Horizon Scanning in Oncology

Pembrolizumab (Keytruda®) as first-line therapy for PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (NSCLC)

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology No. 91
ISSN online 2076-5940

Horizon Scanning in Oncology

Pembrolizumab (Keytruda®) as first-line therapy for PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (NSCLC)

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, October 2019

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft

Authors: Lynda McGahan, MSc
Internal review: Priv.-Doz. Dr. phil. Claudia Wild; Nicole Grössmann, MSc
External review: OA Dr. Maximilian Hochmair
Onkologische Ambulanz und Tagesklinik, Otto Wagner Spital Wien

DISCLAIMER

This technology summary is based on information available at the time of research and on a limited literature search. It is not a definitive statement on safety, effectiveness or efficacy and cannot replace professional medical advice nor should it be used for commercial purposes.

The HTA Core Model® for Rapid Relative Effectiveness for Pharmaceuticals, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. A working version (unpublished) of V3.0 of the Model was used. Use of the HTA Core Model® does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model

CONTACT INFORMATION

Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Vienna
http://www.lbg.ac.at/de/lbg/impressum

Responsible for Contents:

Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicise the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at http://eprints.hta.lbg.ac.at

DSD: Horizon Scanning in Oncology No. 91
ISSN-online: 2076-5940

http://eprints.hta.lbg.ac.at/view/types/

Abstract

Introduction

Non-small cell lung cancer (NSCLC) arises when epithelial cells lining the bronchial tubes undergo aberrant cell growth due to up-regulation of programmed death (PD-1) ligands, thereby affording evasion of immune surveillance. Pembrolizumab, a monoclonal antibody, is an immune checkpoint inhibitor. By blocking PD-1 from binding its ligands, programmed death ligand (PD-L1) and programmed death 2 (PD-L2), pembrolizumab restores T-cell activation, enabling effective detection and destruction of tumour cells.

Methodology

Published and grey literature were identified by searching the Cochrane Library, CRD Database, Embase, Ovid Medline, PubMed, Internet sites and contacting the manufacturer. Quality assessment was conducted to assess the risk of bias at the study level and the applicability of study results. Furthermore, the magnitude of clinically meaningful benefit that can be expected from pembrolizumab was evaluated based on, both the original and adapted version of, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology.

Results of the KEYNOTE-042 trial

KEYNOTE-042, an ongoing, randomised, open-label, phase III trial compared the efficacy and safety of pembrolizumab (200 mg IV; every 3 weeks up to 35 cycles) versus platinum-based chemotherapy (carboplatin + paclitaxel or pemetrexed; up to six cycles) as first-line therapy for 1.274 patients with PD-L1-expressing metastatic NSCLC. Pembrolizumab increased overall survival (OS) by 7.8 months, 4.7 months, and 4.6 months for patients with PD-L1 tumour proportion scores (TPS) ≥50%, ≥20%, and ≥1%, respectively. The OS benefit of pembrolizumab over chemotherapy was demonstrated across three PD-L1 TPS populations; PD-L1 TPS ≥50% derived the greatest benefit. An exploratory analysis found no OS benefit for those with PD-L1 TPS 1–49% (n = 675, 13.4 months versus 12.1 months; HR 0.92, 95% CI 0.77–1.11, no statistically significant difference). No statistically significant differences in progression-free survival (PFS) or overall response rate (ORR) were noted between groups in any PD-L1 TPS population. Pneumonitis (8%) was the most frequently reported adverse event of grade ≥3 in severity. Common immune-mediated AEs occurring in pembrolizumab patients included hypothyroidism (12%), hyperthyroidism (6%), skin reactions (2%), colitis (1%) and hepatitis (1%).

Conclusion

Overall, first-line pembrolizumab monotherapy increases OS for patients with PD-L1-expressing metastatic NSCLC. Comprising 46.6% of the ITT population, the greatest OS benefit of pembrolizumab over chemotherapy was observed in patients with PD-L1 TPS ≥50%. No statistically significant difference in OS was noted between groups for those with PD-L1 TPS 1–49%; and no statistically significant differences in PFS or ORR were noted in any PD-L1 TPS population. Data regarding QoL and CNS activity are needed to ensure patients derive a clinically relevant benefit over time despite manageable toxicity. Further biomarkers are needed to ensure the appropriate patient selection and facilitate comparison with other immune checkpoint inhibitors In the absence of direct comparison trials, physicians may need to discuss whether adding pembrolizumab to chemotherapy would provide greater individual efficacy than chemotherapy alone, especially for PD-L1 TPS 1–49% patients.

Table of Contents

List of Tables

1 Research questions

EUnetHTA
HTA Core Model®

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

Element ID	Research question
Description of the technology	
B0001	What is pembrolizumab?
A0022	Who manufactures pembrolizumab?
A0007	What is the target population in this assessment?
A0020	For which indications has pembrolizumab received marketing authorisation?
Health problem and current use	
A0002	What is NSCLC in the scope of this assessment?
A0004	What is the natural course of NSCLC?
A0006	What are the consequences of NSCLC for society?
A0023	How many people belong to the target population?
A0005	What are the symptoms and the burden of NSCLC?
A0003	What are the known risk factors for NSCLC?
A0024	How is NSCLC currently diagnosed according to published guidelines and in practice?
A0025	How is NSCLC currently managed according to published guidelines and in practice?
Clinical effectiveness	
D0001	What is the expected beneficial effect of pembrolizumab on mortality?
D0005	How does pembrolizumab affect symptoms and findings (severity, frequency) of NSCLC?
D0006	How does pembrolizumab affect progression (or recurrence) of NSCLC?
D0011	What is the effect of pembrolizumab on patients' body functions?
D0012	What is the effect of pembrolizumab on generic health-related quality of life?
D0013	What is the effect of pembrolizumab on disease-specific quality of life?
Safety	
C0008	How safe is pembrolizumab in relation to the comparator(s)?
C0002	Are there harms related to dosage or frequency of applying pembrolizumab?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of pembrolizumab?
A0021	What is the reimbursement status of pembrolizumab?

2 Drug description

Generic/Brand name/ATC code:

Pembrolizumab/Keytruda®/MK-3475/L01XC18

B0001: What is the technology and the comparator(s)?

PD-1, immune checkpoint inhibitor

Up-regulation of programmed death 1 (PD-1) ligand in patients with tumours increases the propensity for cancer cells to evade immune surveillance. Pembrolizumab, a monoclonal antibody, is an immune checkpoint inhibitor. By blocking PD-1 from binding its ligands, programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2), pembrolizumab restores T-cell activation, enabling effective detection and destruction of tumour cells [2].

pembrolizumab (200 mg IV) every 3 weeks for up to 35 cycles

Pembrolizumab is available as single-use vials of 50 mg powder for reconstitution (25 mg/mL) or 100 mg/4 mL infusion solution. It is administered as an intravenous (IV) infusion over 30 minutes, at a dose of 200 mg every three weeks for up to 35 treatments, until disease progression or unacceptable toxicity. For melanoma and previously treated NSCLC, the dose depends on the patient's weight and is 2 mg/kg body weight [3].

monitor for immune-mediated AEs; withhold or discontinue for safety/tolerability

Patients should be monitored for symptoms of immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis. Dose interruption or discontinuation may be necessary in patients that develop pneumonitis, colitis, hypophysitis, thyroid disorders, type 1 diabetes mellitus, nephritis, hepatitis, infusion-related reactions, or intolerance due to adverse events (AEs) [4]. While systemic corticosteroids or immunosuppressants should be avoided prior to starting pembrolizumab, due to the potential for pharmacodynamics interference, they may be used to treat immune-related AEs after starting pembrolizumab [5].

A0022: Who manufactures the technology?

Merck Sharp & Dohme Corporation, a subsidiary of Merck & Company Incorporated

3 Indication

A0007: What is the target population in this assessment?

previously untreated, PD-L1-expressing metastatic NSCLC

Pembrolizumab (Keytruda®) is indicated as first-line monotherapy for patients with PD-L1 expressing (tumour proportion score [TPS] ≥1), locally advanced or metastatic non-small cell lung cancer (NSCLC) without epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements [6].

4 Current regulatory status

A0020: For which indications has the technology received marketing authorisation?

Pembrolizumab was granted its first global approval by the US Food and Drug Administration (FDA) in September 2014 for the treatment of refractory unresectable or metastatic melanoma [7]. In October 2015, pembrolizumab was approved for the treatment of patients with metastatic NSCLC whose tumours express PD-L1 as determined by an FDA-approved test, with progression following platinum-based chemotherapy or targeted therapy for EGFR or ALK aberrations. The companion diagnostic, PD-L1 immunohistochemistry (IHC) 22C3 pharmDx assay (Agilent Technologies, CA, USA), was approved concurrently and CE marked for European use. Approval was based on the overall response rate (ORR) in a subset of phase Ib KEYNOTE-001 patients where at least 50% of tumour cells expressed PD-L1 (TPS ≥50%) and overall survival (OS) data from the phase III KEYNOTE-010 study [2, 7-9].

first global approval; FDA licensed for melanoma in September 2014

In October 2016, the FDA approved pembrolizumab as first-line therapy for metastatic NSCLC demonstrating high PD-L1 expression (TPS ≥50%) without EGFR or ALK aberrations. Approval was based on progression-free survival (PFS) and OS data from the phase III KEYNOTE-024 study [10, 11]. Combination pembrolizumab with pemetrexed and carboplatin received accelerated approval as first-line treatment for metastatic non-squamous NSCLC, irrespective of PD-L1 expression, following results of the KEYNOTE-021 study in May 2017 [12]. From August to October 2018, combination pembrolizumab with chemotherapy was approved as first-line treatment for metastatic non-squamous and squamous NSCLC, based on OS and PFS data from the phase III KEYNOTE-189 and KEYNOTE-407 trials, respectively [13, 14]. In April 2019, first-line pembrolizumab monotherapy indications were expanded to include stage III or IV NSCLC patients who are not candidates for surgery or chemoradiation, and whose tumours express PD-L1 (TPS ≥1). Expanded approval was based on OS data from the phase III KEYNOTE-042 study [6].

FDA: licensed first-line for metastatic NSCLC October 2016

FDA: licensed first-line monotherapy for PD-L1-expressing advanced/metastatic NSCLC in April 2019

Pembrolizumab received marketing authorisation by the European Medicines Agency (EMA) in July 2015, and is approved for the treatment of metastatic melanoma, advanced NSCLC, classical Hodgkin lymphoma, urothelial cancer, advanced renal cell carcinoma, and head and neck squamous cell carcinoma [3]. It is licensed as first-line monotherapy for metastatic NSCLC exhibiting high PD-L1 expression without EGFR or ALK aberrations, and as second-line therapy following progression on platinum-based chemotherapy. Pembrolizumab in combination with chemotherapy is licensed as first-line treatment of metastatic non-squamous and squamous NSCLC. An application to extend the first-line indication of pembrolizumab in NSCLC with PD-L1 (TPS ≥1) is currently under EMA review, based on OS data from KEYNOTE-042 [15].

EMA approvals: first-line for high PD-L1 metastatic NSCLC, in combination with chemotherapy for metastatic NSCLC; second-line

application: extend first-line indication to NSCLC with PD-L1 (TPS ≥1)

5 Burden of disease

A0002: What is NSCLC?

