Pembrolizumab (Keytruda®) as monotherapy for the adjuvant treatment of non-small cell lung carcinoma (NSCLC)

General information

Drug description [1]

Keytruda® is a programmed death receptor-1 (PD-1)-blocking antibody.

Indication [2]

Pembrolizumab (Keytruda®) as monotherapy is indicated for the adjuvant treatment of adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy.

Incidence

- In Austria, in 2020, the age-standardised incidence rate[1] of cancer of the lung, trachea and bronchus was 67.4 per 100,000 men and 41.1 per 100,000 women [3].
- In 2017 - 2019, NSCLC accounted for approximately 79% of all lung cancer cases reported to cancer registries via hospitals, practices, or pathologies (based on cancer registry data from the individual German states). 15% were small cell lung cancer, and in approximately 5% of cases, no assignment was possible due to nonspecific histology information. Adenocarcinomas formed the largest group within NSCLC at 54%, followed by squamous cell carcinomas (28%) [4].

Current treatment [4]

Adjuvant systemic therapy

- Numerous randomized trials have been conducted over the past 35 years to improve survival rates after surgical resection. Inclusion criteria, composition of the study cohorts, treatment protocols, and follow-up periods vary.
- The following conclusions can be drawn from the results of individual studies, from meta-analyses, and from subgroup analyses:
  - Adjuvant chemotherapy significantly increased 5-year survival rates in patients with stage II-III NSCLC after R0 resection and may also be considered in stage IB (UICC 7th edition) with additional risk factors.
  - The benefit of adjuvant chemotherapy is not limited to certain age groups. However, there are insufficient data for patients >75 years of age.
  - Adjuvant chemotherapy should start 4-8 weeks after surgery. A benefit is only proven if chemotherapy is started within 60 days after surgery.
  - Adjuvant chemotherapy should consist of a cisplatin-containing combination. The efficacy of carboplatin has been prospectively demonstrated in only one study in stage IB (UICC 7th edition).
  - Most data are available for the combination of cisplatin and vinorelbine, given over 4 courses of treatment. Depending on comorbidity, side effects, and approval status, other cisplatin-containing combinations may be chosen, e.g., with docetaxel, etoposide, gemcitabine, or pemetrexed.
  - Combining chemotherapy with an anti-angiogenesis inhibitor did not prolong survival or increase survival.
  - Data on the value of immune checkpoint inhibitors in adjuvant systemic therapy are available with the Impower 010 trial using atezolizumab. Here, an improvement in disease-free survival was shown. The approval is limited to patients with a high risk of recurrence after R0 resection, a PD-L1 expression on tumour cells of >50% and an EGFR/ALK WT constellation after adjuvant chemotherapy.

Regulatory status

EMA [2]	FDA [1, 5]
Approval status for this indication: On 14 September 2023, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Keytruda®. The CHMP adopted a new indication as follows: ❖ Keytruda® as monotherapy is indicated for the adjuvant treatment of adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy. **Other indications**: Keytruda® is indicated:	**Approval status for this indication**: On 26 January 2023, the FDA approved pembrolizumab (Keytruda®) for adjuvant treatment following resection and platinum-based chemotherapy for stage IB (T2a ≥4 cm), II, or IIIA NSCLC. **Other indications**: Keytruda® is indicated: ❖ 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. ❖ 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.

[1] European Standard Population 2013.

- as monotherapy for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma.
- as monotherapy 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.
- 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®.
- as monotherapy for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.
- 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.
- as monotherapy or in combination with platinum and 5-fluorouracil chemotherapy, for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (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.
- in combination with axitinib, for the first-line treatment of advanced renal cell carcinoma (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.
- as monotherapy for adults with MSI-H or dMMR colorectal cancer (CRC) in the following settings:
- 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.
- for the treatment of patients with resectable (tumors ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
- 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®.
- 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.
- 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.
- for the treatment of adult and paediatric patients with refractory primary mediastinal large B-Cell lymphoma (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.
- in combination with enfortumab vedotin, for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy. This indication is approved under accelerated approval based on tumour response rate and durability of response.
- as a single agent 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.
- as a single agent 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.
- for the treatment of adult and paediatric patients with unresectable or metastatic MSI-H or dMMR solid tumours, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
- for the treatment of patients with unresectable or metastatic MSI-H or dMMR CRC as determined by an FDA-approved test.
- 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 GEJ adenocarcinoma. This indication is approved under accelerated approval based on tumour response rate and durability of response.
- in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma.

