

**EVIDENCE BRIEFING**  
**October 2018**

**Pembrolizumab (Keytruda) for  
relapsed/refractory classical Hodgkin lymphoma**

<b>NIHRI ID</b>	24281	<b>NICE ID</b>	10051
<b>Developer/Company</b>	Merck Sharp & Dohme Ltd	<b>UKPS ID</b>	649922

**Licencing and market  
availability plans**

Currently in phase III clinical trials.

**SUMMARY**

Pembrolizumab is a medicinal product that is being investigated as treatment for patients with relapsed or refractory classical Hodgkin lymphoma (cHL). Hodgkin lymphoma is a type of cancer of the lymphatic system and it is the most common type. The condition is called relapsed or refractory when it recurs after a period of improvement or when it does not respond to treatment. The most common symptom of Hodgkin lymphoma is a swelling in the neck, armpit or groin.

Pembrolizumab, given by intravenous infusion, acts by binding to a protein called anti-programmed death-ligand 1 (PD-L1) that is found on the cancer cells or immune cells trying to attack cancer cells. Binding to this protein can lead to the activation of the body's immune system to fight tumour cells. In cHL, pembrolizumab has promising results. If licensed it will provide a treatment option for cHL patients who have failed ASCT or are not eligible for it.

## PROPOSED INDICATION

Relapsed or refractory classical Hodgkin lymphoma (cHL).<sup>1</sup>

## TECHNOLOGY

### DESCRIPTION

Pembrolizumab (Keytruda; MK-3475) is a humanised monoclonal antibody (mAb) which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.<sup>2</sup>

Pembrolizumab is being investigated for the treatment of relapsed/refractory classical Hodgkin lymphoma who have had received chemotherapy or failed autologous stem cell transplant (ASCT) or who are not candidates for ASCT.<sup>1</sup>

In the phase III trial (NCT02684292, MK-3475-204/KEYNOTE-204) participants receive pembrolizumab 200 mg administered intravenously (IV) on day 1 of each 3-week cycle for up to 35 cycles.<sup>3</sup>

### INNOVATION AND/OR ADVANTAGES

Therapeutic strategies targeting immune checkpoints have shown significant clinical activity in solid tumours and hematologic malignancies. In cHL, 2 monoclonal antibodies directed against PD-1, nivolumab and pembrolizumab, are the most promising thus far.<sup>4</sup>

Currently there are no recommended treatment options for cHL patients who have received chemotherapy with partial or complete response or failed ASCT or who are not candidates for ASCT.

### DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab is currently licenced as a monotherapy in the UK for the treatment of:<sup>2</sup>

- advanced (unresectable or metastatic) melanoma in adults
- metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a  $\geq 50\%$  tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations – first line
- locally advanced or metastatic NSCLC in adults whose tumour express PD-L1 with a  $\geq 1\%$  TPS and who have received at least one prior chemotherapy regimen
- adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant ineligible and have failed BV
- locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy

- locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin containing chemotherapy and whose tumours express PD-L1 with a combined positive score  $\geq 10$
- recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a  $\geq 50\%$  TPS and progressing on or after platinum-containing chemotherapy

Pembrolizumab in combination with pemetrexed and platinum chemotherapy is licensed in the UK for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.<sup>2</sup>

The most common adverse events of pembrolizumab (affecting more than one in ten people) include anaemia, neutropenia, thrombocytopenia, decreased appetite, diarrhoea, nausea, vomiting, constipation, rash, pruritus and fatigue, asthenia, oedema, dysgeusia, and increased alanine aminotransferase.<sup>2</sup>

Pembrolizumab is currently in phase III clinical trials for the treatment of multiple malignant conditions.<sup>5</sup>

