Pembrolizumab (Keytruda®) as monotherapy for the treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumours in adults with unresectable or metastatic colorectal cancer, advanced or recurrent endometrial carcinoma and unresectable or metastatic gastric, small intestine, or biliary cancer

General information

Drug description	Indication [1]
Pembrolizumab (Keytruda®) is an anti–programmed death-1 (PD-1) monoclonal antibody.	Pembrolizumab (Keytruda®) as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with: ❖ unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy; ❖ advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation; ❖ unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

Current treatment [2]

- ❖ There are multiple treatment options currently available for the generic treatment of solid tumours which include surgery, chemotherapy, radiotherapy, hormone therapy, immunotherapies (e.g. monoclonal antibodies) and targeted cancer drugs (e.g. cancer growth blockers).
- ❖ The treatment provided will vary according to type of cancer, how big the cancer is, if the cancer has spread to other areas of the body and according to the patients' general health.
- ❖ Regarding the specific treatment of MSI-H/dMMR tumours, NICE guidance recommends use of nivolumab plus ipilimumab as a first line therapy for patients with metastatic colorectal cancer with MSI-H or dMMR.

Regulatory status

EMA [1]

Approval status for this indication: On 24 March 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Keytruda®.

<u>The CHMP adopted new indications as follows:</u>

- ❖ Keytruda as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:
  - unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy;
  - advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation;
  - unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

Other indications: Keytruda® 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%

FDA [3-5]

Approval status for this indication: On **23 May 2017**, the FDA granted accelerated approval to pembrolizumab (Keytruda®) for adult and paediatric patients with unresectable or metastatic, **MSI-H or dMMR solid tumours** that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

- ✓ Accelerated approval
- ✓ Priority review
- ✓ Limitations of Use: The safety and effectiveness of Keytruda® in paediatric patients with MSI-H central nervous system cancers have not been established.
- ✓ The approval was based on data from 149 patients with MSI-H or dMMR cancers enrolled across five uncontrolled, multi-cohort, multi-centre, single-arm clinical trials. 90 patients had colorectal cancer and 59 patients were diagnosed with one of 14 other cancer types.

On **21 March 2022**, the FDA approved pembrolizumab (Keytruda®), as a single agent, for patients with **advanced endometrial carcinoma** that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and who are not candidates for curative surgery or radiation.

Other indications: Keytruda is indicated:

- ❖ Melanoma
  - for the treatment of patients with unresectable or metastatic melanoma.
  - for the adjuvant treatment of adult and paediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma 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.

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.
- 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 Keytruda®.

❖ Classical Hodgkin lymphoma (cHL)
- as monotherapy for the treatment of adult and paediatric 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.

❖ Urothelial carcinoma
- as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.
- as monotherapy for the treatment of 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 (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.
- in combination with lenvatinib, for the first-line treatment of advanced RCC in adults.

- 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 Keytruda®

❖ 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.

❖ cHL
- for the treatment of adult patients with relapsed or refractory cHL.
- for the treatment of paediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.

❖ 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: Keytruda® is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

❖ Urothelial carcinoma
- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
  - are not eligible for any platinum-containing chemotherapy, or
  - 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.

❖ Gastric cancer
- in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma (this indication is approved under accelerated approval based on tumour response rate and durability of response).
- for the treatment of patients with locally advanced or metastatic oesophageal or GEJ (tumours with epicentre 1 to 5 centimetres above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
  - in combination with platinum- and fluoropyrimidine-based chemotherapy, or
  - as a single agent after one or more prior lines of systemic therapy for patients with tumours of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test.

❖ Cervical cancer

- as monotherapy for the adjuvant treatment of adults with RCC at increased risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions.

❖ Colorectal cancer
- as monotherapy for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults.

❖ Oesophageal carcinoma
- in combination with platinum and fluoropyrimidine based chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10.

❖ Triple-negative breast cancer (TNBC)
- in combination with chemotherapy, for the treatment of locally recurrent unresectable or metastatic TNBC in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease.