- first-line treatment of metastatic CRC;
- treatment of unresectable or metastatic CRC after previous fluoropyrimidine-based combination therapy.

❖ as monotherapy for the treatment of the following MSI-H or dMMR tumours in adults with:
- 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.

❖ 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.

❖ 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 triple-negative breast cancer (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.

❖ 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.

❖ 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.

❖ in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction (GEJ) adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

❖ in combination with fluoropyrimidine and platinum-containing chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

❖ in combination with gemcitabine and cisplatin, for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.

❖ for the treatment of patients with locally advanced or metastatic esophageal 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.

❖ in combination with chemoradiotherapy, for the treatment of patients with FIGO 2014 Stage III-IVA 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.

❖ 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.

❖ for the treatment of patients with HCC secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen.

❖ in combination with gemcitabine and cisplatin, for the treatment of patients with locally advanced unresectable or metastatic biliary tract cancer.

❖ for the treatment of adult and paediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.

❖ 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.

❖ in combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient as determined by an FDA-approved test or not MSI-H, 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 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 are not candidates for curative surgery or radiation.

❖ 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.

❖ for the treatment of patients with recurrent or metastatic cSCC or locally advanced cSCC that is not curable by surgery or radiation.

❖ 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 Classical Hodgkin Lymphoma and Adult Primary Mediastinal Large B-Cell Lymphoma: Additional Dosing Regimen of 400 mg Every 6 Weeks
- for use at an additional recommended dosage of 400 mg every 6 weeks for cHL and Primary Mediastinal Large B-Cell Lymphoma in adults. 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.

Manufacturer

Keytruda® is manufactured by Merck Sharp & Dohme

Costs

4 ml Keytruda concentrate for solution for infusion 25mg/ml = **€ 3,428.00** (ex-factory price) [6]

Warnings and precautions [1, 2]

- **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.
- **Traceability**
  - In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
- **Assessment of PD-L1 status**
  - When assessing the PD-L1 status of the tumour, it is important that a well-validated and robust methodology is chosen to minimise false negative or false positive determinations.
- **Patients excluded from clinical studies**
  - Patients with the following conditions were excluded from clinical studies: active CNS metastases; ECOG PS ≥ 2 (except for urothelial carcinoma and RCC); HIV infection, hepatitis B or hepatitis C infection (except for BTC); active systemic autoimmune disease; interstitial lung disease; prior pneumonitis requiring systemic corticosteroid therapy; a history of severe hypersensitivity to another monoclonal antibody; receiving immunosuppressive therapy and a history of severe immune-mediated adverse reactions from treatment with ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (> 10 mg/day prednisone or equivalent) for greater than 12 weeks.
  - Patients with active infections were excluded from clinical studies and were required to have their infection treated prior to receiving pembrolizumab. Patients with active infections occurring during treatment with pembrolizumab were managed with appropriate medical therapy. Patients with clinically significant renal (creatinine > 1.5 x ULN) or hepatic (bilirubin > 1.5 x ULN, ALT, AST > 2.5 x ULN in the absence of liver metastases) abnormalities at baseline were excluded from clinical studies, therefore information is limited in patients with severe renal and moderate to severe hepatic impairment.
  - There are limited data on the safety and efficacy of Keytruda® in patients with ocular melanoma. After careful consideration of the potential increased risk, pembrolizumab may be used with appropriate medical management in these patients.
- **Patient card**
  - All prescribers of Keytruda® must be familiar with the Physician Information and Management Guidelines. The prescriber must discuss the risks of Keytruda® therapy with the patient. The patient will be provided with the patient card with each prescription.