NSCLC accounts for 80–85% of all lung cancers

NSCLC is the most common epithelial lung cancer and accounts for approximately 80–85% of all lung cancers. Adenocarcinoma, the most frequent histological type, has a survival rate of approximately 4–6% at five years [16]. Approximately 7–35% of NSCLC patients have driver gene alterations in EGFR, ALK or ROS1, while 1–3% have BRAF mutations. The median survival for patients with metastatic disease without EGFR mutations or ALK rearrangements is approximately one year [17]. NSCLC tumours express the immune checkpoint PD-L1 that negatively regulates T-cell proliferation and induces cell death in tumour-specific T-cells. Among patients with treatment-naïve, advanced NSCLC, 30% express PD-L1 in a high percentage of tumour cells (TPS ≥50%), while 30–50% of patients demonstrate a lower level of PD-L1 expression (TPS 1–49%) [11, 18].

PD-L1 expression: TPS ≥50% in 30%; TPS 1–49% in 30–50% of patients

A0004: What is the natural course of NSCLC?

staged I-IV by invasiveness

Lung cancer typically arises when epithelial cells lining the bronchial tubes undergo aberrant cell growth. To facilitate treatment, lung cancer is staged from I through IV based on tumour size, and presence or absence of lymph node involvement and metastases (TNM). Stage I lung cancer is <3 cm and localized to one lobe; stage II has spread to other parts of the lung or lymph nodes; stage III may be large or spread to lymph nodes between the lungs; and stage IV has metastasized to the adjacent bones, lung, brain, liver or any other organ [15, 19].

metastasizes to bone, liver, brain, lymph nodes

A0006: What are the consequences of NSCLC for the society?

52–58% present with advanced cancer; relapse and metastasize early

Lung cancer is the second most commonly diagnosed cancer. While the implementation of smoking cessation programs and multidisciplinary treatments have reduced the incidence and mortality, 52–58% of lung cancer patients present with advanced-stage disease when curative treatment is no longer feasible. PD-L1 is a poor prognostic factor in NSCLC [20], leading to a high rate of relapse and early formation of micro-metastases [21].

A0023: How many people belong to the target population?

4,877 Austrians were diagnosed with NSCLC in 2016

about 1,625 patients diagnosed with metastatic NSCLC in Austria (2016)

Lung cancer is the leading cause of cancer-related death in men and the second in women worldwide. The age standardized incidence rate for the European Standard Population was 57.9 per 100,000 persons per year in 2015. In Austria, 2,868 men and 2,009 women were newly diagnosed with lung cancer in 2016; and 3,949 people died due to lung cancer [22]. It was the second most common cancer in men and women (12% of all cancers). Approximately 6.2% of people will be diagnosed with lung cancer during their lifetime and approximately one-third of newly diagnosed patients have distant metastases. Assuming this, about 1,625 patients in Austria (2016) had metastatic NSCLC at the time of diagnosis. Over the past decade, both the age-standardized incidence and the death rates were rising by 30% for women, while those of men fell by 13% and 17%, respectively. The average age at diagnosis is approximately 70 years [16].

average age at diagnosis 70 years

A0005: What are the symptoms and the burden of disease or health condition?

NSCLC symptoms include: cough, chest pain, weight loss, shortness of breath

Many lung cancers are not symptomatic until they have spread. Symptoms of NSCLC include incessant cough, bloody sputum, chest pain, wheezing or hoarseness, weight loss or loss of appetite, shortness of breath, fatigue, and recurrent bronchitis or pneumonia. Lung cancer may metastasize to bone, brain, liver or lymph nodes causing pain, headaches, improper balance, seizures, jaundice or lumps near the body's surface [23].

A0003: What are the known risk factors for NSCLC?

main risk factor: smoking

Overall, the risk of lung cancer increases with age, tobacco use, radiation exposure, air pollution, and occupational exposure to asbestos, arsenic, chromium beryllium, nickel, second-hand smoking and other agents. The risk of developing lung cancer is typically tenfold higher in smokers compared to lifetime non-smokers. Smoking cessation decreases precancerous lesions and reduces the risk of developing lung cancer [19, 23].

A0024: How is NSCLC currently diagnosed according to published guidelines and in practice?

diagnosis: x-ray, CT and biopsy

While some lung cancers may be found through screening, most are identified when they become symptomatic. Following a clinical history and physical exam, a chest x-ray may be done to identify any abnormal areas in the lungs. A computed tomography (CT) scan may show the size, shape and location of any lung tumours or enlarged lymph nodes, and guide a needle biopsy if a suspected area is identified. Lung cancer is diagnosed by examining cells derived through biopsy, cytology or sputum sampling for the presence of cancer cells. IHC and molecular tests may be conducted to identify specific changes in the gene expression of cancer cells to target first-line treatment for NSCLC patients with genetic aberrations in EGFR, ALK or ROS1 genes [24, 25]. While a variety of assays are available to evaluate PD-L1 expression on tumour cells, PD-L1 IHC 22C3 pharmDx is the only companion diagnostic that is approved by the FDA and CE marked for European use in guiding pembrolizumab therapy [7].

PD-L1 status: IHC assay

6 Current treatment

A0025: How is NSCLC currently managed according to published guidelines and in practice?

treatment by NSCLC stage: surgery, radiation therapy, chemotherapy

Depending on the tumour stage, histology, and the patients' overall health, surgery, radiation therapy and/or platinum-based chemotherapy may be used alone or in combination to treat NSCLC. Treatment per NSCLC stages involves the following options [19].

- Stage I and II NSCLC patients typically undergo surgery to remove the cancer. Stage II patients and a subset of patients with stage Ib tumours may benefit from postoperative adjuvant chemotherapy.

- Patients with stage I or II cancers that are not surgical candidates, due to co-morbidities or limited lung function, may undergo local radiation therapy.
- Stage III NSCLC patients are highly heterogeneous and may undergo a combination of treatment modalities including chemotherapy and radiation and/or surgery depending on the extent and localization of disease.
- Patients with stage IV disease are treated with systemic therapy or a symptom-based palliative approach.

advanced or metastatic NSCLC

In appropriately selected patients, chemotherapy, molecularly targeted therapy, and/or immunotherapy may be used to treat advanced or metastatic NSCLC [25-28].

- While the optimal chemotherapy regimen for use with concurrent radiotherapy is not known, cisplatin plus etoposide, carboplatin, or vinorelbine and paclitaxel are commonly used. Chemotherapy upregulates PD-L1 expression on tumour cells, resulting in additive and synergistic antitumor activity. Combination pemetrexed and cisplatin is recommended for non-squamous NSCLC patients.
- The standard dose fractionation regimen of radiotherapy with chemotherapy for stage III NSCLC is 60 Gy in 30 daily fractions. Intensity modulated radiation therapy is preferred over 3D radiotherapy due to the reduced risk for pneumonitis.

targeted therapies

- Patients with ALK translocations benefit from crizotinib, ceritinib, alectinib, lorlatinib or brigatinib therapy. First-line therapy for ROS1-translocated NSCLC is crizotinib, cabozantinib, or ceritinib. Loratinib may be used following progression on ceritinib, brigatinib or alectinib. First-line therapy for stage IV patients with BRAF V600E is combination dabrafenib plus trametinib. Advanced neurotrophic receptor tyrosine kinase (NTRK)-positive NSCLC may benefit from second-line larotrectinib or entrectinib.
- Patients with EGFR mutations may benefit from TKIs such as first generation erlotinib or gefitinib, or second-generation afatinib or dacomitinib. Third generation TKI osimertinib also targets the EGFRT790M mutation associated with acquired resistance to EGFR-TKIs.
- Pembrolizumab, nivolumab, atezolizumab, and durvalumab block PD-L1 on T-lymphocytes and are used as second-line therapies for advanced NSCLC. Pembrolizumab is recommended as first-line monotherapy for metastatic NSCLC exhibiting high PD-L1 expression without EGFR or ALK aberrations; those with rapid disease progression may benefit from concurrent chemotherapy. Non-squamous and squamous NSCLC patients with low PD-L1 expression may benefit from pembrolizumab in combination with pemetrexed and carboplatin or cisplatin, respectively. Alternatively nonsquamous NSCLC patients may receive combination platinum-based chemotherapy, bevacizumab, and atezolizumab. An application to extend the first-line indication of pembrolizumab in NSCLC patients with PD-L1 (TPS $\geq$1) is under EMA review. While combined nivolumab and ipilimumab provided NSCLC patients with PD-L1 expression >1% in the CheckMate 227 trial improved PFS compared with chemotherapy, further data is awaited to determine the role of nivolumab and ipilimumab in the first-line management of advanced NSCLC.

7 Evidence

systematic literature search in 5 databases: 115 hits

A literature search was conducted on 17 July 2019 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were "pembrolizumab", "Keytruda", "L01XC18", "non small cell lung cancer", "NSCLC", "lung cancer", "metastatic", "locally advanced", "Programmed cell death 1 ligand 1" and "PD-L1". The manufacturer was also contacted and submitted three oral presentations [29-31], two conference abstracts [32, 33], a clinical trial [6] and a pooled analysis [34], of which one was previously identified by systematic literature search [6]. A manual search identified two statistical reports [16, 22], six FDA approval documents [4, 7, 10, 35-37], three EMA marketing authorization notifications [3, 5, 15], eight clinical guidance documents [19-21, 23, 24, 26-28], three clinical trial articles [8, 11, 12] and a cost document [38]. Ongoing trials information was found on www.clinicaltrials.gov and www.clinicaltrialsregister.eu.

manual search: 29 additional references

overall: 144 references included: 2 studies

Overall, 144 references were identified. Included in this reported are:

- KEYNOTE-042, phase III [6, 39]
- KEYNOTE-024, phase III [11]

study level risk of bias assessed based on EUnetHTA internal validity for RCTs

To assess the risk of bias at the study level, the assessment of the methodological quality of the evidence was conducted based on the EUnetHTA internal validity for randomised controlled trials (RCTs) [40]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patient and treating physician, selective outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table 5 of the Appendix.

The external validity of the included trial was assessed using the EUnetHTA guideline on applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals, considering the following elements: population, intervention, comparator, outcomes and setting [41].

magnitude of meaningful clinical benefit assessed based on ESMO-MCBS

To evaluate the magnitude of "meaningful clinical benefit" that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS) was used [42]. Additionally, an adapted version (due to perceived limitations) of the ESMO-MCBS was applied [43]. Details of the magnitude of the clinically meaningful benefit scale are reported in Table 3.

7.1 Quality assurance

internal and external review

This report has been reviewed by an internal reviewer and an external reviewer. The latter was asked for the assessment of the following quality criteria:

- How do you rate the overall quality of the report?
- Are the therapy options in the current treatment section used in clinical practice and are the presented standard therapies correct?
- Is the data regarding prevalence, incidence, and amount of eligible patients correct?
- Are the investigated studies correctly analysed and presented (data extraction was double-checked by a second scientist)?
- Was the existing evidence from the present studies correctly interpreted?
- Does the current evidence support the final conclusion?
- Were all important points mentioned in the report?

quality assurance method

The LBI-HTA considers the external assessment by scientific experts from different disciplines a method of quality assurance of scientific work. The final version and the policy recommendations are under full responsibility of the LBI-HTA.

7.2 Clinical efficacy and safety – phase III studies

KEYNOTE-042: pembrolizumab versus chemotherapy as first-line treatment for PD-L1-expressing advanced or metastatic NSCLC

KEYNOTE-042 (NCT02220894) is an ongoing, multicentre, randomised, open-label, interventional phase III study involving 1,274 previously untreated patients with PD-L1-expressing advanced or metastatic NSCLC, without EGFR or ALK mutations [6]. The study was designed to evaluate whether pembrolizumab prolongs OS compared to standard of care platinum-based chemotherapy. Efficacy analyses were based on all randomly assigned patients comprising the intent-to-treat (ITT) population. Safety analyses involved all patients who received at least one dose of the study drug; 636 patients in the pembrolizumab group and 615 in the chemotherapy group. The study has an estimated completion date of March 2021; however, results of the second interim analysis, as reported by Mok et al 2019 [6], are discussed in this review.

