral stem cell support.

Pembrolizumab will be given intravenously at a dose of 2mg/kg (outpatient treatment should be clinically appropriate for most patients) delivered once every 3 weeks. Treatment response will be assessed by serial hCG measurements and repeat imaging. If no benefit is seen after 5 doses then therapy will be stopped. Once the hCG is normal or, if hCG is not reliable (as may be the case in some patients with placental site trophoblastic tumour / epithelioid trophoblastic tumour) when the imaging does not show any tumour, a further 5 doses of consolidation treatment will be given.

Only one course of treatment with pembrolizumab will be given.

The following data collection will be required:

- i) Response to treatment assessed by normalisation of the serum pregnancy hormone levels (hCG)
- ii) Response to treatment as assessed by reduction in tumour size/disappearance on imaging
- iii) progression free survival and overall survival
- iv) treatment related toxicity, short and long term
- v) quality of life using the EQ5D-5L instrument if possible

As pembrolizumab is not licensed for use in GTN any provider organisation treating patients with this intervention will be required to ensure that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Clinical commissioning policy development plan

It has been assessed that the development of a full clinical commissioning policy is not needed at this time. The present urgent policy statement will be reviewed after two years by which time further research evidence may be available that may suggest a significant change in eligibility criteria may be indicated.

Should the subsequent published clinical commissioning policy be revised to 'not routinely commissioned', patients started on treatment under this policy statement will continue to have access to it provided they and the clinician responsible for their care continue to believe that it is the right treatment for them.

5 Mechanism for funding

NHS England will reimburse activity undertaken within the terms of this policy statement, as follows: the treatment will only be provided at, or under the care of, the Highly Specialised Service providers for gestational trophoblastic tumours.

6 Date of policy statement approval and review

The policy statement is effective from January 2017.

A clinical commissioning policy is not planned to be developed at this stage. If a clinician, supported by peers, seeks a reappraisal by the Clinical Panel then a new 'Preliminary Policy Proposition' should be submitted. For guidance email Edmund.jessop@nhs.net.

This policy statement will be formally reviewed by October 2019.

7 References

EI-Helw et al 2005. High-dose chemotherapy and peripheral blood stem cell support in refractory gestational trophoblastic neoplasia. *British Journal of Cancer* 93: 620 – 621.

Ghorani et al 2017. Pembrolizumab induces long term complete remission in patients with chemotherapy resistant gestational trophoblastic neoplasia despite classical HLA deficiency. *Lancet* 390; 2343 - 5.

Huang et al 2017. Complete serological response to pembrolizumab in a woman with chemoresistant metastatic chorioncarcinoma. *J Clin Oncol* 35(27):3172-3174

National Institute for Health and Care Excellence 2015. Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab. Technology appraisal guidance [TA357] Updated: 12 September 2017.

National Institute for Health and Care Excellence 2017. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy. Technology appraisal guidance [TA428].

Seckl MJ, Sebire NJ, Berkowitz RS 2010. Gestational trophoblastic disease. *Lancet* 376: 717-29.