Study characteristics [7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	Dual primary endpoints	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)

PEARLS/ KEYNOTE-091 NCT02504372	1,177 (1:1)	pembrolizumab 200 mg IV once every 3 weeks	saline placebo IV once every 3 weeks	disease-free survival in the overall population and in the population with PD-L1 TPS of ≥50%	35.6 months (IQR 27.1–45.5)	**ongoing**[2], randomised, triple-blind, multicentre, phase 3 study	PD-L1	Merck Sharp & Dohme, a subsidiary of Merck & Co.	PEARLS/ KEYNOTE-091 [8]

Inclusion criteria[3]	Exclusion criteria	Patient characteristics at baseline (I vs. C, ITT population)
❖ ≥18 years ❖ Provided written informed consent for tumour testing. ❖ Pathologically confirmed NSCLC (any histology) of stage IB (tumours of ≥4 cm in diameter), II, or IIIA per the AJCC staging system after complete surgical resection (lobectomy, sleeve lobectomy, bi-lobectomy, or pneumonectomy) including negative margins (R0). ❖ Available tumour sample obtained during resection for PD-L1 assessment. ❖ Systematic complete or lobe-specific mediastinal lymph node dissection was recommended; at a minimum, the subcarinal (level 7) and a lobe-specific node must have been examined to establish the absence of N2 disease. ❖ Known PD-L1 expression status determined in part two. ❖ Written informed consent for study participation. ❖ No evidence of disease on clinical examination and radiographic assessment per RECIST version 1.1, assessed by local review after surgery but within 12 weeks before randomisation. ❖ ECOG PS of 0 or 1 ❖ Adequate organ function within 10 days of treatment initiation, assessed via absolute neutrophil count, platelet count, haemoglobin concentration, and concentrations of creatinine, total bilirubin, alanine aminotransferase, and aspartate aminotransferase. ❖ Adjuvant chemotherapy was not mandatory but was to be considered for patients with stage IB disease and strongly recommended for those with stage II and IIIA disease, according to national and local guidelines. ❖ Participants without previous adjuvant chemotherapy were to receive their first study treatment administration within 12 weeks of surgery. Participants who received adjuvant chemotherapy were to receive no more than four chemotherapy cycles initiated within 12 weeks of surgery and receive their first study treatment administration at least 3 weeks but no more than 12 weeks from the last chemotherapy dose.	❖ Previous neoadjuvant or adjuvant radiotherapy for the current malignancy. ❖ Patients with a history of HIV, those with active hepatitis B or C infection, and those with active autoimmune disease requiring treatment within the past 2 years. ❖ Patients whose samples are inadequate for PD-L1 determination. ❖ No prior or planned neoadjuvant or adjuvant radiotherapy and/or neoadjuvant chemotherapy for the current malignancy. ❖ No prior treatment with anti-PD-1, anti-PD-L1/2, anti-CD137, CTLA-4 modulators or any other immune-modulating agents; patients receiving live vaccine within 30 days prior to the first infusion of study treatment. ❖ No current participation in an interventional clinical trial or treatment with an investigational agent or use of an investigational device within 4 weeks of the first infusion of study treatment. ❖ No chronic use of immunosuppressive agents and/or systemic corticosteroids or any use in the last 3 days prior to the first infusion of study treatment. ❖ No history of interstitial lung disease OR a history of (non-infectious) pneumonitis that required oral or IV steroids (other than COPD exacerbation) or current pneumonitis. ❖ No active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). ❖ No history of a haematologic or primary solid tumour malignancy, unless in remission for at least 5 years. ❖ No previous allogeneic tissue/solid organ transplant. ❖ No active infection requiring therapy. ❖ No surgery or chemotherapy related toxicity (non-haematological toxicity resolved to grade 1	❖ Median age: 65.0 vs. 65.0 years ❖ Male sex: 68% vs. 69% ❖ ECOG PS: • 0: 64% vs. 58% • 1: 36% vs. 42% ❖ Smoking status: • Current: 13% vs. 15% • Former: 73% vs. 73% • Never: 15% vs. 11% ❖ Histology: • Non-squamous: 67% vs. 62% • Squamous: 33% vs. 38% ❖ Disease stage: • IB: 14% vs. 14% • II: 56% vs. 58% • IIIA: 30% vs. 28% • IV: 0 vs. <1% ❖ Regional lymph node stage: • No: 39% vs. 44% • N1: 39% vs. 38% • N2: 21% vs. 18% ❖ Received adjuvant chemotherapy: • No: 14% vs. 14% • Yes: 86% vs. 86% o 1-2 cycles: 6% vs. 5% o 3-4 cycles: 80% vs. 80% ❖ PD-L1 TPS: • <1%: 39% vs. 40% • 1-49%: 32% vs. 32% • ≥50%: 28% vs. 28% ❖ EGFR mutation: • No: 37% vs. 37% • Yes: 7% vs. 6% • Unknown: 56% vs. 57%