ITT (n = 1,274): stratified by region, ECOG status, histology, and PD-L1 TPS

Eligible patients were 18 years or older, with untreated, pathologically confirmed, PD-L1-expressing locally advanced or metastatic NSCLC, without EGFR or ALK mutations. Patients were excluded if they had symptomatic central nervous system (CNS) metastases, a history of non-infectious pneumonitis requiring glucocorticoids, active autoimmune disease, were receiving systemic immunosuppressant therapy, or had a known active hepatitis B or C virus infection. Study participants were stratified by region of enrolment (Asia versus rest of world), Eastern Cooperative Oncology Group (ECOG) performance status score (0 versus 1), histology (squamous versus non-squamous), and PD-L1 TPS (≥50% versus 1–49%).

Patients were randomised 1:1 to receive pembrolizumab (200 mg IV) every three weeks for up to 35 cycles, or investigator's choice of carboplatin (area under the curve [AUC] 5–6 mg/mL/min, maximum dose 750–900 mg) with paclitaxel (200 mg/m^2 IV) or pemetrexed (500 mg/m^2 IV) every three weeks for up to six cycles. Participants with non-squamous histologies received optional pemetrexed (500 mg/m^2 IV) every three weeks. Patients were treated until progression or unacceptable toxicity. Cross-over from chemotherapy to pembrolizumab was not permitted. Pembrolizumab was withheld for drug-related toxicities and severe or life-threatening AEs. Chemotherapy participants received vitamin B12 (1,000 mg) a week prior to their first dose of pemetrexed (and every three cycles thereafter), folic acid (350–1,000 mcg daily), and were pre-medicated with oral or injectable steroids. In the as-treated population, the median number of doses administered was nine (range 1–36) in the pembrolizumab group and six (range 1–42) in the chemotherapy group.

200 mg pembrolizumab versus carboplatin + paclitaxel or pemetrexed

median number of doses: 9 for pembrolizumab versus 6 for chemotherapy

While the trial is estimated for completion in March 2021, the first interim analysis was conducted on August 30, 2017, six months after the final patient was enrolled. The second interim analysis was conducted on February 26, 2018, 38.3 months after the first patient was enrolled. At second interim analysis, median follow-up of 12.8 months (interquartile range [IQR] 6.0–20.0), 14% (87/636) of pembrolizumab patients continued treatment and 5% (30/615) of chemotherapy patients were receiving pemetrexed maintenance therapy. At least one subsequent anticancer therapy was received by 38% (240/637) of patients in the pembrolizumab group and 44% (383/637) of patients in the chemotherapy group, including 19 (3%) and 126 (20%) who received subsequent immunotherapy, respectively. After excluding patients still taking pembrolizumab or those who completed or discontinued treatment without later disease progression, 51% (240/474) of patients in the pembrolizumab group and 56% (282/504) of patients in the chemotherapy group received subsequent therapy.

continued treatment at 12.8 months: 14% of pembrolizumab and 5% of chemotherapy patients

subsequent therapy: 51% of pembrolizumab and 56% of chemotherapy patients

The primary endpoint was OS (time from randomisation to all-cause death). Secondary endpoints were PFS (time from randomisation to RECIST-defined disease progression or all cause death) and ORR (percentage of patients with a confirmed complete [CR] or partial response [PR]) as assessed by independent central radiologic review (BICR), and safety. Endpoints were evaluated up to 38 months after randomisation. Efficacy hypotheses were analysed sequentially by PD-L1 TPS, in the order of 50% or greater, 20% or greater, then 1% or greater. Hypotheses were tested only if the superiority of pembrolizumab over chemotherapy was established for the preceding hypothesis. Exploratory endpoints were OS, PFS, and ORR in patients with PD-L1 TPS 1–49%. Tumours were assessed according to RECIST version 1.1 at baseline, every nine weeks for 45 weeks, and every twelve weeks thereafter. Patients were contacted every two months to assess survival. AEs were graded for severity according to the National Cancer Institute Common Terminology Criteria (CTCAE) version 4.0.

primary endpoint: OS

secondary endpoints: PFS, ORR, and safety

exploratory endpoints: OS, PFS, and ORR for PD-L1 TPS 1–49

The ITT population (n = 1,274) had a median age of 63 years (range 57–69), 70% were male, 30% were East Asian, 78% were current or former smokers, 38% had squamous histology, 69% had an ECOG performance score of 1, 5% had brain metastases, and 47% had a PD-L1 TPS ≥50% at randomisation. Detailed patient characteristics including inclusion- and exclusion criteria can be found in Table 5 and study quality is described in Table 6 of the appendix, respectively. Clinical efficacy data are presented in Table 1 and AEs are listed in Table 2.

ITT: median age 63 years, 30% East Asian, 78% smokers, 38% squamous histology, 69% ECOG score of 1, 47% PD-L1 TPS ≥ 50

7.2.1 Clinical efficacy

D0001: What is the expected beneficial effect of pembrolizumab on mortality?

median OS pembrolizumab vs. chemotherapy:

PD-L1 TPS ≥ 50: 20.0 months vs. 12.2 months

PD-L1 TPS ≥ 20: 17.7 months vs. 13.9 months

PD-L1 TPS ≥ 1: 16.7 months vs. 12.1 months

consistent OS benefit across PD-L1 TPS populations

The primary endpoint of median OS for the PD-L1 TPS ≥50% population was 20.0 months (95% confidence interval [CI] 15.4–24.9) in the pembrolizumab group and 12.2 months (95% CI 10.4–14.2) in the chemotherapy group. In the PD-L1 TPS ≥20% population, median OS was 17.7 months (95% CI 15.3–22.1) for pembrolizumab recipients and 13.0 months (95% CI 11.6–15.3) for chemotherapy recipients. The median OS for the PD-L1 TPS ≥1% population was 16.7 months (95% CI 13.9–19.7) in the pembrolizumab group and 12.1 months (95% CI 11.3–13.3) in the chemotherapy group. The estimated percentages of patients alive at 24 months in the pembrolizumab and chemotherapy groups were 45% and 30%, respectively, in the PD-L1 TPS ≥50% population; 41% and 30% in the PD-L1 TPS ≥20% population; and 39% and 28% in the PD-L1 TPS ≥1% population. The OS benefit of pembrolizumab over chemotherapy was demonstrated across all three PD-L1 TPS populations (PD-L1 TPS ≥50%: n = 599, HR 0.69, 95% CI 0.56–0.85 p = 0.0003; PD-L1 TPS ≥20%: n = 818, HR 0.77, 95% CI 0.64–0.92, p = 0.0020; PD-L1 TPS ≥1%: n = 1,274, HR 0.81, 95% CI 0.71–0.93, p = 0.0018). In the exploratory subgroup analysis, median OS in the PD-L1 TPS 1–49% population was 13.4 months (95% CI 10.7–18.2) for pembrolizumab recipients and 12.1 months (95% CI 11.0–14.0) in chemotherapy recipients (n = 675 PD-L1 TPS 1–49%, HR 0.92, 95% CI 0.77–1.11 no statistically significant difference [NSSD]).

D0006: How does pembrolizumab affect progression (or recurrence) of NSCLC?

median PFS pembrolizumab vs. chemotherapy:

PD-L1 TPS ≥ 50: 7.1 months vs. 6.4 months

PD-L1 TPS ≥ 20: 6.2 months vs. 6.6 months

PD-L1 TPS ≥ 1: 5.4 months vs. 6.5 months

The secondary endpoint, BICR-assessed median PFS, was 7.1 months (95% CI 5.9–9.0) in pembrolizumab recipients and 6.4 months (95% CI 6.1–6.9) in chemotherapy recipients in the PD-L1 TPS 50% or greater population; 6.2 months (95% CI 5.1–7.8) and 6.6 months (95% CI 6.2–7.3) in the PD-L1 TPS 20% or greater population; and 5.4 months (95% CI 4.3–6.2) and 6.5 months (95% CI 6.3–7.0) in the PD-L1 TPS 1% or greater population, respectively. As the difference in PFS between groups did not reach the pre-specified superiority boundary in the PD-L1 TPS 50% or greater population (n = 599 TPS ≥50%, HR 0.81, 95% CI 0.67–0.99 p = 0.0170), that for the PD-L1 TPS 20% or greater and 1% or greater populations was not tested.

D0005: How does pembrolizumab affect symptoms and findings (severity, frequency) of NSCLC?

The secondary endpoint, BICR-assessed ORR was 39% (118/299; 95% CI 34–45) in pembrolizumab recipients and 32% (96/300; 95% CI 27–38) in chemotherapy recipients in the PD-L1 TPS 50% or greater population; 33% (138/413; 95% CI 29–38) and 29% (117/405; 95% CI 25–34) in the PD-L1 TPS 20% or greater population; and 27% (174/637; 95% CI 24–31) and 27% (169/637; 95% CI 23–30) in the PD-L1 TPS 1% or greater population, respectively.

The median duration of response (DOR) was 20.2 months in the pembrolizumab group in all PD-L1 TPS populations, and was 10.8 months, 8.3 months, and 8.3 months, respectively in the PD-L1 TPS 50% or greater, 20% or greater, and 1% or greater populations in the chemotherapy group.

median ORR and DOR pembrolizumab vs. chemotherapy:

PD-L1 TPS ≥ 50: 39% vs. 32%; 10.8 vs. 20.2 months

PD-L1 TPS ≥ 20: 33% vs. 29%; 8.3 vs. 20.2 months

PD-L1 TPS ≥ 1: 27% vs. 27%; 8.3 vs. 20.2 months

D0011: What is the effect of pembrolizumab on patients'body functions?

Pembrolizumab may cause immune-mediated AEs including pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis [4]. In the as-treated population, immune-mediated AEs occurring exclusively in the pembrolizumab group include thyroiditis (2%), hepatitis (1%), hypophysitis (<1%), nephritis (<1%), myocarditis (<1%), and pancreatitis (<1%). Hypothyroidism, pneumonitis, hyperthyroidism, skin reactions, colitis and adrenal insufficiency were more commonly reported in the pembrolizumab group than the chemotherapy group (77 [12%] versus 9 [1%], 53 [8%] versus 3 [<1%], 39 [6%] versus 4 [<1%], 15 [2%] versus 2 [<1%], 7 [1%] versus 2 [<1%], and 4 [<1%] versus 1 [<1%]). Pembrolizumab may cause foetal harm based on its mechanism of action.

immune-mediated AEs: pneumonitis, colitis, hepatitis, nephritis, pancreatitis, thyroid disorders, and endocrinopathies

foetal toxicity

D0012: What is the effect of pembrolizumab on generic health-related quality of life?

No evidence was reported regarding the effect of pembrolizumab on generic health-related QoL.

generic health-related QoL: no evidence

D0013: What is the effect of pembrolizumab on disease-specific quality of life?