## PATIENT GROUP

### DISEASE BACKGROUND

Hodgkin lymphoma is a cancer of the lymphatic system.<sup>6</sup> It is a monoclonal B-cell lymphoid neoplasm characterised by the presence of a variable percentage of malignant Reed–Sternberg (RS) cells within an extensive immune cell infiltrate.<sup>4</sup> It is classified into two groups by the WHO, classical and nodular. Classical Hodgkin lymphoma (cHL) is the most common form of Hodgkin lymphoma.<sup>6</sup>

Hodgkin lymphoma is caused by a mutation in the DNA of a type of B-lymphocytes. The mutation in the DNA causes cells to multiply uncontrollably. The abnormal lymphocytes usually begin to multiply in one or more lymph nodes in a particular area of the body, such as the neck or groin. Over time these abnormal lymphocytes spread into other parts of the body such as bone marrow, spleen, liver, skin and lungs.<sup>7</sup>

Relapsed or refractory is a disease which has recurred after a period of improvement or which does not respond to treatment.<sup>8,9</sup>

The most common symptom of Hodgkin lymphoma is a swelling in the neck, armpit or groin. The swelling is usually painless, although some people find that it aches. Other symptoms include night sweats, unintentional weight loss, fever, persistent cough or feeling of breathlessness, persistent itching, abdominal pain, indigestion, fatigue, increased risk of infections and excessive bleeding.<sup>10</sup>

Although the exact cause is not known, the risk of developing Hodgkin lymphoma is increased if the immune system is weakened, if the patient is taking immunosuppressant medication and where there has been previous exposure to the Epstein Barr virus.<sup>11</sup>

### CLINICAL NEED AND BURDEN OF DISEASE

Hodgkin lymphoma is not among the 20 most common cancers in the UK, accounting for less than 1% of all new cancer cases (2015). In males in the UK, Hodgkin lymphoma is the 19th most common cancer, with around 1,200 new cases in 2015. In females in the UK, Hodgkin lymphoma is not among the 20 most common cancers, with around 910 new cases in 2015.<sup>12</sup>

Classical Hodgkin lymphoma is the most common form of Hodgkin lymphoma. It made up 60% of all Hodgkin lymphoma cases diagnosed in the UK between 2010 and 2012.<sup>13</sup>

In 2016, there were 1,717 newly registered cases of Hodgkin lymphoma in England.<sup>14</sup> Applying the above percentage to this figure, the estimated number of cHL cases would be 1,030. Incidence rates due to Hodgkin lymphoma are projected to rise between 2014 and 2035 in the UK from 4.48 per 100,000 to 4.87 per 100,000 in males and fall from 3.21 per 100,000 to 3.17 per 100,000 in females.<sup>15</sup>

Latest published survival statistics (2016, patients diagnosed in 2011-2015) report stated age-standardised 1-year survival rate of 90% and 5-year survival rate of 81.8% for patients with Hodgkin lymphoma in England.<sup>16</sup>

In 2017, there were 286 deaths due to Hodgkin lymphoma in England.<sup>17</sup> According to the Hospital Episode Statistics (HES) data, in 2016-17 there were 20,841 admissions due to Hodgkin lymphoma which resulted in 16,407 FCE bed days (ICD-10 code C81).<sup>18</sup>

## PATIENT TREATMENT PATHWAY

### PATIENT PATHWAY

More than 80% of patients with cHL are cured with initial treatment and among patients who relapse, ~50% can be cured with high-dose chemotherapy and ASCT. However, for those patients who progress after ASCT or are ineligible for an autologous or allogeneic stem cell transplant due to refractory disease, age, or organ dysfunction, there are limited treatment options, and long-term remissions are uncommon.<sup>19</sup>

The standard treatment approach for medically fit patients with relapsed/refractory disease is salvage chemotherapy followed by autologous stem cell transplant (ASCT) which provides 5-yr Progression Free Survival (PFS) rates of 50–60% for those patients with chemosensitive disease, and 40–45% in patients with primary refractory cHL. The outcome for patients with cHL relapsing after ASCT is poor with a median overall survival (OS) of 1–2 years.<sup>4</sup>