[2] The PEARLS trial is currently ongoing; the estimated study completion date is 02/2024.
[3] For detailed in-and exclusion criteria, please see Study Protocol.

	❖ Female patients with childbearing potential must have a negative urine or serum pregnancy test at screening.	❖ ALK translocation: • No: 38% vs. 32% • Yes: 1% vs. 1% • Unknown: 61% vs. 66%

Efficacy (I vs. C)	Safety (I vs. C)
Interim analysis (data cutoff 20 September 2021; median follow up 35.6 months): **Overall population (n=590 vs. n=587)** Median disease-free survival: 53.6 months (95% CI, 39.2-NR) vs. 42.0 months (31.3-NR); HR 0.76 (95% CI, 0.63–0.91), p=0.0014 Disease recurrence before randomisation: 1% vs. 1% HR for disease-free survival in a protocol-specified sensitivity analysis in which participants who had disease recurrence before randomization were censored on the randomisation date: 0.74 (95% CI, 0.62–0.89) Patients who died as of data cutoff: 17% vs. 19% Median OS: NR vs. NR; HR 0.87 (95% CI, 0.67–1.15), p=0.17 **PD-L1 TPS of ≥50% population (n=168 vs. n=165)** Median disease-free survival: NR (95%, CI 44.3-NR) vs. NR (95% CI, 35.8-NR); HR 0.82 (95% CI, 0.57–1.18); p=0.14 Disease recurrence before randomisation: 1% vs. 0% HR for disease-free survival in a protocol-specified sensitivity analysis in which participants who had disease recurrence before randomization were censored on the randomisation date: 0.79 (95% CI, 0.54–1.14)	**AEs of any grade and cause**: n=556/580 (96%) vs. 529/581 (91%) **AEs grade ≥3**: n=198/580 (34%) vs. n=150/581 (26%) **AEs leading to treatment discontinuation**: n=115/580 (20%) vs. 34/581 (6%) **AEs leading to death[4]:** n=11/580 (2%) vs. n=6/581 (1%) **Serious AEs:** n=142/580 (24%) vs. n=90/581 (15%) **AEs attributed to treatment by the investigator**: n=436/580 (75%) vs. 305/581 (52%) **TRAES grade ≥3**: n=88/580 (15%) vs. n=25/581 (4%) **Serious TRAEs**: n=68/580 (12%) vs. n=13/581 (2%)

Patient-reported outcomes

Currently, there are no results available.