❖ Endometrial carcinoma
- in combination with lenvatinib, for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.

❖ Cervical cancer
- in combination with chemotherapy with or without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1.

✓ **Medicine under additional monitoring**

- as a single agent 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 (this indication is approved under accelerated approval based on tumour response rate and durability of response).

❖ Merkel cell carcinoma (MCC)
- for the treatment of adult and paediatric patients with recurrent locally advanced or metastatic MCC (this indication is approved under accelerated approval based on tumour response rate and durability of response).

❖ RCC
- in combination with axitinib, for the first-line treatment of adult patients with advanced RCC.
- in combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC.
- for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

❖ 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 in any setting and are not candidates for curative surgery or radiation.

❖ Tumour mutational burden-high (TMB-H) cancer
- for the treatment of adult and paediatric 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 (this indication is approved under accelerated approval based on tumour response rate and durability of response). Limitations of Use: The safety and effectiveness of Keytruda® in paediatric 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 or locally advanced cSCC that is not curable by surgery or radiation.

❖ TNBC
- for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
- 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 (this indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Costs [6]

4 ml Keytruda® concentrate for solution for infusion 25mg/ml = **€3,428.00** (ex-factory price)

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 Keytruda® 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-foetal toxicity:**
- Can cause foetal harm. Advise females of reproductive potential of the potential risk to a foetus and to use effective method of contraception.

Study characteristics [3]:
Pembrolizumab for patients with unresectable or metastatic MSI-H or dMMR solid tumours that have progressed following prior treatment and who have no satisfactory alternative treatment options OR with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
-	149[1] patients across 5 trials	pembrolizumab, 200 mg every 3 weeks, or pembrolizumab, 10 mg/kg every 2 weeks	-	NA	5 uncontrolled, multi-cohort, multi-centre, single-arm clinical trials	MSI-H, dMMR	NA	Link: NA

Efficacy	Safety
ORR (by blinded independent central radiologists' review according to RECIST 1.1): 39.6% (95% CI, 31.7-47.9) Responses lasted **≥6 months** for 78% of those who responded to pembrolizumab. There were **11 complete responses and 48 partial responses**. ORR was similar irrespective of whether patients were diagnosed with colorectal cancer (36%) or a different cancer type (46% across the 14 other cancer types).	The **most common adverse reactions** to pembrolizumab: fatigue, pruritus, diarrhoea, decreased appetite, rash, pyrexia, cough, dyspnoea, musculoskeletal pain, constipation, and nausea. Pembrolizumab is **associated** with immune-mediated side effects, including pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis**.**

ESMO-MCBS version 1.1

Not applicable for the outcomes assessed.

Study characteristics: Pembrolizumab in patients with unresectable or metastatic MSI-H or dMMR endometrial carcinoma [7-10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)

[1] 90 patients had colorectal cancer and 59 patients were diagnosed with one of 14 other cancer types.

KEYNOTE-158 NCT02628067	233[2]/ 90[3]	pembrolizumab IV 200 mg once every 3 weeks for 35 cycles[4]	-	ORR per RECIST version 1.1, as assessed by independent central radiologic review	ongoing[5], non-randomized, open-label, multicohort, multisite phase II study	MSI-H, dMMR	Funded by Merck Sharp & Dohme Corp.	[8] (KEYNOTE-158) [9] (KEYNOTE-158, endometrial cancer)

