Pembrolizumab (Keytruda®) as pre- and post-operative treatment of resectable non-small cell lung carcinoma (NSCLC)

General information

Drug description [1]

Pembrolizumab (Keytruda®) is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2.

Indication [2]

Pembrolizumab (Keytruda®), in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable NSCLC at high risk of recurrence in adults.

Incidence [3]

In Austria, in 2022, the age-standardised[1] incidence rate was 68.0/100,000 in men and 45.8/100,000 in women.

Current treatment [4]

The treatment recommendation for stage IA to IIIC NSCLC available from the Onkopedia website is displayed in Figure 1 of the Appendix.

Regulatory status

EMA [2]

Approval status for this indication: On 22 February 2024, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Keytruda® to include the pre- and post-operative treatment of adults whose NSCLC can be removed by surgery and who are at high risk of recurrence.

The CHMP adopted a new indication as follows:

- Keytruda®, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable NSCLC at high risk of recurrence in adults.

Other indications: Keytruda® is indicated:

- 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 adjuvant treatment of adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy.
- 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.

FDA [5, 6]

Approval status for this indication: On 16 October 2023, the FDA approved pembrolizumab (Keytruda®) with platinum-containing chemotherapy as neoadjuvant treatment, and with continuation of single-agent pembrolizumab as post-surgical adjuvant treatment for resectable (tumours ≥4 cm or node positive) 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 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®.
- for the treatment of patients with resectable (tumours ≥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 adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC.

[1] European Standard Population 2013.

- ❖ in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic 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.
- ❖ 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 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 (5-FU) 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:
  - 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;
- ❖ 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 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 cancer.
- ❖ 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 platinumcontaining 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 adults with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥1) as determined by an FDA-approved test. 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.
- ❖ 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.
- ❖ 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 hepatocellular carcinoma (HCC) secondary to hepatitis B who have received prior systemic therapy other than a PD1/PD-L1-containing regimen.

- 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 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 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 BTC in adults.
❖ in combination with gemcitabine and cisplatin, for the treatment of patients with locally advanced unresectable or metastatic BTC.
❖ 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 cutaneous squamous cell carcinoma (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 cHL 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.

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)

Posology [1]

❖ For the adjuvant treatment of melanoma, NSCLC, or RCC, KEYTRUDA should be administered until disease recurrence, unacceptable toxicity, or for a duration of up to one year.

Warnings and precautions [1, 5]

❖ **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 fetal 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.

❖ **Use of pembrolizumab in combination with chemotherapy**
- Pembrolizumab in combination with chemotherapy should be used with caution in patients ≥ 75 years after careful consideration of the potential benefit/risk on an individual basis.

Study characteristics [7-10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
KEYNOTE-671 NCT03425643	797 (1:1)	neoadjuvant pembrolizumab (200 mg) once every 3 weeks, given with cisplatin-based chemotherapy for 4 cycles, followed by surgery and adjuvant pembrolizumab (200 mg) once every 3 weeks for up to 13 cycles	placebo once every 3 weeks given with cisplatin-based chemotherapy for 4 cycles, followed by surgery and placebo once every 3 weeks for up to 13 cycles	event-free survival[2] and OS	25.2 months	**ongoing**[3], randomized, double-blind, phase 3 trial	PD-1	Merck Sharp and Dohme	KEYNOTE-671 [10]

Inclusion criteria[4]	Exclusion criteria	Patient characteristics at baseline (I vs. C, n=397 vs. 400)
❖ ≥18 years with previously untreated and pathologically confirmed resectable Stage II, IIIA, or IIIB (N2) NSCLC. ❖ If male, must agree to use contraception or practice abstinence as well as refrain from donating sperm during the treatment period and for the time needed to eliminate each study intervention after the last dose of study intervention. ❖ If female, may participate if not pregnant or breastfeeding, and at least one of the following conditions apply: • not a woman of childbearing potential; or	❖ One of the following tumour locations/types: • NSCLC involving the superior sulcus; • Large cell neuro-endocrine cancer; or • Sarcomatoid tumour. ❖ History of (non-infectious) pneumonitis /interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease that requires steroids. ❖ Active infection requiring systemic therapy. ❖ Had an allogenic tissue/sold organ transplant. ❖ Known severe hypersensitivity (≥ Grade 3) to pembrolizumab, its active substance and/or any of its excipients. ❖ Known severe hypersensitivity (≥ Grade 3) to any of the study chemotherapy agents and/or to any of their excipients. ❖ Active autoimmune disease that has required systemic treatment in past 2 years.	❖ Median age (range): 63 (26–83) vs. 64 (35–81) years ❖ ≥65 years: 44.3% vs. 46.5% ❖ Male sex: 70.3% vs. 71.0% ❖ Race or ethnic group: • American Indian or Alaska Native: vs. 0.3% vs. 0 • Asian: 31.2% vs. 31.2% • Black: 1.5% vs. 2.5% • Multiple: 0.8% vs. 2.5% • White: 63.0% vs. 59.8% • Missing data: 3.3% vs. 4.0% ❖ Geographic region: • East Asia: 31.0% vs. 30.2% • Other: 69.0% vs. 69.8% ❖ ECOG PS score:

[2] The time from randomization to the first occurrence of local progression that precluded the planned surgery, unresectable tumour, progression or recurrence, or death.
[3] The KEYNOTE-671 trial is currently ongoing; the estimated study completion date is 06/2026.
[4] For detailed in- and exclusion criteria, please see trial protocol.

• a woman of childbearing potential who agrees to follow contraceptive guidance during the treatment period and for the time needed to eliminate each study intervention after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. ❖ Available formalin-fixed paraffin embedded tumour tissue sample blocks for submission. If blocks are not available, have unstained slides for submission for central PD-L1 testing. ❖ ECOG PS of 0 to 1 within 10 days of randomization. ❖ Adequate organ function.	❖ Known history of human immunodeficiency virus infection. ❖ Known history of Hepatitis B or Hepatitis C. ❖ Known history of active tuberculosis. ❖ History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the participant's participation for the full duration of the trial, or is not in the best interest of the participant to participate. ❖ Known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the trial. ❖ Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor. ❖ Received prior systemic anti-cancer therapy including investigational agents for the current malignancy prior to randomization/allocation. ❖ Received prior radiotherapy within 2 weeks of start of trial treatment. ❖ Received a live vaccine within 30 days prior to the first dose of trial drug. ❖ Currently participating in or has participated in a trial of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of trial treatment. ❖ Diagnosis of immunodeficiency or is receiving either systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior the first dose of trial drug. ❖ Known additional malignancy that is progressing or requires active treatment within the past 5 years.	• 0: 63.7% vs. 61.5% • 1: 36.3% vs. 38.5% ❖ Smoking status: • Current smoker: 24.2% vs. 25.8% • Former smoker: 62.2% vs. 62.5% • Never smoked: 13.6% vs. 11.8% ❖ Pathological stage at baseline: • II: 29.7% vs. 30.2% • III: 70.3% vs. 69.8% • IIIA: 54.7% vs. 56.2% • IIIB: 15.6% vs. 13.5% ❖ Tumor stage: • T1: 13.9% vs. 15.2% • T2: 26.7% vs. 31.5% • T3: 30.5% vs. 27.2% • T4: 29.0% vs. 26.0% ❖ Node stage: • N0: 37.3% vs. 35.5% • N1: 20.4% vs. 17.8% • N2: 42.3% vs. 46.8% ❖ Histologic features: • Nonsquamous: 56.9% vs. 56.8% • Squamous: 43.1% vs. 43.2% ❖ PD-L1 tumour proportion score: • ≥50%: 33.2% vs. 33.5% • <50%: 66.8% vs. 66.5% • 1–49%: 32.0% vs. 28.8% • <1%: 34.8% vs. 37.8% ❖ EGFR mutation status: • No: 28.0% vs. 31.8% • Yes: 3.5% vs. 4.8% • Unknown: 68.5% vs. 63.5% ❖ ALK translocation status: • No: 26.2% vs. 33.2% • Yes: 3.0% vs. 2.2% • Unknown: 70.8% vs. 64.5%

Efficacy (I vs. C), interim analysis data	**Safety** (I vs. C, n=396 vs. n=399), interim analysis data
<u>**Data cutoff 29 July 2022; median follow-up time 25.2 months**</u> **Event-free survival at 24 months:** 62.4% (95% CI, 56.8-67.5) vs. 40.6% (95% CI, 34.8-46.3); HR for disease progression, disease recurrence, or death 0.58 (95% CI, 0.46-0.72); p<0.001 **Median event-free survival**: not reached (95% CI, 34.1 months-not reached) vs. 17.0 months (95% CI, 14.3-22.0)	**TRAEs:** 96.7% vs. 95.0% **TRAEs grade ≥3:** 44.9% vs. 37.3% **Serious TRAEs:** 17.7% vs. 14.3% **TRAEs leading to death**[5]**:** 1% vs. 0.8%

