Pembrolizumab (Keytruda®) as monotherapy for the adjuvant treatment of adults and adolescents aged 12 years and older with stage IIB, IIC or III melanoma who have undergone complete resection

General information

Drug description	Indication [1]
Pembrolizumab (Keytruda®) is a programmed death receptor-1 (PD-1)-blocking antibody.	Pembrolizumab (Keytruda®) as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with stage IIB, IIC or III melanoma who have undergone complete resection.

Current treatment [2]

- Patients with stage IIB and IIC melanoma have a deep or ulcerated primary tumour.
- These patients occur in similar numbers, and have the same risk of recurrence and death, as those with stage IIIA and IIIB melanoma.
- Despite the equivalent risk, the current standard of care is observation for stage II B/C and adjuvant therapy for stage III A/B melanoma.

Regulatory status

EMA [1]

Approval status for this indication: On 19 May 2022, 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 for the treatment of melanoma as follows:

- Keytruda® as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with stage IIB, IIC or III melanoma and who have undergone complete resection.

Other indications: Keytruda® is indicated:

- **Melanoma**
  - as monotherapy for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma (positive CHMP opinion).
- **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.
  - 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)**

FDA [3, 4]

Approval status for this indication: On 3 December 2021, the FDA approved pembrolizumab (Keytruda®) for the adjuvant treatment of adult and pediatric (≥12 years of age) patients with stage IIB or IIC melanoma following complete resection.

- ✓ **Priority review**
- ✓ **Orphan designation**

Other indications: Keytruda® is indicated:

- **Melanoma**
  - for the treatment of patients with unresectable or metastatic melanoma.
- **NSCLC**
  - in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous 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 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.

- 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.
- 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.

❖ **Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers**
- Colorectal cancer (CRC)
  - as monotherapy for adults with MSI-H or dMMR CRC in the following settings:
    first-line treatment of metastatic CRC;
    treatment of unresectable or metastatic CRC after previous fluoropyrimidine-based combination therapy.
- Non-colorectal cancers
  - as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:
    advanced or recurrent endometrial carcinoma (EC), who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and

❖ **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 pediatric 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.

❖ **MSI-H or dMMR cancer**
- for the treatment of 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 (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 MSI-H central nervous system cancers have not been established.

❖ **MSI-H or dMMR CRC**
- for the treatment of patients with unresectable or metastatic MSI-H or dMMR CRC.

❖ **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).

❖ **Oesophageal cancer**
- for the treatment of patients with locally advanced or metastatic oesophageal or GEJ (tumours with epicenter 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**
- in combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

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.

❖ **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 as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, for the treatment of adults with locally advanced, or early-stage TNBC at high risk of recurrence.
- 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.

❖ **EC**
- in combination with lenvatinib for the treatment of advanced or recurrent EC 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).

❖ **Renal cell carcinoma (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.

❖ **EC**
- in combination with lenvatinib, for the treatment of patients with advanced EC 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.
- as a single agent, for the treatment of patients with advanced EC 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 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 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).

Costs

4 ml Keytruda® concentrate for solution for infusion 25 mg/ml = **€ 3,428.00** (ex-factory price) **[5]**

Warnings and precautions [3]

- **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: KEYNOTE-716 [6-8]

Pembrolizumab vs. placebo as adjuvant therapy incompletely resected stage IIB or IIC melanoma

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
KEYNOTE-716 NCT03553836	976 (1:1)	pembrolizumab IV 200 mg (*2 mg/kg in paediatric patients*) every 3 weeks[1]	placebo every 3 weeks[2]	recurrence-free survival (investigator-assessed)	**ongoing**, international, double-blind, randomised, placebo-controlled, phase 3 study	PD-1	Merck Sharp & Dohme	[7]

Efficacy (I vs. C) (n=976)

<u>First interim analysis data</u>

Median time since randomisation at the first interim analysis (data cut-off on 4 December, 2020): 14.4 months (IQR 10.2–18.7) vs. 14.3 months (10.1–18.7)