ESMO-MCBS version 1.1 [10]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	Adjuvant	1	-	Disease-free survival: + 11.6 months	0.76 (0.63-0.91)	Improvements in DFS alone (HR<0.65) in studies without mature survival data	A	-	-	-	A
Adapted	Adjuvant	1	-	Disease-free survival: + 11.6 months	0.76 (0.63-0.91)	Improvements in DFS alone (HR 0.65-0.8) without mature survival data	B	-	-	-	B

Risk of bias (RCT) [11]

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 low risk	yes low risk	yes low risk	unclear[5] unclear risk	yes[6] high risk	**Unclear risk**

Ongoing trials [12]

NCT number/trial name	Description	Estimated study completion date
NCT02504372/PEARLS/KEYNOTE-091	Please see above.	02/2024
NCT04267848	Integration of immunotherapy into adjuvant therapy for resected NSCLC: ALCHEMIST Chemo-IO (ACCIO, phase 3 trial)	12/2024

[4] Four (1%) participants treated with pembrolizumab died due to events attributed to treatment by the investigator: due to both cardiogenic shock and myocarditis, septic shock and myocarditis, pneumonia, and sudden death (n=1 each). No deaths were attributed to treatment in the placebo group.
[5] The PEARLS trial is ongoing; currently, interim analysis data is available.
[6] The funder of the study, in collaboration with representatives of the EORTC Lung Cancer Group and ETOP, participated in study design, data analysis, data interpretation, and writing of this report.

NCT03425643/ KEYNOTE-671	Efficacy and safety of pembrolizumab with platinum doublet chemotherapy as neoadjuvant/adjuvant therapy for participants with resectable stage II, IIIA, and resectable IIIB NSCLC (MK-3475-671/, phase 3 trial)	06/2026

Available assessments

- In December 2020, NIHR published a Health Technology Briefing "Pembrolizumab with or without standard adjuvant therapy after resection for non-small-cell lung cancer – adjuvant" [13].
- No further assessments were identified via NICE, CADTH, G-BA and ICER.

Other aspects and conclusions

- In September 2023, the **CHMP adopted a new indication** for Keytruda®, as monotherapy is indicated for the adjuvant treatment of adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy. In January 2023, the **FDA approved** pembrolizumab (Keytruda®) for adjuvant treatment following resection and platinum-based chemotherapy for stage IB (T2a ≥4 cm), II, or IIIA NSCLC.
- **PEARLS/KEYNOTE-091** (NCT02504372) is an **ongoing,** randomised, triple-blind**, phase 3 trial**, assessing **pembrolizumab as adjuvant therapy** for completely resected stage IB–IIIA NSCLC. Included patients are ≥18 years, with completely resected, pathologically confirmed stage IB (tumours of ≥4 cm in diameter), II, or IIIA NSCLC per the AJCC staging system of any histology or PD-L1 expression level, and an ECOG PS of 0 or 1. Adjuvant chemotherapy was to be considered for stage IB disease and was strongly recommended for stage II and IIIA disease, according to national and local guidelines. Patients who had previous neoadjuvant or adjuvant radiotherapy for the current malignancy, had a history of HIV, those with active hepatitis B or C infection, and those with active autoimmune disease requiring treatment within the past 2 years and patients whose samples are inadequate for PD-L1 determination, were excluded.
- **Dual primary endpoints** were **disease-free survival** in the overall population and in the population with PD-L1 TPS ≥50%. In the overall population, median disease-free survival was 53.6 months (95% CI, 39.2-NR) vs. 42.0 months (95% CI, 31.3-NR); HR 0.76 (95% CI, 0.63–0.91), p=0.0014. In the PD-L1 TPS of ≥50% population, median disease-free survival was not reached in either the pembrolizumab group (95% CI, 44.3-NR) or the placebo group (95% CI, 35.8-NR); HR 0.82 (95% CI, 0.57–1.18); p=0.14.
- Currently, **no patient-reported outcome** data is available.
- The **original and adapted ESMO-MBCS** were applied, resulting in a magnitude of **clinical benefit grade of A and B**, respectively.
- Since the PEARLS trial is currently ongoing and not all predefined outcomes have been reported yet, the **risk of bias** is considered **unclear.** However, it is increased by the involvement of the sponsor in study design, data analysis, data interpretation.
- Beside the PEARLS trial, **two further ongoing phase 3** trials, evaluating adjuvant pembrolizumab in patients with resected NSCLC, were identified.
- **Final analysis data**, including **QoL data** is **required** to substantiate the interim analysis results of the PEARL trial.

