Pembrolizumab (Keytruda®) is indicated for the treatment of adult and paediatric patients with relapsed or refractory classical Hodgkin lymphoma (cHL)

General information

Drug description	Indication [1]
Pembrolizumab is a programmed death-1 (PD-1) inhibitor.	Pembrolizumab as monotherapy is indicated for the treatment of adult and pediatric patients aged 3 years and older with relapsed or refractory cHL who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

Current treatment [2]

- For relapsed/refractory cHL NICE recommends:
  - Brentuximab vedotin as an option for treating CD30-positive disease in adults only if they have already had ASCT or they have already had at least 2 previous therapies when ASCT or multi-agent chemotherapy are not suitable.
  - Nivolumab is recommended, within its marketing authorisation, as an option for treating adults after ASCT and treatment with brentuximab vedotin.
  - Pembrolizumab is not recommended for treating relapsed or refractory cHL in adults who have had ASCT and brentuximab vedotin. Pembrolizumab is recommended for use within the Cancer Drugs Fund as an option for treating relapsed or refractory cHL in adults who have had brentuximab vedotin and cannot have ASCT, 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 ASCT or who are not candidates for ASCT.

Regulatory status

EMA [1]

Approval status for this indication: On 28 January 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Keytruda®.

The CHMP adopted an extension to an existing indication as follows:

- Keytruda® as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory cHL who have failed ASCT or following at least two prior therapies when ASCT is not a treatment option.

Other indications: Pembrolizumab is indicated

- **Melanoma:**
  - as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults.
  - as monotherapy for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.
- **Non-small cell lung carcinoma (NSCLC):**
  - as monotherapy for the first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK-positive tumour mutations.
  - in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK-positive mutations.

FDA [3, 4]

Approval status for this indication: On 14 October 2020, the FDA extended the approval of pembrolizumab (Keytruda®) for the following indications:

- adult patients with relapsed or refractory cHL and
- paediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.

Other indications: Pembrolizumab is indicated:

- **Melanoma:**
  - for the treatment of patients with unresectable or metastatic melanoma.
  - for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.
- **NSCLC:**
  - in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumour aberrations.
  - in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC.
  - as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumour aberrations, and is:
    - stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
    - metastatic.
  - as a single agent for the treatment of patients with metastatic NSCLC whose tumours express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.
- **Small Cell Lung Cancer (SCLC):**

• in combination with carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of metastatic squamous NSCLC in adults. • as monotherapy for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK-positive tumour mutations should also have received targeted therapy before receiving pembrolizumab. ❖ **Urothelial carcinoma (UC):** • as monotherapy for the treatment of locally advanced or metastatic UC in adults who have received prior platinum-containing chemotherapy. • as monotherapy for the treatment of locally advanced or metastatic UC in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10. ❖ **Head and neck squamous cell carcinoma (HNSCC)** • as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, for the first-line treatment of metastatic or unresectable recurrent HNSCC in adults whose tumours express PD-L1 with a CPS ≥ 1. • as monotherapy for the treatment of recurrent or metastatic HNSCC in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy. ❖ **Renal cell carcinoma (RCC):** • in combination with axitinib, for the first-line treatment of advanced RCC in adults. ❖ **Colorectal cancer (CRC):** • as monotherapy for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults. ✓ **Medicine under additional monitoring**	• for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. ❖ **HNSCC:** • in combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC. • as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumours express PD-L1 (CPS ≥1) as determined by an FDA-approved test. • as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy. ❖ **Primary Mediastinal Large B-Cell Lymphoma (PMBCL):** • for the treatment of adult and paediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy. Limitations of use: Pembrolizumab is not recommended for the treatment of patients with PMBCL who require urgent cytoreductive therapy. ❖ **UC:** • for the treatment of patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 (CPS ≥10) as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. • for the treatment of patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. • for the treatment of patients with Bacillus Calmette-Guerin-unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in situ with or without papillary tumours who are ineligible for or have elected not to undergo cystectomy. ❖ **Microsatellite Instability-High or Mismatch Repair Deficient Cancer:** • for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) o solid tumours that have progressed following prior treatment and who have no satisfactory alternative treatment options,1 or o colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Limitations of Use: The safety and effectiveness of pembrolizumab in pediatric patients with MSI-H central nervous system cancers have not been established. ❖ **Microsatellite Instability-High or Mismatch Repair Deficient CRC:** • for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR CRC. ❖ **Gastric Cancer:** • for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumours express PD-L1 (CPS ≥1) as determined by an FDA-approved test, with disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy. ❖ **Oesophageal Cancer:** • for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the oesophagus whose tumours express PD-L1 (CPS ≥10) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy. ❖ **Cervical Cancer:**