Patients who had a **first recurrence of disease or died**: 11% vs. 17%; HR 0.65 (95% CI 0.46–0.92), p=0.0066

Estimated **12-month recurrence-free survival rate:** 90% (95% CI 87–93) vs. 83% (79–86)

Median recurrence-free survival: not reached in either group

<u>Second interim analysis data</u>

Data cut-off on 21 June, 2021; **median follow-up** of 20.9 months (16.7–25.3) vs. 20.9 months (16.6–25.3)

Patients who had a **first recurrence or died**: 15% vs. 24%; HR 0.61 (95% CI 0.45–0.82)

Estimated **18-month recurrence-free survival rate**: 86% (95% CI 82–89) vs. 77% (95% CI 73–81)

Median recurrence-free survival: not reached in either group

Safety (I vs. C) (n=969)

<u>First interim analysis data</u>

AEs of any cause: 93% vs. 89%

Any-cause endocrine disorders: 25% vs. 5%

AEs led to death: n=0/483 vs. n=4/486[3]

Discontinuation due to AEs: 75/483 (16%) vs. 20/486 (20%)

Treatment-related events of any grade: n=386/483 (80%) vs. n=296/486 (61%)

Treatment-related endocrine disorders: n=118/483 (24%) vs. 15/486 (3%)

Grade 3–4 treatment-related events: n=78/483 (16%) vs. n=21/486 (4%)

<u>Second interim analysis data</u>

[1] For 17 cycles or until disease recurrence or unacceptable toxicity.

[2] For 17 cycles or until disease recurrence or unacceptable toxicity.

[3] One each due to pneumonia, COVID-19-related pneumonia, suicide, and recurrent cancer.

Recurrence at the time of the second interim analysis: 15% vs. 24% Patients who developed **distant metastasis** as a first recurrence (including distant metastases diagnosed within 30 days of a local, regional, or locoregional event): 6% vs. 12% Patients with a recurrence event at the second interim analysis who received **subsequent systemic therapy** after the first recurrence: 58% vs. 38%; among these patients, 10% vs. 17% received **anti-PD-1 therapy**, 17% vs. 8% received **combination anti-PD-1 and anti-CTLA-4 therapy,** and 21% vs. 8% received **BRAF–MEK targeted therapy**. 46 patients had either **crossed over** from the placebo group to the pembrolizumab group (n=45) or had been re-treated (n=1) with pembrolizumab in part 2 of the study.	At the **second interim analysis,** the incidence of any cause and treatment-related events were similar to that at the first interim analysis, with one death due to an AE (COVID-19-related pneumonia) reported in the pembrolizumab group and no additional deaths due to AEs reported in the placebo group. **Discontinuation due to AEs**: 85/483 (18%) vs. 23/486 (5%) There were **no** treatment-related deaths.

ESMO-MCBS version 1.1 [9]

Pembrolizumab vs. placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	adjuvant	1	-	Estimated 12-month recurrence-free survival rate: +7%	0.65 (0.46–0.92)	Improvement in DFS alone (HR<0.65) in studies without mature survival data	A	-	-	-	A
Adapted	adjuvant	1		Estimated 12-month recurrence-free survival rate: +7%	0.65 (0.46–0.92)	Improvement in DFS alone (primary endpoint) (HR 0.65 - 0.8) without mature survival data	B	-	-	-	B

Risk of bias (RCT) [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**
yes	yes	yes	unclear[4]	yes[5]	unclear

Study characteristics: KEYNOTE-054 [11-14]

Adjuvant pembrolizumab vs. placebo in resected stage III melanoma

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
EORTC1325/ KEYNOTE-054 NCT02362594	1019 (1:1)	pembrolizumab IV 200 mg every 3 weeks for up to 18 doses or until disease	placebo every 3 weeks for up to 18 doses or until disease recurrence or	recurrence-free survival in the ITT-population and in patients with	**ongoing**[6], international, double-blind, randomised, controlled, phase 3 trial	PD-1	Merck Sharp & Dohme	[12]

[4] The KEYNOTE-716 trial is ongoing; currently, only results from the planned first and second interim analyses are available.