### CURRENT TREATMENT OPTIONS

For relapsed/refractory cHL NICE recommends:<sup>20</sup>

- Brentuximab vedotin as an option for treating CD30-positive disease in adults only if they have already had autologous stem cell transplant or they have already had at least 2 previous therapies when autologous stem cell transplant or multi-agent chemotherapy are not suitable.
- Nivolumab is recommended, within its marketing authorisation, as an option for treating in adults after autologous stem cell transplant and treatment with brentuximab vedotin.
- Pembrolizumab is not recommended for treating relapsed or refractory classical Hodgkin lymphoma in adults who have had autologous stem cell transplant and brentuximab vedotin. Pembrolizumab is recommended for use within the Cancer Drugs Fund as an option for treating relapsed or refractory classical Hodgkin lymphoma in adults who have had brentuximab vedotin and cannot have autologous stem cell transplant, only if pembrolizumab is stopped after 2 years of treatment or earlier if the person has a stem cell

transplant or the disease progresses and the conditions in the managed access agreement for pembrolizumab are followed.

Currently, there is no recommendation for patients who have not been treated with brentuximab vedotin and failed autologous stem cell transplant (ASCT) or who are not candidates for ASCT

## PLACE OF TECHNOLOGY

If licensed, Pembrolizumab will offer a treatment option for patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have received chemotherapy or failed to achieve a response or progressed after autologous stem cell transplant (ASCT), or who are not candidates for ASCT.<sup>a</sup>

## CLINICAL TRIAL INFORMATION

<b>Trial</b>	KEYNOTE-204, NCT02684292, MK-3475-204; 18 years and older; pembrolizumab vs brentuximab vedotin; phase III
<b>Sponsor</b>	Merck Sharp & Dohme Corp.
<b>Status</b>	Ongoing
<b>Source of Information</b>	Trial registry <sup>3</sup>
<b>Location</b>	EU (including UK), USA, Canada and other countries.
<b>Design</b>	Randomised, open label, parallel assignment
<b>Participants</b>	n=300 (planned); aged 18 years and older; classical Hodgkin lymphoma; relapsed/refractory, patients have failed to achieve a response or progressed after ASCT, or patients are not ASCT candidates.
<b>Schedule</b>	Randomised to pembrolizumab 200 mg administered IV on day 1 of each 3-week cycle for up to 35 cycles; or BV 1.8 mg/kg (maximum 180 mg per dose) IV on day 1 of each 3-week cycle for up to 35 cycles.
<b>Follow-up</b>	40 months
<b>Primary Outcomes</b>	<ul style="list-style-type: none"><li>• Progression-free Survival (PFS) [Time frame: up to approximately 40 months]</li><li>• Overall survival (OS) [Time frame: up to approximately 40 months]</li></ul>
<b>Secondary Outcomes</b>	Objective Response Rate (ORR) [Time frame: up to approximately 40 months]
<b>Key Results</b>	-
<b>Adverse effects (AEs)</b>	-
<b>Expected reporting date</b>	Primary completion date reported as July 2020.

## ESTIMATED COST

Pembrolizumab is already marketed in the UK; 100mg/4ml concentrate for solution for infusion vials (25mg/mL) costs £2,630 vial.<sup>21</sup>

<sup>a</sup> Information provided by company

## ADDITIONAL INFORMATION

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE technology appraisal guidance in development. Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (GID-TA10144). Expected publication date: to be confirmed
- NICE technology appraisal guidance. Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma (TA540). September 2018.
- NICE technology appraisal guidance. Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma (TA462). July 2017.
- NICE quality standard. Haematological cancers (QS150). June 2017.

### NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.

### OTHER GUIDANCE

- ESMO. Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2018.<sup>22</sup>
- National Comprehensive Cancer Network. Hodgkin lymphoma version 1.2017. 2017.<sup>23</sup>
- London Cancer. Guidelines for the management of non-Hodgkin's and Hodgkin's lymphoma in adults. 2015.<sup>24</sup>


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