[5] 4 participants (1.0%) in the pembrolizumab group died from immune-mediated lung disease, pneumonia, and sudden cardiac death in 1 participant each during the neoadjuvant–surgery phase and from atrial fibrillation in 1 patient during the adjuvant phase. 3 participants (0.8%) in the placebo group died from acute coronary syndrome,

Total deaths: 22.2% **Estimated percentage of participants who were alive at 24 months**: 80.9% (95% CI, 76.2-84.7) vs. 77.6% (95% CI, 72.5-81.9); p=0.02 **Median OS**: not reached vs. 45.5 months (95% CI, 42.0 to not reached) **Restricted mean survival time at 48 months**: 39.7 months vs. 36.6 months; difference 3.1 months; 95% CI, 0.6-5.6 **Major pathological response:** 30.2% (95% CI, 25.7-35.0) vs. 11.0% (95% CI, 8.1-14.5); difference 19.2 percentage points (95% CI, 13.9-24.7); p<0.0001; threshold, p= 0.0001 **Pathological complete response**: 18.1% (95% CI, 14.5-22.3) vs. 4.0% (95% CI, 2.3-6.4); difference, 14.2 percentage points (95% CI, 10.1-18.7); p<0.0001; threshold, p= 0.0001	**TRAES leading to discontinuation of all trial treatment:** 12.6% vs. 5.3% **At least 1 AE of any cause among the participants who underwent surgery[6]:** 71.1% vs. 71.3% **Death from any cause within 30 days after surgery:** 1.8% vs. 0.6% **Death from any cause within 31 to 90 days after surgery:** 2.2% vs. 0.9% **Potentially immune-mediated AEs and infusion reactions:** 25.3% vs. 10.5% **Potentially immune-mediated AEs and infusion reactions of grade ≥3:** 5.8% vs. 1.5% **Potentially immune-mediated AEs and infusion reactions leading to death:** 0.3% vs. 0

Patient-reported outcomes

According to the trial protocol, patient-reported outcomes are predefined as endpoints, but results are not (yet) available.

ESMO-MCBS version 1.1 [11]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
The ESMO-MCBS is not applicable because the primary endpoint "event-free survival" could not be assessed, and the primary endpoint "OS" has not yet been met.											

Risk of bias (RCT) [12]

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[7] unclear risk	yes[8] high risk	unclear

Ongoing trials [13]

NCT number/trial name	Description	Estimated study completion date
KEYNOTE-671/ NCT03425643	Please see above.	06/2026

Other aspects and conclusions

- In February 2024, the **CHMP adopted a new indication** for Keytruda®, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable NSCLC at high risk of recurrence in adults. In October 2023, the **FDA approved** Keytruda® with platinum-containing chemotherapy as neoadjuvant treatment, and with continuation of single-agent pembrolizumab as post-surgical adjuvant treatment for resectable (tumours ≥4 cm or node positive) NSCLC.
- KEYNOTE-671 (NCT03425643) is an **ongoing,** randomized, double-blind, **phase 3 trial** to evaluate perioperative pembrolizumab in patients with early-stage NSCLC. Patients ≥18 years of age with previously untreated, pathologically confirmed, stage II, IIIA, or IIIB NSCLC that was considered to be resectable after surgical consultation and investigator assessment, an ECOG score of 0 or 1 and an ability to provide a tumour sample for PD-L1 assessment, were included. Patients with NSCLC involving the superior sulcus, large cell neuro-endocrine cancer or sarcomatoid tumour and who have a history of (non-infectious) pneumonitis /interstitial lung disease that required steroids or have current pneumonitis/interstitial lung disease that requires steroids, were excluded.
- The **dual primary end points** were **event-free survival and OS**. Event-free survival at 24 months was 62.4% vs. 40.6% in the placebo group (HR 0.58; 95% CI, 0.46-0.72; p<0.001). The estimated 24-month overall survival was 80.9% vs. 77.6% (p = 0.02), which did not meet the significance criterion.
- According to the trial protocol, evaluation of **PROs** is provided. However, currently there are **no results available**.
- The **ESMO-MCBS could not applied**, because the primary endpoint "event-free survival" could not be assessed, and the primary endpoint "OS" has not yet been met.
- Due to the ongoing status of the trial and the lack of final analysis data, the **risk of bias was considered unclear**. However, the risk is increased by the industry-funded background of the trial.
- Beside the KEYNOTE-671 trial, no further trials evaluating the indication assessed herein were identified.
- In conclusion, final analysis data and PRO´s, as well as further phase 3 data are required to define the role of pembrolizumab for the pre- and post-operative treatment of resectable NSCLC.

pneumonia, and pulmonary haemorrhage in 1 participant each during the neoadjuvant–surgery phase).