No evidence was reported regarding the effect of pembrolizumab on disease-specific QoL.

disease-specific QoL: no evidence

Table 1: Efficacy results of KEYNOTE-042 second interim analysis [6, 39]

Descriptive statistics and estimate variability	Treatment group	Pembrolizumab	Chemotherapy
	Number of subject	637	637
	Median OS, n; m (95% CI) PD-L1 TPS ≥50 PD-L1 TPS ≥20 PD-L1 TPS ≥1 PD-L1 TPS 1–49% 24 m OS, %[1] PD-L1 TPS ≥50 PD-L1 TPS ≥20 PD-L1 TPS ≥1	 n = 299; 20.0 (15.4–24.9) n = 413; 17.7 (15.3–22.1) n = 637; 16.7 (13.9–19.7) n = 338; 13.4 (10.7–18.2) 45 41 39	 n = 300; 12.2 (10.4–14.2) n = 405; 13.0 (11.6–15.3) n = 637; 12.1 (11.3–13.3) n = 337; 12.1 (11.0–14.0) 30 30 28
	BICR-assessed median PFS, m (95% CI) PD-L1 TPS ≥50 PD-L1 TPS ≥20 PD-L1 TPS ≥1	 7.1 (5.9–9.0) 6.2 (5.1–7.8) 5.4 (4.3–6.2)	 6.4 (6.1–6.9) 6.6 (6.2–7.3) 6.5 (6.3–7.0)
	BICR-assessed ORR, n/N; % (95% CI) PD-L1 TPS ≥50 PD-L1 TPS ≥20 PD-L1 TPS ≥1	 118/299; 39 (34–45) 138/413; 33 (29–38) 174/637; 27 (24–31)	 96/300; 32 (27–38) 117/405; 29 (25–34) 169/637; 27(23–30)
	Median DOR, m PD-L1 TPS ≥50 PD-L1 TPS ≥20 PD-L1 TPS ≥1	 20.2 20.2 20.2	 10.8 8.3 8.3
Effect estimate per comparison	*Comparison groups*	Pembrolizumab versus chemotherapy	
	OS (PD-L1 TPS ≥50) (primary endpoint) (subgroup analysis, n = 599)	HR for death	0.69
		95% CI	0.56–0.85
		P-value	0.0003
	OS (PD-L1 TPS ≥20) (primary endpoint) (subgroup analysis, n = 818)	HR for death	0.77
		95% CI	0.64–0.92
		P-value	0.0020
	OS (PD-L1 TPS ≥1) (primary endpoint) (subgroup analysis, n = 1,274)	HR for death	0.81
		95% CI	0.71–0.93
		P-value	0.0018
	OS (PD-L1 TPS 1–49%, subgroup) (exploratory analysis) (subgroup analysis, n = 675)	HR for death	0.92
		95% CI	0.77–1.11
		P-value	NSS
	BICR-assessed PFS (PD-L1 TPS ≥50) (secondary endpoint) (subgroup analysis, n = 599)	HR	0.81
		95% CI	0.67–0.99
		P-value	0.0170
	BICR-assessed PFS (PD-L1 TPS ≥20) (secondary endpoint) (subgroup analysis, n = 818)	HR	0.94
		95% CI	0.80–1.11
		P-value	NSS
	BICR-assessed PFS (PD-L1 TPS ≥1) (secondary endpoint) (subgroup analysis, n = 1,274)	HR	1.07
		95% CI	0.94–1.21
		P-value	NSS

Abbreviations: BICR = blinded independent central review; CI = confidence interval; CR = complete response; DOR = duration of response; HR = hazard ratio; m = months; n = number; N = total number; NSS = not statistically significant; OR = odds ratio; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival; PR = partial response; SD = stable disease; TPS = tumour proportion score

[1] Estimated percentages of patients alive at 24 months

7.2.2 Safety

C0008: How safe is pembrolizumab in relation to the comparator(s)?

In the safety population (n = 1,251), treatment-related AE of any grade occurred in 63% of pembrolizumab patients and 90% of chemotherapy patients. AEs commonly reported in at least 5% of pembrolizumab and chemotherapy recipients respectively, included fatigue (8% versus 17%), increased alanine aminotransferase (ALT) (7% versus 9%), increased aspartate aminotransferase (6% versus 7%), decreased appetite (6% versus 18%), anaemia (6% versus 37%), diarrhoea (5% versus 7%), and nausea (5% versus 30%). The most commonly reported AE was hypothyroidism (11%) in pembrolizumab recipients, and anaemia (37%) in chemotherapy recipients. Treatment-related AEs of grade ≥3 severity that occurred in 20 or more patients were pneumonitis in the pembrolizumab group, and anaemia, neutropenia, and decreased white blood cells, platelets and neutrophils in the chemotherapy group. Treatment-related AEs led to death in 13 (2%) pembrolizumab patients and 14 (2%) chemotherapy patients.

common AEs: hypothyroidism, fatigue, increased ALT/ AST, decreased appetite, anaemia, nausea and diarrhoea

common grade ≥3 AEs: pneumonitis, pruritus, rash and myalgia

deaths due to AEs: 2% for both groups

C0002: Are the harms related to dosage or frequency of applying pembrolizumab?

Patients received a median of nine (range 1–36) doses of pembrolizumab or six (range 1–36) doses of chemotherapy. Treatment-related AEs of grade ≥3 severity were observed in 18% and 41% of patients in the pembrolizumab- and chemotherapy groups, respectively. Approximately 57 (9%) of pembrolizumab patients and 58 (9%) of chemotherapy patients discontinued treatment. Pneumonitis occurred in 8% of pembrolizumab patients; events of grade ≥3 severity accounted for 23 (3%). One person died due to pneumonitis, concurrent with multiple comorbid conditions and disease progression.

9% discontinued pembrolizumab due to AEs

grade ≥ 3 AEs: 3% due to pneumonitis

Pembrolizumab may cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis [4]. Infusion-related reactions were reported in 2% and 4% of patients in the pembrolizumab and chemotherapy groups, respectively.

infusion reaction: 2% for pembrolizumab vs. 4% for chemotherapy

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of pembrolizumab?

Study participants had a median age of 63 years (range 57–69) with good performance status (ECOG 0–1). Patients with a history of autoimmune disease, immunodeficiency, active infections or uncontrolled illnesses were excluded from study. Subgroup analysis by age demonstrated no statistically significant difference in OS between study groups in patients older than 65 years of age. The clinical specificity of elderly patients with comorbidities, co-medication, reduced functional reserve and immunosenescence may affect the efficacy and or toxicity of immune-checkpoint inhibitors [44, 45].

susceptibles: elderly, comorbid, reduced functional status, immune compromised

Immune-mediated AEs occurred in 28% of pembrolizumab patients and 7% of chemotherapy patients. Events of grade ≥3 severity that occurred in five or more pembrolizumab recipients were pneumonitis, severe skin reactions, and hepatitis. One patient in the pembrolizumab group died due to pneumonitis concurrent with comorbid conditions and disease progression. While patients

immune-mediated AEs: 28% of pembrolizumab patients vs. 7% of chemotherapy patients

with compromised immune systems or autoimmune disease were excluded from the study population, side effects of greater severity may be expected in this population.

pembrolizumab may cause foetal harm

Based on its mechanism of action, pembrolizumab may cause foetal harm and adverse reactions in breastfed infants. Females are advised to use effective contraception and not to breast feed for four months after taking their final dose [4].

Table 2: Most frequent adverse events of KEYNOTE-042 [6, 39]

Adverse Event (according to CTCAE version 4.0)	**Pembrolizumab** (n = 636)		**Chemotherapy** (n = 615)	
	Any Grade n (%)	Grade 3, 4, or 5 n (%)	Any Grade n (%)	Grade 3, 4, or 5 n (%)
Any Event	339 (63)	113 (18)	553 (90)	252 (41)
Discontinued due to AE	57 (9)	48 (8)	58 (9)	43 (7)
Event leading to death	13 (2)	13 (2)	14 (2)	14 (2)
Event occurring in ≥ 5% of patients in either group				
Hypothyroidism	69 (11)	1 (<1)	2 (<1)	0 (0)
Fatigue	50 (8)	3 (<1)	102 (17)	8 (1)
Pruritus	46 (7)	2 (<1)	15 (2)	0 (0)
Rash	46 (7)	3 (<1)	27 (4)	0 (0)
ALT increased	45 (7)	9 (1)	53 (9)	5 (<1)
Pneumonitis	43 (7)	20 (3)	0 (0)	0 (0)
AST increased	41 (6)	4 (<1)	42 (7)	2 (<1)
Decreased appetite	40 (6)	5 (<1)	109 (18)	9 (1)
Hyperthyroidism	37 (6)	1 (<1)	1 (<1)	0 (0)
Anaemia	35 (6)	4 (<1)	229 (37)	80 (13)
Diarrhoea	34 (5)	5 (<1)	46 (7)	1 (<1)
Nausea	31 (5)	0 (0)	184 (30)	7 (1)
Arthralgia	27 (4)	0 (0)	46 (7)	0 (0)
Asthenia	27 (4)	3 (<1)	60 (10)	10 (2)
Myalgia	20 (3)	1 (<1)	50 (8)	0 (0)
Vomiting	15 (2)	0 (0)	97 (16)	2 (<1)
Leukopenia	10 (2)	0 (0)	35 (6)	10 (2)
Constipation	8 (1)	0 (0)	68 (11)	0 (0)
Stomatitis	7 (1)	0 (0)	31 (5)	0 (0)
Neutropenia	5 (<1)	1 (<1)	88 (14)	46 (7)
PSN	3 (<1)	0 (0)	41 (7)	6 (1)
Thrombocytopenia	3 (<1)	1 (<1)	56 (9)	10 (2)
WBC count decreased	3 (<1)	0 (0)	71 (12)	32 (5)
Alopecia	2 (<1)	0 (0)	136 (22)	7 (1)
Neutrophil count decreased	2 (<1)	0 (0)	86 (14)	54 (9)
Platelet count decreased	2 (<1)	0 (0)	64 (10)	20 (3)
Neuropathy peripheral	1 (<1)	0 (0)	50 (8)	5 (<1)

Adverse events of interest in the as-treated population				
Any event	177 (28%)	51 (8)	44 (7)	9 (1)
Hypothyroidism	77 (12)	1 (<1)	9 (1)	0 (0)
Pneumonitis	53 (8)	23 (3)	3 (<1)	1 (<1)
Hyperthyroidism	39 (6)	1 (<1)	4 (<1)	0 (0)
Severe skin reactions	15 (2)	11 (2)	2 (<1)	1 (<1)
Infusion reactions	10 (2)	1 (<1)	26 (4)	6 (1)
Thyroiditis	10 (2)	0 (0)	0 (0)	0 (0)
Hepatitis	9 (1)	7 (1)	0 (0)	0 (0)
Colitis	7 (1)	4 (<1)	2 (<1)	1 (<1)
Adrenal insufficiency	4 (<1)	2 (<1)	1 (<1)	0 (0)
Hypophysitis	3 (<1)	3 (<1)	0 (0)	0 (0)
Nephritis	3 (<1)	1 (<1)	0 (0)	0 (0)
Myocarditis	1 (<1)	1 (<1)	0 (0)	0 (0)
Pancreatitis	1 (<1)	0 (0)	0 (0)	0 (0)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; PSN = peripheral sensory neuropathy

7.3 Clinical effectiveness and safety – further studies

KENOTE-024: pembrolizumab versus chemotherapy as first-line for PD-L1-positive NSCLC without EGFR or ALK aberrations

KEYNOTE-024 (NCT02142738) is an ongoing multicentre, randomised, open-label, phase III trial to evaluate the safety and efficacy of first-line pembrolizumab monotherapy versus platinum-based chemotherapy in 305 patients with PD-L1 expressing metastatic NSCLC, without EGFR or ALK mutations [11]. Patients were randomised 1:1 to pembrolizumab (200 mg IV) every three weeks for 35 cycles or investigator's choice of platinum-based chemotherapy. Both cross-over to pembrolizumab following progression and treatment beyond RECIST-defined progression were allowed based on investigator-assessed continued clinical benefit. The primary endpoint was BICR-assessed PFS; secondary endpoints included OS, ORR and safety. Efficacy was assessed in the ITT population while safety was assessed in the as-treated population. Tumours were evaluated every nine weeks according to RECIST version 1.1. AEs were graded according to the CTCAE version 4.0.