[5] The study was designed by academic investigators and employees of the sponsor. The sponsor funded the study, participated in study design, data collection, data analysis, data interpretation, and the writing of this report. The sponsor maintained the study database.

[6] The KEYNOTE-054 trial is currently ongoing; estimated study completion date is 07/2026.

		recurrence or unacceptable toxicity	unacceptable toxicity	PD-L1-positive tumours				

Efficacy (I vs. C)	**Safety** (I vs. C), Immune-related AEs (irAEs, n=1011)
Median follow-up: 42.2 months vs. 42.5 months **ITT-population (n=1019):** 3.5-year distant metastasis-free survival rate: 65.3% (95% CI 60.9–69.5) vs. 49.4% (44.8–53.8); HR 0.60 (95% CI 0.49–0.73); p<0.0001 Patients who developed distant metastases or died: 34% vs. 49% 3.5-year recurrence-free survival rate: 59.8% (95% CI 55.3–64.1) vs. 41.4% (37.0–45.8), HR 0.59 (95% CI 0.49–0.70) **Subgroup of patients with PD-L1-positive tumours (n=853):** Patients with a distant metastasis-free survival event: 32% vs. 47% 3.5-year distant metastasis-free survival rate: 66.7% (95% CI 61.8–71.2) vs. 51.6% (46.6–56.4); HR stratified by stage 0.61 (95% CI 0.49–0.76); p<0.0001 3.5-year recurrence-free survival rate: 61.4% (95% CI 56.3–66.1) vs. 44.1% (39.2–48.8), HR 0.59 (95% CI 0.49–0.73) **Subgroup of patients with PD-L1-negative tumours (n=116):** 3.5-year distant metastasis-free survival rate: 58.0% (95% CI 44.1–69.5) vs. 40.2% (27.0–53.0) **Subgroup of patients with PD-L1 indeterminate status (n=50):** 3.5-year distant metastasis-free survival rate: 59.3% (95% CI 38.6–75.0) vs. 28.6% (11.7–48.2)	**Grade 1 or higher irAEs at 3 months**:19.4% vs. 4.0% **Grade 1 or higher irAEs at 15 months**: 37.4% vs. 9% **Discontinuation** of treatment owing to an irAE among patients who experienced an irAE: 33/190 vs. 6/45

ESMO-MCBS version 1.1 [9]

Adjuvant pembrolizumab vs. placebo in resected stage III melanoma

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	adjuvant	1	-	3.5-year metastasis-free survival: +15.9 months	0.60 (0.49–0.73)	Improvements in DFS alone (HR<0.65) in studies without mature survival data	A	-	-	-	A
Adapted	adjuvant	1	-	3.5-year metastasis-free survival: +15.9 months	0.60 (0.49–0.73)	Improvements in DFS alone (HR<0.65) in studies without mature survival data	A	-	-	-	A

Risk of bias (RCT) [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**
yes	unclear	yes	unclear[7]	yes[8]	**unclear**

First published: 06/2022

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, CRC=colorectal cancer, cSCC=cutaneous squamous cell carcinoma, CTLA-4=cytotoxic T-lymphocyte-associated Protein 4, DFS=disease-free survival, dMMR=mismatch repair deficient,

[7] The KEYNOTE-057 trial is currently ongoing.

[8] Industry-funded trial.

EC=endometrial cancer, 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, 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, ITT=intention-to-treat, MCC=Merkel cell carcinoma, MG=median gain, MSI-H=microsatellite instability-high, n=number of patients, NSCLC=non-small cell lung carcinoma, OS=overall survival, PD-L1=programmed ligand-1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PMBCL=primary mediastinal large B-cell lymphoma, QoL=quality of life, RCC=renal cell carcinoma, SAE=serious adverse event, ST=standard treatment, TMB-H=tumour mutational burden-high, TNBC=triple-negative breast cancer, TPS=tumour proportion score

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