Efficacy (n=79)	**Safety** (n=90)
ORR: 48% (95% CI, 37-60) had an objective response as determined by independent central radiologic review, including **CR**:14% **PR**: 34% **Stable disease**:18% **Progressive disease**: 29% **Median time to response**: 2.3 months (range, 1.3-10.6) **Median duration of response:** not reached (range, 2.9-49.71 months) **Kaplan-Meier estimate of the proportion of patients with response duration ≥1 year** was 88% and **≥2 years** was 73%, with a plateau from **≥3 years** at 68%. ORR among the 38 patients who had received <2 lines of prior therapy: 53% (95% CI, 36-69) ORR among the 41 patients who had received ≥2 lines of prior therapy: 44% (95% CI, 28-60) ORR among the 56 patients with prior radiation therapy: 52% (95% CI, 38-65) ORR among the 23 patients with no prior radiation therapy: 39% (95% CI, 20-61) At data cutoff, 45 patients (57%) had experienced disease progression or died. **Median PFS:** 13.1 months (95% CI, 4.3-34.4 months) **Kaplan-Meier estimate of the PFS rate**: 51% at 1 year, 41% at 2 years, and 37% at 3 and 4 years At the time of data cutoff, 29 (37%) had died. **Median OS**: not reached (95% CI, 27.2 months-not reached). **Kaplan-Meier estimate of the OS rate**: 69% at 1 year and 64% at 2 years, with a plateau at 60% at 3 and 4 years.	**AEs considered by the investigator to be related to study treatment:** n=68/90 (76%) **Treatment-related AEs grade 3 or 4: n**=11/90 (12%) **Discontinuation of treatment due to a treatment-related AE:** n=6/90 (7%) **Immune-mediated AEs grade 3 or 4:** n=6/90 (7%)

ESMO-MCBS version 1.1 [11]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	-	PFS: 13.1 months	-	PFS >6 months	3	-	-	-	3
Not applicable because of the missing control group.											

[2] Cohorts: anal carcinoma (cohort A); biliary adenocarcinoma (except ampulla of Vater cancers; cohort B); well- and moderately differentiated neuroendocrine tumours of the lung, appendix, small intestine, rectum, or pancreas (cohort C); **endometrial carcinoma (except sarcomas and mesenchymal tumours; cohort D);** cervical squamous cell carcinoma (cohort E); vulvar carcinoma (cohort F); small-cell lung carcinoma (cohort G); mesothelioma (cohort H); papillary or follicular thyroid carcinoma (cohort I); salivary gland carcinoma (sarcomas and mesenchymal tumours excluded; cohort J); or any other advanced solid tumour (with the exception of colorectal cancer) that is MSI-H/dMMR (cohort K).

[3] A total of 90 patients with MSI-H/dMMR endometrial cancer were enrolled in cohorts D (n=11) or K (n=79).

[4] For approximately 2 years—or until documented disease progression, unacceptable toxicity, intercurrent illness preventing additional treatment administration, or patient/investigator decision.

[5] The KEYNOTE-158 trial is currently ongoing; the estimated study completion date is 06/2026.

Risk of bias - study level (case series) [12]								
1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	partial	yes	unclear	yes	no
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	unclear	yes	yes	unclear	yes
Overall risk of bias: moderate								
First published: 04/2022								

Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ASCT=autologous stem cell transplant, C=comparator, cHL=classical Hodgkin lymphoma, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CPS=combined positive score, CR=complete response, cSCC=cutaneous squamous cell carcinoma, dMMR=mismatch repair–deficient, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, 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, GEJ=gastroesophageal junction, HCC=hepatocellular carcinoma, HNSCC= head and neck squamous cell carcinoma, HR=hazard ratio, HSCT=haematopoietic stem cell transplantation, I=intervention, Int.=intention, IV=intravenous, MCC=Merkel cell carcinoma, MG=median gain, MSI-H=microsatellite instability-high, n=number of patients, NA=not available, NICE=National Institute for Health and Care Excellence, NSCLC=non-small cell lung cancer, ORR=objective response rate, OS=overall survival, PD-1=programmed-death 1, PD-L1=programmed death-ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PMBCL=primary mediastinal large B-cell lymphoma, PR=partial response, QoL=quality of life, RCC=renal cell carcinoma, RECIST=Response Evaluation Criteria in Solid Tumors, SAE=serious adverse event, ST=standard treatment, TMBH=tumour mutational burden-high, TNBC=triple-negative breast cancer TPS=tumour proportion score

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