BICR-assessed PFS and OS: 10.3 months and 80.2% for pembrolizumab versus 6.0 months and 72.4% for chemotherapy

AEs: 73.4% for pembrolizumab versus 90.0% for chemotherapy

At a median follow-up of 11.2 months (range 6.3–19.7), median PFS was 10.3 months (95% CI 6.7–not reached) for pembrolizumab versus 6.0 months (95% CI 4.2–6.2) for chemotherapy patients. The estimated OS rate at six months was 80.2% in the pembrolizumab group versus 72.4% in the chemotherapy group. Pembrolizumab statistically significantly improved PFS and OS compared to platinum-based chemotherapy as first-line treatment for PD-L1-positive NSCLC (HR for progression or death, 0.50, 95% CI 0.37–0.68, $p < 0.001$; HR for death, 0.60, 95% CI 0.41–0.89, $p = 0.005$, respectively). Compared with chemotherapy, pembrolizumab increased the response rate (44.8% versus 27.8%, the median DOR (not reached [range 1.9+–14.5+] versus 6.3 months [range 2.1+–12.6+] and reduced treatment-related AEs (73.4% versus 90.0%, respectively).

8 Estimated costs

A0021: What is the reimbursement status of the technology?

€ 6,856.0 every 3 weeks

9 doses of pembrolizumab: ~ € 61,704.0

In Austria, single-use vials of 50 mg pembrolizumab powder, for reconstitution (25 mg/mL) and transfer into an intravenous bag, are available at a cost of € 1,714.0 (ex-factory price) [38]. Administered as an intravenous infusion, a 200 mg dose of pembrolizumab would cost € 6,856.0, every three weeks for up to 35 cycles. A median of nine doses (range 1–36) of pembrolizumab would cost approximately € 61,704.0 (range € 6,856.0 - € 239,960). Pembrolizumab is indicated for metastatic NSCLC exhibiting PD-L1 expression without EGFR or ALK aberrations. Since up to 50% of treatment-naïve, advanced NSCLC express PD-L1 [11, 18] and approximately 1,625 patients in Austria (2016) had metastatic NSCLC at diagnosis [22], pembrolizumab would cost approximately € 50,134,500.0 (9 dose treatment period) annually with additional costs for molecular testing and the treatment of AEs.

9 Ongoing research

162 registered studies

Pembrolizumab was compared to chemotherapy as first-line treatment for advanced or metastatic NSCLC in two randomised phase III trials involving patients without targetable EGFR or ALK aberrations. KEYNOTE-024 enrolled patients with PD-L1 ≥50% [11], and KEYNOTE-042 enrolled patients with PD-L1 ≥1% [6]. Several studies are ongoing to investigate pembrolizumab as monotherapy or in combination with other targeted therapies or immunotherapies to treat various stages of NSCLC. In September 2019, searches of www.clinicaltrials.gov and www.clinicaltrialsregister.eu using the search terms “pembrolizumab” and “non-small cell lung cancer” yielded 162 other registered studies (two phase IV, 21 phase III, 135 phase I/II, and four one early phase I/other). Most studies were industry-sponsored or conducted in collaboration with industry.

7 phase II/III studies

Selected recently completed and ongoing phase III or II studies evaluating pembrolizumab in patients with PD-L1-positive advanced NSCLC as first-line in combination with chemotherapy (KEYNOTE-189, KEYNOTE-407), with chemotherapy, bevacizumab, ipilimumab, erlotinib, or gefitinib (KEYNOTE-021), with chemotherapy and canakinumab (CANOPY-1), with ipilimumab (KEYNOTE-598), with lenvatinib (LEAP-007), and with olaparib (KEYLYNK-008):

- **NCT03950674 and NCT02578680:** KEYNOTE-189 is a phase III, randomised, double-blind trial to assess whether adding pembrolizumab to platinum-based chemotherapy increases OS and PFS in patients with untreated metastatic non-squamous NSCLC. Estimated study completion date is January 2020.
- **NCT02775435/ NCT03875092 and NCT03850444 (China extensions):** KEYNOTE-407 is a phase III, randomised, triple-blind, parallel-group study to evaluate the safety and efficacy of carboplatin and paclitaxel or nano particle albumin-bound paclitaxel (nab-paclitaxel)

with or without pembrolizumab as first-line treatment for metastatic squamous NSCLC. Estimated study completion date is February 2021–March 2021.

- **NCT02039674:** KEYNOTE-021 is a phase II, multi-cohort (cohort G), randomised, open-label trial to assess whether adding pembrolizumab to platinum-based chemotherapy, bevacizumab, ipilimumab, erlotinib or gefitinib increases ORR in treatment-naïve NSCLC patients. Estimated study completion date is October 2021.
- **NCT03631199:** CANOPY-1 is a phase III, randomised, double-bind study to determine the safety and efficacy of pembrolizumab plus platinum-based chemotherapy with or without canakinumab in previously untreated patients with locally advanced or metastatic non-squamous NSCLC. Estimated study completion date is October 2022.
- **NCT03302234:** KEYNOTE-598 is a phase III, randomised, double-blind trial to determine the efficacy of pembrolizumab in combination with either ipilimumab or placebo as first-line treatment in patients with metastatic NSCLC. Estimated study completion date is February 2024.
- **NCT03829332:** LEAP-007 is a phase III, randomised, double-blind trial to assess whether combination pembrolizumab and lenvatinib increases PFS and OS in treatment-naïve patients with metastatic NSCLC compared to pembrolizumab monotherapy. Estimated study completion date is March 2024.
- **NCT03976362:** KEYLYNK-008 is a phase III, randomised, triple-blind study to compare the efficacy of pembrolizumab plus maintenance olaparib versus pembrolizumab with maintenance olaparib placebo for increasing PFS and OS of in patients with squamous NSCLC. Estimated study completion date is December 2024.

10 Discussion

Between 2014 and 2015, pembrolizumab was licensed, by the FDA and the EMA, as first-line monotherapy for PD-L1-positive metastatic NSCLC without EGFR or ALK aberrations (PD-L1 TPS ≥50%), and as second-line therapy for PD-L1-positive NSCLC with progression following platinum-based chemotherapy (PD-L1 TPS >1%). Approved concurrently, PD-L1 ICH 22C3 pharmDx is the only FDA and CE marked companion diagnostic assay for guiding pembrolizumab therapy [18]. Pembrolizumab was licensed as first-line monotherapy for patients with any histology NSCLC and PD-L1≥50% based on PFS and OS data from the ongoing KEYNOTE-024 study [11, 46]. In April 2019, the FDA expanded first-line monotherapy indications to include stage III or IV NSCLC patients who are not candidates for surgery or chemoradiation, and whose tumours express PD-L1 TPS ≥1. An application to extend the first-line indication of pembrolizumab in NSCLC with PD-L1 TPS ≥1 is currently under EMA review based on OS data from KEYNOTE-042 [6, 15].

FDA and EMA: second-line: following platinum-based chemotherapy

first-line: monotherapy for PD-L1 expressing NSCLC without EGFR or ALK aberrations (PD-L1 TPS ≥ 50%)

first-line extension for NSCLC (PD-L1 TPS ≥ 1%): FDA approved, under EMA review

KEYNOTE-042

KEYNOTE-042, an ongoing, randomised, open-label, phase III trial compared the efficacy and safety of pembrolizumab (200 mg IV) versus platinum-based chemotherapy (carboplatin + paclitaxel or pemetrexed) as first-line monotherapy for 1,274 patients with PD-L1-expressing metastatic NSCLC. Compared with chemotherapy, pembrolizumab increased OS by 7.8 months, 4.7 months, and 4.6 months for patients with PD-L1 TPS ≥50%, ≥20%, and ≥1%, respectively. The OS benefit of pembrolizumab over chemotherapy was demonstrated across all three PD-L1 TPS populations; those with PD-L1 TPS ≥50% derived the greatest benefit (n = 599 PD-L1 TPS ≥50%, HR 0.69, 95% CI 0.56–0.85 p = 0.0003; n = 818 PD-L1 TPS ≥20%, HR 0.77, 95% CI 0.64–0.92, p < 0.0020; n = 1274 PD-L1 TPS ≥1%, HR 0.81, 95% CI 0.71–0.93, p < 0.0018). However, an exploratory analysis did not find an OS benefit for those with PD-L1 TPS 1–49% (n = 675, 13.4 months versus 12.1 months; HR 0.92, 95% CI 0.77–1.11 NSSD). Approximately 20% of chemotherapy recipients went on to receive subsequent immunotherapy. At second interim analysis, no significant differences in PFS or ORR were noted between groups in any PD-L1 TPS population. Pembrolizumab increased the duration of response by 9.7 months compared to chemotherapy.

OS: pembrolizumab increased OS by 7.8 months, 4.7 months, and 4.6 months for PD-L1 TPS ≥ 50%, ≥ 20%, and ≥ 1%, respectively; no OS benefit for PDL TPS 1–49%

PFS and ORR: NSSD between groups; pembrolizumab

AEs: fatigue, increased ALT/AST, decreased appetite, anaemia, diarrhoea and nausea

Common AEs, reported in at least 5% of pembrolizumab recipients, include fatigue, increased ALT or AST, decreased appetite, anaemia, diarrhoea, and nausea. Immune-mediated AEs include hypothyroidism (12%), pneumonitis (8%), hyperthyroidism (6%), skin reactions (2%), hepatitis (1%), colitis (1%) and adrenal insufficiency (<1%) were also more commonly reported in pembrolizumab patients. Treatment-related AEs led to death in 13 (2%) pembrolizumab patients and 14 (2%) chemotherapy patients.

KEYNOTE-042 limitations: lack of QoL data, CNS activity, and direct comparison with combination pembrolizumab with chemotherapy; clinical specificity in elderly and immune compromised

The results of KEYNOTE-042 hold some limitations. No evidence was reported regarding the effect of pembrolizumab on generic or disease-specific QoL. However, QoL measures are needed to ensure patients achieve a clinically relevant benefit over time despite manageable toxicity. While approximately 12% of patients presented with brain metastases at baseline, no results were reported regarding the CNS activity of pembrolizumab. This is of substantial importance as NCLC patients frequently present with brain metastases and there is concern regarding the ability of pembrolizumab to penetrate the blood brain barrier [47]. Generalizability of the results may be limited in that while study participants had a median age of 63 years with a good performance status, the average age at diagnosis is 70 years in clinical practice. The clinical activity in elderly patients with comorbidities, autoimmune disease, reduced functional reserve, and immunosenescence may affect the efficacy and/or toxicity of pembrolizumab. While a recent pooled analysis reported survival benefit with pembrolizumab compared with chemotherapy in those aged ≥75 years [31, 34], only a randomised clinical trial would define the benefit in this population.

direct comparisons of pembrolizumab monotherapy and in combination with chemotherapy are needed

Based on results of the KEYNOTE-042 study, in April 2019, the FDA expanded the originally approved indication of pembrolizumab monotherapy as a first-line agent for all patients with PD-L1 TPS ≥1%, without EGFR or ALK aberrations. The survival benefit of combination pembrolizumab with chemotherapy over chemotherapy alone was demonstrated in NSCLC patients, including those with PD-L1 TPS 1–49%, in the KEYNOTE-189 and KEYNOTE-407 trials, respectively [13, 14]. These results suggest that patients with PD-L1 TPS1–49% would benefit from combination pembrolizumab with chemotherapy as standard of care. However, without direct comparison trials, physicians and patients may need to discuss whether adding pembrolizumab to chemother-

apy would provide greater individualized efficacy over pembrolizumab monotherapy for those in other PD-L1 TPS populations considering the associated AEs.

high risk of bias: allocation concealment not maintained, open-label study, 46.6% PD-L1 TPS ≥ 50%, suboptimal comparator; industry funded

Several methodological limitations of KEYNOTE-042 compromise the internal and external validity of the phase III trial. Patients were randomised 1:1 pembrolizumab versus chemotherapy via an interactive voice/web-based response system [39] that generated a random allocation sequence. However, allocation concealment was not maintained and may influence how participants were assigned to a given treatment group. Internal validity may be compromised in an open-label study where patients and treating physicians are aware of treatment allocation, and the investigator chooses the chemotherapeutic comparator. While a BIRC assessed outcomes as a means of ensuring an unbiased estimate of treatment effect, OS is an objective outcome unlikely to bias the trial results. Selective reporting is unlikely, as the primary endpoint of OS and secondary endpoints of PFS, ORR and DOR were reported as specified in the protocol. Approximately 46.6% of patients enrolled had a TPS ≥50%, which lends potential bias for the over-performing efficacy of pembrolizumab in the ITT population. Since, subgroup analyses can solely indicate potential benefits for patients, subsequent studies are necessary to clarify the efficacy and safety in a specific patient population [48, 49].. The risk of bias may be increased by industry involvement in funding the study, assisting with study design, data collection, analysis and interpretation, and writing of the report.