- for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumours express PD-L1 (CPS) ≥1) as determined by an FDA-approved test.

❖ **Hepatocellular Carcinoma (HCC):**
- for the treatment of patients with HCC who have been previously treated with sorafenib.

❖ **Merkel Cell Carcinoma (MCC):**
- for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic MCC.

❖ **RCC:**
- in combination with axitinib, for the first-line treatment of patients with advanced RCC.

❖ **Endometrial Carcinoma:**
- in combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.

❖ **Tumor Mutational Burden-High (TMB-H) Cancer:**
- for the treatment of adult and pediatric patients with unresectable or metastatic tumour mutational burden-high (TMB-H ≥10 mutations/megabase) solid tumours, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
  Limitations of Use: The safety and effectiveness of pembrolizumab in pediatric patients with TMB-H central nervous system cancers have not been established.

❖ **Cutaneous Squamous Cell Carcinoma (cSCC):**
- for the treatment of patients with recurrent or metastatic cSCC that is not curable by surgery or radiation.

❖ **Triple-Negative Breast Cancer (TNBC):**
- in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumours express PD-L1 (CPS ≥10) as determined by an FDA approved test.

❖ **Adult Indications**: Additional Dosing Regimen of 400 mg Every 6 Weeks:
- for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications.

Costs

4 ml Keytruda® concentrate for solution for infusion 25 mg/ml = € 3,428.00 (ex-factory price) [5]
KEYNOTE-204 patients received pembrolizumab at a dose of 200 mg IV every 3 weeks → **1 dose = € 6,856.00**

Warnings and precautions [4]

❖ **Immune-Mediated Adverse Reactions:**
- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and solid organ transplant rejection.
- Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
- Withhold or permanently discontinue based on severity and type of reaction.

❖ **Infusion-related reactions:** Interrupt, slow the rate of infusion, or permanently discontinue pembrolizumab based on the severity of reaction.

❖ **Complications of allogeneic HSCT:** Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody.

❖ Treatment of patients with **multiple myeloma** with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

❖ **Embryo-Fetal toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective method of contraception.

Study characteristics [6-8]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
KEYNOTE-204 NCT02684292	304	pembrolizumab 200 mg IV every 3 weeks (n=148)	Brentuximab vedotin 1.8 mg/kg IV every 3 weeks (n=152)	**PFS** by BICR per IWG criteria + **OS**	randomized, international, open-label, phase III study	-	Merck Sharp & Dohme Corp.	[6] (Abstract)