[6] Most commonly procedural pain.

[7] KEYNOTE-671 is ongoing; currently, only interim analysis data is available.

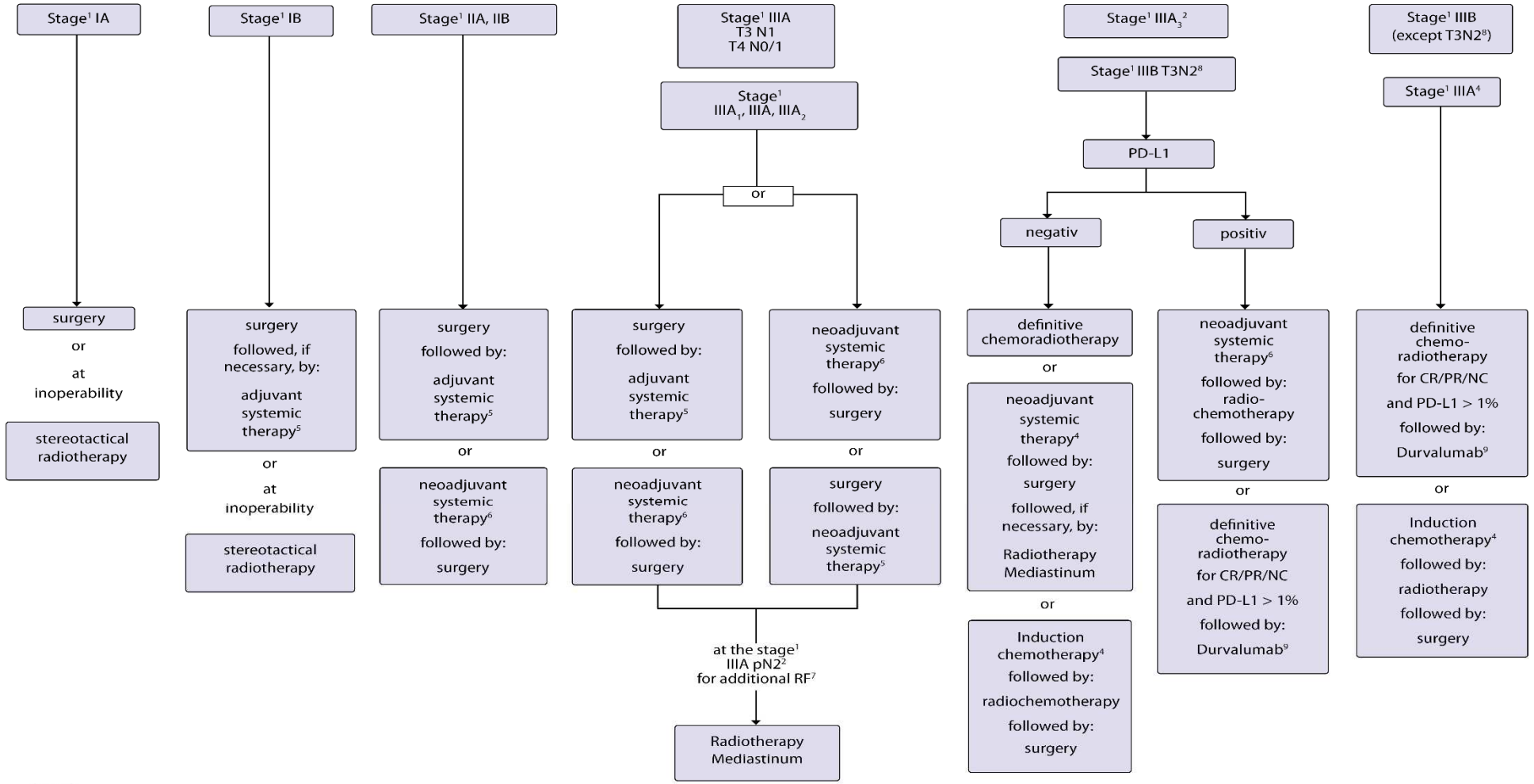
[8] A panel of academic advisors and employees of the sponsor designed the trial. A medical writer who was employed by the sponsor assisted with the preparation of the manuscript.