ESMO-MCBS grade (original/adapted scale):
PD-L1 TPS ≥ 50%: 4/5
PD-L1 TPS ≥ 20%: 2/3
PD-L1 TPS ≥ 1%: 2/2

PD-L1 TPS ≥ 50% → meaningful clinical benefit

lack of safety subgroup analyses

Given the non-curative treatment setting of pembrolizumab and the statistically significant primary endpoint of median OS in the three TPS populations, we applied Form 2b of the ESMO-MCBS. The ESMO-MCBS was used in order to assess whether pembrolizumab satisfies the criteria for a "meaningful clinical benefit" (score 4 or 5). Both the original v1.1 as well as the adapted version of the MCBS were applied. Application of the original and the adapted versions of the ESMO-MCBS, to the KEYNOTE-042 study resulted in grades 4 and 5 for the PD-L1 TPS ≥50% population, 2 and 3 for PD-L1 TPS ≥20%, and 2 for both in those with PD-L1 TPS ≥1%, respectively. Therefore, a "meaningful clinical benefit" of pembrolizumab could only be identified for patients with PD-L1 TPS ≥50%, according to the original scale and the adapted framework. However, results for the two subgroups (PD-L1 TPS ≥20% and PD-L1 TPS ≥50%) are limited due to the lack of information of adverse events for this specific patient population.

consistency in OS benefits and safety compared with former studies; discrepancy in PFS due to patient characteristics and availability of therapy

The clinical efficacy and safety data from KEYNOTE-042 are consistent with previous studies that suggest pembrolizumab improves OS with manageable toxicity in untreated PD-L1-positive metastatic NSCLC patients lacking EGFR or ALK aberrations. Consistent with existing studies of PD-L1 inhibition, KEYNOTE-001 [8] and KEYNOTE-010 [9], the greatest relative survival benefit was achieved in patients with PD-L1 TPS ≥50%. However, these OS results should be interpreted with caution as nearly half of patients had PD-L1 ≥50%. No significant difference in OS was noted between groups for patients with PD-L1 TPS 1–49%. Heterogeneity in the OS data across PD-L1 TPS populations suggests that a substantial number of patients progress rapidly within six months of treatment without obtaining meaningful benefit from immunotherapy. In the phase III KEYNOTE-024 study, pembrolizumab monotherapy improved PFS and OS, and was associated with fewer AEs compared with platinum-based chemotherapy in NSCLC patients with high PD-L1 expressing tumours [11]. The OS observed in the PD-L1 TPS ≥50% population of KEYNOTE-042 was numerically lower than that reported in KEYNOTE-24 and was not accompanied by significant PFS benefits. While pembrolizumab increased

PFS by 4.3 months compared to chemotherapy in KEYNOTE-024, pembrolizumab conferred no statistically significant difference over chemotherapy in KEYNOTE-042. Discrepancy in PFS findings between studies may be due to differing regions of enrolment, smoking history and availability of subsequent therapy. Safety profiles were similar in that grade ≥3 treatment-related AEs were fewer with pembrolizumab than with chemotherapy. The incidence of most immune-mediated AEs was in keeping with those previously observed with pembrolizumab monotherapy [8, 9, 11].

several ongoing studies evaluating pembrolizumab as monotherapy or in combination with chemotherapy, targeted therapies or immunotherapies

Several studies are ongoing to investigate pembrolizumab as monotherapy or in combination with other targeted therapies or immunotherapies to treat various stages of NSCLC. Ongoing phase III trials KEYNOTE-189 and KEYNOTE-407 assess whether adding pembrolizumab to chemotherapy increases OS and PFS in non-squamous and squamous metastatic NSCLC, respectively. KEYNOTE-021 is a randomised, multi-cohort, open-label, phase II study to evaluate whether adding pembrolizumab to platinum-based chemotherapy, bevacizumab, ipilimumab, erlotinib, or gefitinib increases ORR in treatment-naïve NSCLC patients. The safety and efficacy of pembrolizumab in combination with chemotherapy with or without canakinumab in patients with non-squamous metastatic NSCLC is under evaluation in the phase III CANOPY-1 trial. The randomised, double-blind trials, KEYNOTE-598 and LEAP-007, are evaluating the efficacy of pembrolizumab in combination with ipilimumab or lenvatinib, respectively versus pembrolizumab monotherapy for metastatic NSCLC. KEYLYNK-008, a phase III, randomised, triple-blind study is comparing the efficacy of pembrolizumab plus maintenance olaparib versus pembrolizumab with maintenance olaparib placebo for increasing PFS and OS in squamous NSCLC.

cost: € 6,856.0 per month; ~ € 61,704.0 for 9 doses with additional costs for molecular testing

Administered as an intravenous infusion, the recommended dose of 200 mg of pembrolizumab costs € 6,856.0 every three weeks for up to 35 cycles. A median of nine doses (range 1–36) of pembrolizumab would cost approximately € 61,704.0 (range € 6,856.0 - € 239,960). Pembrolizumab is indicated for metastatic NSCLC exhibiting PD-L1 expression without EGFR or ALK aberrations. Since up to 50% of treatment-naïve, advanced NSCLC express PD-L1 [11, 18] and approximately 1,625 patients in Austria (2016) had metastatic NSCLC at diagnosis [22], pembrolizumab would cost approximately € 50,134,500.0 (9 dose treatment period) annually with additional costs for molecular testing and the treatment of AEs.

PD-L1 as a biomarker: currently no threshold defining PD-L1 positivity; novel biomarkers needed for patient selection

Elevated PD-L1 expression is commonly used as a biomarker of therapeutic efficacy for pembrolizumab, nivolumab and atezolizumab. At least four monoclonal antibodies (clones 22-C3, 28-8, SP142, and SP263) have been developed as companion diagnostics of different PD-1 or PD-L1 inhibitors. Research comparing these four antibodies on different staining platforms demonstrates that three of four reagents are comparable in terms of sensitivity, specificity and reproducibility [50]. Standardization of PD-L1 testing is warranted due to the availability of various staining techniques, antibodies, and differing levels of positivity. There is currently no consensus on a threshold defining PD-L1 positivity, multiple definitions that are used hamper comparison across studies. PD-L1 is not an ideal biomarker because of its dynamic status, it is inducible by interferon exposure, therefore tumours that do not express PD-L1 at baseline may become PD-L1-positive as a result of an inflammatory background [51]. In addition to PD-L1 expression, novel biomarkers are needed to identify patients most likely to benefit from pembrolizumab therapy. Total mutation burden, T-cell inflamed gene expression profile, PD-

L2 expression, history of smoking and presence of specific tumour neoantigens may be useful in predicting response to therapy [52]. Further research is needed regarding the mechanisms of primary and secondary resistance to identify the optimal treatment approach after first-line pembrolizumab and to evaluate the efficacy and safety of pembrolizumab in the real-world setting.

Overall, the KEYNOTE-042 phase III, randomized, open-label study demonstrates that first-line pembrolizumab monotherapy increases OS for patients with PD-L1-expressing metastatic NSCLC. Comprising 46.6% of the ITT population, the greatest OS benefit of pembrolizumab over chemotherapy was observed in patients with PD-L1 TPS ≥50%. No statistically significant difference in OS was noted between groups for those with PD-L1 TPS 1–49%; and no statistically significant differences in PFS or ORR were noted between groups in any PD-L1 TPS population. Data regarding QoL and CNS activity are needed to ensure patients derive a clinically relevant benefit over time despite manageable toxicity. Further biomarkers are needed to ensure the appropriate patient selection and facilitate comparison with other immune checkpoint inhibitors. In the absence of direct comparison trials, physicians may need to discuss whether adding pembrolizumab to chemotherapy would provide greater individual efficacy than chemotherapy alone, especially for PD-L1 TPS 1–49% patients.

KEYNOTE-042: OS benefit for PD-L1 TPS ≥ 50%, PD-L1 TPS ≥ 20%, and PD-L1 TPS ≥ 1%; NSSD in OS for PD-L1 TPS 1–49%; NSSD in PFS or ORR

appropriate biomarkers are needed

optimal therapeutic sequencing remains unknown

Table 3: Benefit assessment based on original ESMO-MCBS and adapted benefit assessment based on adapted ESMO-MCBS [42, 43]

ESMO-MCBS	Active substance	Indication	PD-L1 TPS	*n*	Int	PE	Form	MG standard treatment *months*	Efficacy				Safety		AJ	FM
									MG months	*HR (95% CI)*	*Score calculation*	*PM*	*Toxicity*	*QoL*		
Adapted ESMO-MCBS	Pembrolizumab	NSCLC	≥1%	1,274	NC	OS	2a	>12-<24	+4.6	0.81 0.71-0.93	HR > 0.75 OR Gain <1.5 months	1	-23% grade 3-5 AEs	NA	+1	**2**
Original ESMO-MCBS	Pembrolizumab	NSCLC	≥1%	1,274	NC	OS	2a	>12-<24	+4.6	0.81 0.71-0.93	HR >0.70–0.75 AND Gain ≥1.5 months	2	-	NA	-	**2**
Adapted ESMO-MCBS	Pembrolizumab	NSCLC	≥20%	818	NC	OS	2a	>12-<24	+4.7	0.77 (0.64-0.92)	HR > 0.75 OR Gain <1.5 months	1	-23% grade 3-5 AEs*	NA	+1	**2**
Original ESMO-MCBS	Pembrolizumab	NSCLC	≥20%	818	NC	OS	2a	>12-<24	+4.7	0.77 (0.64-0.92)	HR ≤0.70 AND Gain ≥3-<5 months	3	-	NA	-	**3**
Adapted ESMO-MCBS	Pembrolizumab	NSCLC	≥50%	599	NC	OS	2a	>12-<24	+7.8	0.69 (0.56-0.85)	HR ≤0.70 AND Gain ≥5 months	4	-23% grade 3-5 AEs*	NA	+1	**5**
Original ESMO-MCBS	Pembrolizumab	NSCLC	≥50%	599	NC	OS	2a	>12-<24	+7.8	0.69 (0.56-0.85)	HR ≤0.70 AND Gain ≥5 months	4	-	NA	-	**4**

*Abbreviations: AJ = Adjustments; CI = confidence interval; FM = final adjusted magnitude of clinical benefit grade; HR = hazard ratio; Int = treatment intention; m = months; MG = median gain; NA = not available; OS = overall survival; PE = primary endpoint; PM = preliminary magnitude of clinical benefit grade; QoL = quality of life; * Adverse events are based on the total population and not on the respective subgroup population.*

DISCLAIMER

The scores achieved with the ESMO Magnitude of Clinical Benefit Scale are influenced by several factors: by the specific evaluation form used, by the confidence interval (CI) of the endpoint of interest, and by score adjustments due to safety issues. Ad form: Every individual form measures a different outcome. The meaning of a score generated by form 2a is not comparable to the exact same score resulting from the use of form 2c. To ensure comparability, we report the form that was used for the assessment. Ad CI: The use of the lower limit of the CI systematically favours drugs with a higher degree of uncertainty (broad CI). Hence, we decided to avoid this systematic bias and use the mean estimate of effect. Ad score adjustments: Cut-off values and outcomes that lead to an up- or downgrading seem to be arbitrary. In addition, they are independent of the primary outcome and, therefore, a reason for confounding. Hence, we report the adjustments separately.