Efficacy (I vs. C)	Safety (I vs. C)
Primary PFS analysis: Statistically significant improvement was observed with I vs. C; HR 0.65 (95% CI 0.48-0.88; p=0.002) **Median PFS, months:** 13.2 vs. 8.3 **12-month PFS rates:** 53.9% vs. 35.6% Benefit was observed in all **subgroups** tested, including patients with no auto-SCT (HR 0.61), primary refractory disease (HR 0.52), prior brentuximab vedotin (HR 0.34) and brentuximab vedotin naive (HR=0.67). Significant improvement in **PFS-secondary**[1] was observed in I vs. C: HR 0.62 (95% CI 0.46-0.85) **Median PFS-secondary, months**: 12.6 vs. 8.2 **PFS (per investigator assessment):** longer with I vs. C; HR 0.49 (95% CI 0.36-0.67) **Median PFS (per investigator assessment), months:** 19.2 vs. 8.2 **ORR:** 65.6% vs. 54.2% **CR rates:** 24.5% vs. 24.2% **Median DOR, months**: 20.7 (range 0.0+ to 33.2+) vs. 13.8 (range 0.0+ to 33.9+) **QoL**: Completion and compliance rates were >90% for both groups at baseline and remained high (>80%) at week 24. Improvement was observed at week 24 with pembrolizumab in the QLQ-C30 global health status (GHS)/quality of life (LSM difference; 95% CI: 8.60, 3.89-13.3; p=0.0004) and physical functioning (6.42, 1.87-10.62; p=0.0054) scores vs. brentuximab vedotin, which showed a worsening. Similar improvements were seen for pembrolizumab in EQ5D utility (0.09, 0.04-0.14; p=0.0004) and VAS scores (6.12, 1.91-10.34; p=0.0046). Pembrolizumab demonstrated an improvement in QLQ-C30 GHS/QoL score vs. Brentuximab vedotin in patients who progressed (11.76, 5.66-17.86; p=0.0002) and did not progress (5.10, –2.53, 12.73; p=0.187). Prolonged TTD was observed with pembrolizumab vs. brentuximab vedotin for QLQ-C30 GHS/QoL (HR, 0.40; 95% CI, 0.22-0.74; p=0.003) and physical functioning score (HR, 0.56; 95% CI, 0.32-0.97; p=0.034).	**Grade 3-5 TRAEs**: 19.6% vs. 25.0% **Death**[2]**:** n=1 vs. n=0 **GVHD**: Of 14 patients in KEYNOTE-204 who proceeded to allogeneic HSCT after treatment with pembrolizumab, 8 patients reported acute GVHD and 3 patients reported chronic GVHD, none of which were fatal. **Hepatic VOD**: n=0 **Engraftment syndrome post-transplant**: n=1 [9]

Risk of bias (study level) [10]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
unclear	unclear	no, open-label	unclear	unclear	unclear[3]

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Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ASCT=autologous stem cell transplant, BICR= blinded independent central review, C=comparator, cHL= classical Hodgkin lymphoma, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CPS= combined positive score, CR=complete response, CRC=colorectal carcinoma, cSCC=cutaneous squamous cell carcinoma, dMMR=deficient mismatch repair, DOR=duration of response, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, EQ-5D=European Quality of Life 5 Dimensions, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, FU=fluorouracil, GHS=global health status, GVHD=graft-versus-host-disease, HCC=hepatocellular carcinoma, HER2=human epidermal growth factor receptor 2, HNSCC=head and neck squamous cell carcinoma, HR=hazard ratio, HSCT=haematopoietic stem-cell transplantation, I=intervention, Int.=intention, IV=intravenous, IWG=International Working Group, LSM=least-squares mean, MCC=Merkel cell carcinoma, MG=median gain, MSI-H=microsatellite instability-high, n=number of patients, NICE=National Institute for Health and Care Excellence, NSCLC=non-small cell lung cancer, OS=overall survival, PD= programmed death, PD-L1=programmed death-ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PMBCL=primary mediastinal large B-cell lymphoma, QLQ-C30=quality of life questionnaire, QoL=quality of life, RCC=renal cell carcinoma, SAE=serious adverse event, SCLC=small cell lung cancer, SCT=stem cell transplant, ST=standard treatment, TMB-H=tumor mutational burden-high, TNBC=triple-negative breast cancer, TPS=tumour proportion score, TRAE=treatment-related adverse event, TTD=time to deterioration, UC=urothelial carcinoma, VAS=visual analogue scale, VOD=veno-occlusive disease

[1] PFS-secondary = PFS excluding clinical and imaging data after auto-SCT or allo-SCT
[2] Death due to TRAE (pneumonia).
[3] Only abstract available; KEYNOTE-204 trial is ongoing until 07/2025.

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