Abbreviations: 5-FU=5-fluorouracil, AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ASCT=autologous stem cell transplant, BTC=biliary tract carcinoma, 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, CPS=combined Positive Score, CRC=colorectal cancer, cSCC=cutaneous squamous cell carcinoma, dMMR=mismatch repair deficient, ECOG=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, FIGO=Fédération Internationale de Gynécologie et d'Obstétrique, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GEJ= gastro-oesophageal junction, HCC=hepatocellular carcinoma, HNSCC=head and neck squamous cell carcinoma, HR=hazard ratio, HSCT=heamatopoietic stem cell transplantation, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, MG=median gain, MSI-H=microsatellite instability high, n=number of patients, NICE=National Institute for Health Care Excellence, NSCLC=non-small cell lung cancer, OS=overall survival, PD-1=programmed cell death protein 1, PD-L1=programmed death 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, TNBC=triple-negative breast cancer, TMB-H= tumour mutational burden-high, TPS=tumour proportion score, TRAE=treatment-related adverse event

References:

1. European Medicines Agency (EMA). Keytruda: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf].
2. European Medicines Agency (EMA). Keytruda - opinion on variation to marketing authorisation. [Available from: https://www.ema.europa.eu/en/medicines/human/variation/keytruda-1].
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. 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). Keytruda. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125514s160lbl.pdf].
6. U.S. Food and Drug Administration (FDA). FDA approves neoadjuvant/ adjuvant pembrolizumab for resectable non-small cell lung cancer. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-neoadjuvant-adjuvant-pembrolizumab-resectable-non-small-cell-lung-cancer].
7. Protocol for: Wakelee H, Liberman M, Kato T, et al. Perioperative pembrolizumab for early-stage non–small-cell lung cancer. N Engl J Med 2022;387:491-503. DOI: 10.1056/NEJMoa2302983.
8. Supplement to: Wakelee H, Liberman M, Kato T, et al. Perioperative pembrolizumab for early-stage non–smallcell lung cancer. N Engl J Med 2022;387:491-503. DOI: 10.1056/NEJMoa2302983.
9. U.S. National Library of Medicine, ClinicalTrials.gov. Efficacy and Safety of Pembrolizumab (MK-3475) With Platinum Doublet Chemotherapy as Neoadjuvant/Adjuvant Therapy for Participants With Resectable Stage II, IIIA, and Resectable IIIB (T3-4N2) Non-small Cell Lung Cancer (MK-3475-671/KEYNOTE-671). [Available from: https://classic.clinicaltrials.gov/ct2/show/NCT03425643].
10. Wakelee H, Liberman M, Kato T, et al., for the KEYNOTE-671 Investigators. Perioperative Pembrolizumab for Early-Stage Non–Small-Cell Lung Cancer. N Engl J Med 2023;389:491-503.
11. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. . Annals of Oncology 28: 2340–2366, 2017.
12. 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].
13. U.S. National Library of Medicine, ClinicalTrials.gov. [Available from: https://www.clinicaltrials.gov/].

Appendix – Figure 1: Therapy algorithm for stage IA to IIIC non-small cell lung cancer



Legend:

curative intent therapy;

[1] *clinical stages;*
[2] *Individual therapy should be determined in an interdisciplinary tumor board involving all diagnostic and therapeutic disciplines;*
[3] *negative: PD-L1 <1%; positive ≥1%;*
[4] *surgery - umbrella term for all forms of tumor resection or ablation*
[5] *adjuvant systemic therapy after resection includes*
- *platinum-containing chemotherapy in stages IIA - IIIA and*
- *in case of EGFRmut (del 19, L858R) in stages IB - IIIA: osimertinib (for classification change from UICC 7th edition or according to UICC 8th edition see chapter 6.1.2.) and*
- *for PD-L1 expression on tumor cells ≥50% in stages IIA - IIIA in EGFR/ALK wild-type: atezolizumab;*
- *or a combination of these options*

[6] *platinum-containing combination chemotherapy + nivolumab; for divergent approvals in respective countries.*
[7] *Additional risk factors: multiple N2 infestations and capsular overgrowth;*
[8] *pT3 criterium based on extent of the tumor, infiltration of the chest wall or size between 5-7 cm*
[9] *see currently valid marketing authorization information; approval in Switzerland independent of PD-L1 status.*