11 References

[1] (EUnetHTA) ENfHTA. HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals. Version 3.0. 2013 [cited 2019-08-17];Available from: http://meka.thl.fi/htacore/model/HTA%20Core%20Model%20for%20Rapid%20REA%20of%20Pharmaceuticals%203.0.pdf.

[2] Sul J, Blumenthal GM, Jiang X, He K, Keegan P, Pazdur R. FDA Approval Summary: Pembrolizumab for the Treatment of Patients With Metastatic Non-Small Cell Lung Cancer Whose Tumors Express Programmed Death-Ligand 1. Oncologist. 2016;21(5):643-50. Epub 2016/03/31.

[3] European Medicines Agency: Keytruda European Public Assessment Report (EPAR) Summary. 2017 [Cited 2019-09-13];Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda#product-information-section.

[4] U.S. Food and Drug Administration Drugs@FDA Keytruda ® Label Information. 2019 [Cited 2019-08-13];Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125514s047lbl.pdf.

[5] Pembrolizumab label at eMC. UK Electronic Medicines Compendium. 2017 [cited 2019-09-08];Available from: https://www.medicines.org.uk/emc/product/6947/smpc#INTERACTIONS.

[6] Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 2019;393(10183):1819-30. Epub 2019/04/09.

[7] Poole R. Pembrolizumab: First global approval. Drugs. 2014;74(16):1973-81.

[8] Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small cell lung cancer. N Engl J Med. 2015;372(21):2018-28.

[9] Herbst RS, Baas P, Kim DW, Felip E, Gracia JL, Han J-Y, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540-50.

[10] Pai-Scherf L, Blumenthal GM, Li H, Subramaniam S, Mishra-Kalyani PS, He J, et al. FDA Approval Summary: Pembrolizumab for Treatment of Metastatic Non-Small Cell Lung Cancer: First-Line Therapy and Beyond. The Oncologist. 2017;22(11):1392-9.

[11] Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016;375(19):1823-33. Epub 2016/10/11.

[12] Langer CJ, Borghaei H, Papadimitrakopoulou V, Patnaik A, Powell SF, al. e. Carboplatin and pemetrexed with or without pembrolizumab for advanced non-squamous non-small cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. The Lancet Oncology. 2016;11:1497-508.

[13] Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018;378(22):2078-92. Epub 2018/04/17.

[14] Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gumus M, Mazieres J, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med. 2018;379(21):2040-51. Epub 2018/10/04.

[15] European Medicines Agency: Keytruda® Assessment Report. 2019 [Cited 2019-09-14];Available from: https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-3820-ii-0060-epar-assessment-report-variation_en.pdf.

[16] National Cancer Institute. SEER Stat Fact Sheets: Lung and Bronchus Cancer. 2019 [Cited 2019-09-17];Available from: https://seer.cancer.gov/statfacts/html/lungb.html.

[17] Karim S, Leighl N. Pembrolizumab for the treatment of thoracic malignancies: current landscape and future directions. Future oncology (London, England). 2016;12(1):9-23. Epub 2015/12/04.

[18] Reck M. Pembrolizumab as first-line therapy for metastatic non-small-cell lung cancer. Immunotherapy. 2018;10(2):93-105.

[19] Midthun D. Overview of the initial treatment and prognosis of lung cancer. 2019 [Cited 2019-09-17];UpToDate [Internet] Available from: https://www.uptodate.com Subscription required.

[20] Seetharamu N, Budman DR, Sullivan KM. Immune checkpoint inhibitors in lung cancer: past, present and future. Future oncology (London, England). 2016;12(9):1151-63.

[21] Doholaria B, Hammond W, Shreders A, Lou Y. Emerging therapeutic agents for lung cancer. Journal of hematology & oncology. 2017;9(138).

[22] Statistik Austria. Krebserkrankungen-Luftrohre, Bronchien, Lunge. 2016 [Cited 2019-09-17];Available from: http://www.statistik.at/web_en/statistics/PeopleSociety/health/cancer_incidence/cancer_incidence_overview/index.html.

[23] National Cancer Institute. Non-Small Cell Lung Cancer Treatment. 2019 [Cited 2019-09-17];Available from: https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq.

[24] Thomas KW, Gould MK. Overview of the initial evaluation, diagnosis, and staging of patients with suspected lung cancer. 2019 [Cited 2019-09-17];UpToDate [Internet] Available from: https://www.uptodate.com Subscription required.

[25] Melosky B. Rapidly changing treatment algorithms for metastatic nonsquamous non-small-cell lung cancer. Current Oncology. 2018;25:S68-S76.

[26] Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman J, Chirieac LR, et al. Non-Small Cell Lung Cancer, Version 5.2017 NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network: JNCCN. 2017;15(4):504-35.

[27] Sequist LV, Neal JW. Personalized, genotype-directed therapy for advanced non-small cell lung cancer. 2019 [Cited 2019-09-17];UpToDate [Internet] Available from: https://www.uptodate.com Subscription required.

[28] Hellmann MD, West HJ. Management of advanced non-small cell lung cancer lacking a driver mutation: immunotherapy. 2019 [Cited 2019-09-17];UpToDate [Internet] Available from: https://www.uptodate.com Subscription required.

[29] Lopes G, Wu Y, Kudaba I, Kowalski D, Cho BC, Turna H, et al. Pembrolizumab versus platinum-based chemotherapy as first-line therapy for advanced/metastatic NSCLC with a PD-L1 TPS ≥1%: open-label, phase 3 KEYNOTE-042 study. Oral presentation at American Society of Clinical Oncology Annual Meeting. J Clin Oncol. 2018;36(18_suppl).

[30] Mok T, Wu Y, Kudaba I, Kowalski D, Cho BC, Turna H, et al. Final analysis of the phase 3 KEYNOTE-042 study: pembrolizumab versus platinum-based chemotherapy as first-line therapy for patients with PD-L1-positive locally advanced or metastatic NSCLC. Oral presentation at European Lung Cancer Conference. ESMO. 2019.

[31] Hosomi Y, Nosaki K, Saka H, Baas P, de Castro G, Reck M, et al. Pembrolizumab in elderly patients with PD-L1-positive advanced NSCLC: a pooled analysis from KEYNOTE-010, -024, and -042. Oral presentation at Japanese Society of Medical Oncology Annual Meeting. JSMO. 2019.

[32] Wu Y, Zhang L, Fan Y, Zhou J, Zhang L, Zhou Q, et al. KEYNOTE-042 China study: firt-line pembrolizumab versus chemotherapy in Chinese patients with advanced NSCLC with PD-L1 TPS ≥1. Oral presentation at World Conference on Lung Cancer. WCLC. 2019.

[33] Wu Y, Zhang L, Fan Y, Zhou J, Zhang L, Zhou Q, et al. Pembrolizumab versus platinum-based chemotherapy in Chinese patients with previously untreated advanced NSCLC with a PD-L1 ≥11%: results of the KEYNOTE-042 China extension study. Abstract at American Association for Cancer Research Annual Meeting. AACR. 2019.

[34] Nosaki K, Saka H, Hosomi Y, Baas P, de Castro G, Reck M, et al. Safety and efficacy of pembrolizumab monotherapy in elderly patients with PD-L1-positive advanced non-small cell lung cancer: pooled analysis from the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 studies. Lung Cancer. 2019;https://doi.org/10.1016/j.lungcan.2019.07.004.

[35] U.S. Food and Drug Administration Drugs@FDA Alimta® Label Information. 2019 [Cited 2019-09-09];Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021462s021lbl.pdf.

[36] U.S. Food and Drug Administration Drugs@FDA Taxol® Label Information. 2019 [Cited 2019-09-09];Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020262s049lbl.pdf.

[37] U.S. Food and Drug Administration Drugs@FDA Paraplatin® Label Information. 2019 [Cited 2019-09-09];Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020452s005lbl.pdf.

[38] Grössmann N, Rothschedl E, Wolf S. Horizon Scanning in Oncology 40th Prioritization - 3rd quarter 2019. 2019;Available from: http://eprints.hta.lbg.ac.at/1196/1/HSO_39th_Prioritisation.pdf.

[39] Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Supplementary Appendix to: Mok T, Wu Y, Kudaba I, Kowalski D, Cho B, Turna H, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019;393(10183):1819-30.

[40] Assessment E-EnfHT. Internal validity of randomized controlled trials. 2013;Available from: http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Internal_Validity.pdf.

[41] Assessment E-EnfHT. EUnetHTA guidelines. Levels of evidence. Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals. . February 2013;Available from: http://www.eunethta.eu/sites/default/files/sites/5026.fedimbo.belgium.be/files/Applicability.pdf.

[42] Cherny N, Dafni U, Bogaerts J, Latino N, Pentheroudakis G, Douillard J, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of oncology : official journal of the European Society for Medical Oncology. 2017;28(10):2340-66.

[43] Wild C, Grössmann N, Bonanno PV, Bucsics A, Furst J, Garuoliene K, et al. Utilisation of the ESMO-MCBS in practice of HTA. Annals of oncology : official journal of the European Society for Medical Oncology. 2016;27(11):2134-6.

[44] Ferrara R, Mezquita L, Auclin E, Chaput N, Besse B. Immunosenescence and immunecheckpoint inhibitors in non-small cell lung cancer patients: Does age really matter? Cancer Treatment Reviews. 2017;60:60-8.

[45] Sgambato A, Cassaluce F, Gridelli C. The role of checkpoint inhibitors immunotherapy in advanced non-small cell lung cancer in the elderly. Expert Opin Biol Ther. 2017:1-7.

[46] Pai-Scherf L, Blumenthal GM, Li H, Subramaniam S, Mishra-Kalyani PS, He K, et al. FDA approval summary: Pembrolizumab for treatment of metastatic non-small cell lung cancer: First-line therapy and beyond. Oncologist. 2017;22(11):1392-9.

[47] Dang TO, Ogunniyi A, Barbee MS, Drilon A. Pembrolizumab for the treatment of PD-L1 positive advanced or metastatic non-small cell lung cancer. Expert review of anticancer therapy. 2016;16(1):13-20.

[48] Rothwell PM. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. The Lancet. 2005;365(9454):176-86.

[49] Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and baseline comparisions in clinical trial reporting: current practice and problems. Stat Med. 2002;21(19):2917-30.