First published: 10/2023
Last updated: 03/2024

Abbreviations: AE=adverse event, AJ=adjustment, AJCC=American Joint Committee on Cancer, ALK=anaplastic lymphoma kinase, ASCT=autologous stem cell transplantation, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, cHL=classical Hodgkin lymphoma, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, COPD=chronic obstructive pulmonary disease, CPS=combined positive score, CRC=colorectal carcinoma, cSCC=cutaneous Squamous Cell Cancer, dMMR=mismatch repair deficient, ECOG PS=Eastern Cooperative Oncology Group performance status, 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, G-BA=Gemeinsamer Bundesausschuss, GEJ=gastroesophageal junction, HCC=hepatocellular carcinoma, HNSCC=head and neck squamous cell carcinoma, HSCT=haematopoietic stem cell transplantation, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, IQR=interquartile range, IV=intravenous, MG=median gain, n=number of patients, MSI-H=microsatellite instability-high, NICE=National Institute for Health Care Excellence, NIHR=National Institute for Health Research, NSCLC=non-small cell lung cancer, OS=overall survival, PD-1=programmed Cell Death Protein 1, PD-L1= programmed death-1 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, RECIST=Response Evaluation Criteria in Solid Tumours, SAE=serious adverse event, ST=standard treatment, TRAE=treatment-related adverse events, TMB-H=tumour mutational burden high, TNBC=triple-negative breast cancer, TPS=tumour proportion score, UICC= Union for International Cancer Control.

References:

1. U.S. Food and Drug Administration (FDA). Keytruda. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125514s135lbl.pdf].
2. European Medicines Agency (EMA). Medicines. Keytruda. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/keytruda].
3. Statistik Austria. Krebserkrankungen. Krebsinzidenz nach ausgewählten Lokalisationen und Geschlecht. [Available from: https://www.statistik.at/statistiken/bevoelkerung-und-soziales/gesundheit/krebserkrankungen].
4. Onkopedia, Griesinger F, et al. Onkopedia Guidelines. Lung Cancer, non small lung cancer (NSCLC). [Available from: https://www.onkopedia-guidelines.info/en/onkopedia/guidelines/lung-cancer-non-small-lung-cancer-nsclc/@@guideline/html/index.html].
5. U.S. Food and Drug Administration (FDA). FDA approves pembrolizumab as adjuvant treatment for non-small cell lung cancer. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-adjuvant-treatment-non-small-cell-lung-cancer].
6. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
7. Supplement to: O'Brien M, Paz-Ares L, Marreaud S, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. Lancet Oncol 2022; 23: 1274–86.
8. O'Brien M, Paz-Ares L, Marreaud S, et al., on behalf of the EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 Investigators. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. Lancet Oncol 2022; 23: 1274–86.
9. U.S. National Library of Medicine, ClinicalTrials.gov. Study of Pembrolizumab (MK-3475) vs Placebo for Participants With Non-small Cell Lung Cancer After Resection With or Without Standard Adjuvant Therapy (MK-3475-091/KEYNOTE-091) (PEARLS). [Available from: https://classic.clinicaltrials.gov/ct2/show/NCT02504372].
10. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 2017; 28: 2340–2366.
11. European Network for Health Technology Assessment (EUnetHTA). Levels of evidence. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf].
12. U.S. National Library of Medicine, ClinicalTrials.gov. [Available from: https://classic.clinicaltrials.gov/ct2/home].
13. National Institute for Health and Research (NIHR). Pembrolizumab with or without standard adjuvant therapy after resection for nonsmall-cell lung cancer - adjuvant. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/28449-Adjuvant-Pembrolizumab-for-NSCLC-V1.0-DEC2020-NON-CONF.pdf].