[50] Hirsh FR, McElhinny A, Stanforth D, Ranger-Moore J, Jansson M, Kulangara K, et al. PD-L1 immunohistochemistry assays for lung cancer: results from phase 1 of the blueprint PD-L1 IHC Assay Comparison Project. J Thorac Oncol. 2017;12:208-22.

[51] Rihawi K, Gelsomino F, Sperandi F, Melotti B, Fiorentino M, Casolari L, et al. Pembrolizumab in the treatment of metastatic non-small cell lung cancer: A review of current evidence. Therapeutic Advances in Respiratory Disease. 2017;11(9):353-73.

[52] Dello Russo C, Gagliardi D, Ramlogan R, Navarra P. Optimizing Patient Selection to Maximize Drug Efficacy: the Expanding Role of Pharmacogenomics in the Clinical Development of Pembrolizumab for the Treatment of Non-small Cell Lung Cancer. Clinical Therapeutics. 2019;41(5):982-91.

12 Appendix

Table 4: Administration and dosing of pembrolizumab or chemotherapy [4-6, 39]

	Pembrolizumab	Chemotherapy
Administration mode	Pembrolizumab IV over 30 minutes [4]	Carboplatin AUC 5 or 6 IV over 30-60 minutes; pemetrexed IV over 10 minutes; paclitaxel IV over 3 hours or local standard practice [39]
Description of packaging	50 mg white lyophilized powder in a single-dose vial for reconstitution using 2.3 mL of sterile water (resulting concentration 20 mg/mL); 100 mg/mL (25 mg/mL) colourless solution in a single-dose vial; withdraw required volume from vial and transfer into IV bag containing 0.9% sodium chloride injection, USP or 5% dextrose injection, USP (final concentration 1mg/mL-10 mg/mL) [4]	Subjects received open label vials or kits containing 1 vial per kit box. The name of the product, strength or potency was on the label text [39]. Carboplatin is supplied as 600 mg/60 mL aqueous solution in multidose vials. Paclitaxel is available in 100 mg (16.7 mL) and 300 mg (50 mL) multidose vials [36]. Pemetrexed is available in 500 mg vials [35].
Total volume contained in packaging for sale	50 mg pembrolizumab powder formulated in 3.1 mg L-histidine, 0.4 mg polysorbate 80 and 140 mg sucrose in a single-dose vial; 100 mg pembrolizumab in 4 mL of solution in a single-dose vial [4]	Carboplatin 10 mg/mL (60 mL) + paclitaxel 6 mg/mL (16.7 mL) or pemetrexed (500 mg/vial)
Dosing	Pembrolizumab (200 mg IV) every 3 weeks for up to 35 treatments [6]. Discontinue pembrolizumab in patients with life-threatening AEs, grade 3/4 or recurrent pneumonitis, grade 4 diarrhoea/colitis, grade 3/4 elevated liver enzymes, hypophysis, hypothyroidism, nephritis, myocarditis or other immune-mediate AEs; withhold for grade 2 pneumonitis, grade 2/3 diarrhoea/colitis, grade 2 elevated liver enzymes, hypophysis or nephritis, grade 1/2 myocarditis or other immune-mediated AEs [39].	Investigator's choice of carboplatin AUC 5 or 6 + paclitaxel (200 mg/m^2) or pemetrexed (500 mg/m^2) every 3 weeks for up to 6 cycles, followed by optional pemetrexed 500 mg/m^2 for patients with non-squamous histology. Participants receive one intramuscular injection of vitamin B12 (1000 mcg) during week preceding first pemetrexed dose and every 3 cycles thereafter; and folic acid (350-100 mcg daily). Patients receiving chemotherapy should be pre-medicated with oral or injectable steroids according to the approval product label and/or standard practice [39].
Median treatment duration	Until DP, unacceptable toxicity, investigator decision, patient withdrawal or up to 35 cycles of pembrolizumab [6].	Until DP unacceptable toxicity, investigator decision, patient withdrawal or up to 6 cycles of chemotherapy [6].
Contraindications	None [4]	Carboplatin is contraindicated in patients with bone marrow depression or bleeding [37]. Paclitaxel is contraindicated in AIDS-related Kaposi's sarcoma (neutrophils <100 cells/mm^3) or patients with neutrophils <1500 cells/mm^3 [36]. Pemetrexed is contraindicated in those with history of hypersensitivity [35].
Drug interactions	Avoid systemic corticosteroids or immunosuppressant's prior to starting pembrolizumab [5]	Carboplatin potentiates toxicity of nephrotoxic compounds [37]. Caution use of paclitaxel with inhibitors and inducers of CYP2C8; interacts with CYP3A4.[36]. Caution use of ibuprofen or NSAIDs with pemetrexed [35].

Abbreviations: AE = adverse event; AIDS = acquired immunodeficiency syndrome; DP = disease progression; IV = intravenous; NSAID = non-steroidal anti-inflammatory drugs; USP = United States Pharmacopeia

Table 5: Characteristics of KEYNOTE-042 [6]

Title: Pembrolizumab versus chemotherapy for previously untreated, PD-L1 expressing, locally advanced or metastatic NSCLC (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial [6, 39]			
Study identifier	NCT02220894, 3475-042, EudraCT2014-001473-14, JAPIC-CTI152877, MK-3475-042, KEYNOTE-042		
Design	International (32 countries), multicentre (213 sites), randomised, open-label, interventional phase III		
	Duration of main phase:		Estimated trial duration of 3.5 years (first subject entry until last subject's last visit); subject participation for 2.5 years. 3428 patients were screened; 3019 had samples evaluable for PD-L1 expression of whom 1978 had TPS ≥1. December 2014 – March 2017, 1275 patients were randomised 1:1 to receive pembrolizumab (n = 638) or chemotherapy (n = 637). One patient was assigned pembrolizumab after death; therefore, ITT included 637 in each group. Data cut-off: February 26, 2018 Median follow-up: median follow-up 12.8 m (range 6.0–20.4) Mean number of doses: 9 (range 1–36) for pembrolizumab and 6 (range 1–42) for chemotherapy
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		At data cut-off, as-treated population, 636 (14%) of pembrolizumab and 615 (5%) of chemotherapy patients were still receiving assigned treatment. In the ITT population, 240 (38%) of pembrolizumab and 282 (44%) of chemotherapy patients received ≥1 subsequent therapy, including 19 (3%) and 126 (20%) that received subsequent immunotherapy. After excluding patients still taking pembrolizumab or those who had completed or discontinued treatment without later progression, 240 (15%) of 474 pembrolizumab and 282 (56%) of 504 chemotherapy patients received subsequent treatment.
Hypothesis	Superiority The primary hypothesis is that pembrolizumab prolongs OS compared to standard of care platinum-based chemotherapy.		
Funding	Merk Sharp & Dohme Corp.		
Treatments groups	Pembrolizumab (n = 637 efficacy; n = 636 safety; n = 87/636 ongoing and 42 completed 35 cycles at data cut-off February 26, 2018)		Pembrolizumab (200 mg IV) every 3 weeks for up to 35 treatments, or until progression or unacceptable toxicity.
	Chemotherapy (n = 637 efficacy; n = 615 safety; n = 615/636 ongoing and 160 completed 6 cycles at data cut-off February 26, 2018)		Investigators choice of platinum chemotherapy: carboplatin (AUC 5–6 mg/mL/minute, maximum dose 750–900 mg) + paclitaxel (200 mg/m² IV) or pemetrexed (500 mg/m² IV) every 3 weeks for up to 6 cycles. Participants with non-squamous histologies may receive optional treatment with pemetrexed (500 mg/m² IV) every 3 weeks. Patients are treated until progression or unacceptable toxicity. Crossover from chemotherapy to pembrolizumab was not permitted.
Endpoints and definitions	Overall survival Primary endpoint	OS	Time from randomization until all-cause death in participants with TPS of ≥ 50%, ≥ 20%, and ≥ 1% (up to 38 months)
	Progression-free survival Secondary endpoint	PFS	Time from randomization until BICR-assessed PD or all-cause death (RECIST v1.1) in participants with TPS of ≥ 50%, ≥ 20%, and ≥ 1%, (up to 38 months)
	Objective response rate Secondary endpoint	ORR	Percentage of participants with BICR-assessed CR or PR (RECIST v1.1), in those with TPS of ≥ 50%, ≥ 20%, and ≥ 1% (up to 38 months)
	Adverse events Secondary endpoint	AEs	AEs graded by CTCAE version 4.0 (up to 38 months)

<table>
<tr><td colspan="4">Title: Pembrolizumab versus chemotherapy for previously untreated, PD-L1 expressing, locally advanced or metastatic NSCLC (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial [6, 39]</td></tr>
<tr><td>Study identifier</td><td colspan="3">NCT02220894, 3475-042, EudraCT2014-001473-14, JAPIC-CTI152877, MK-3475-042, KEYNOTE-042</td></tr>
<tr><td rowspan="2"></td><td>Discontinued treatment due to adverse events
Secondary endpoint</td><td>—</td><td>Number of patients who discontinued study treatment due to an AE (up to 38 months)</td></tr>
<tr><td>Notes</td><td colspan="2">In the original protocol, the primary endpoint of was OS in patients with PD-L1 TPS ≥50%; secondary endpoints were OS in patients with PD-L1 TPS ≥1% and PFS in patients with TPS ≥50% and ≥1%. Exploratory endpoints were OS and PFS in patients with TPS of 1–49% and OR among those with TPS ≥50%, 1–49%, and ≥1%. After enrolment of 662 patients in the KEYNOTE-010 study, a significant OS benefit was reported in patients with previously treated advanced NSCLC and a PD-L1 TPS of ≥1%. Consequently, the primary endpoints of this study were amended to include PFS and OR, respectively, in these populations. At screening, PD-L1 expression was assessed with PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA).</td></tr>
<tr><td>Database lock</td><td colspan="3">Last update posted March 15, 2019</td></tr>
<tr><td colspan="4">Results and Analysis</td></tr>
<tr><td>Analysis description</td><td colspan="3">Primary Analysis
ITT: efficacy analyses included all patients randomized. Safety analysis included all patients who received at least one dose of study drug. Two interim analyses (August 30, 2017, 6 months after final patient enrolment; Feb 26, 2018, 38.3 months after first patient enrolment) and a final analysis were specified in the final protocol.
OS and PFS were calculated using the Kaplan-Meier method for censored data. Efficacy hypotheses were analysed sequentially by TPS (≥50%, ≥20%, and ≥1%). Hypotheses were tested only if superiority was established for the preceding hypothesis. Family-wise type 1 error was controlled at a one-sided α = 0.025. Accounting for the 0.01576 α spent at first interim analysis, superiority boundaries were adjusted for multiplicity with the Hwang-Shih-DeCani α spending function, with γ parameter set at -0.9023 and an information fraction of 1166 of 1353 (number of study days to second interim analysis and planned final analysis, respectively from date first patient was randomised). Stratified log-rank test assessed between-group differences in OS and PFS. Stratified Cox regression with Efron's method of tie handling was used to estimate HR and associated 95% CIs. The stratified Miettinen and Nurminen method was used to assess between-group differences in response rate. All randomisation stratification factors were applied to all stratified analyses.
A sample size of 1240 patients gave power at the following levels (one-sided α = 0.025): 99% to detect an HR of 0.65 among patients with TPS ≥50% with 398 deaths in the population; 98% to detect piecewise HRs of 0.80 from 0 to 6 months of treatment and 0.64 after 6 months of treatment among patients with TPS ≥20% with 557 deaths; and 91% to detect piecewise HRs of 0.92 for 0 to 6 months of treatment and 0.73 after 6 months of treatment among patients with TPS ≥1 with 900 deaths. Piecewise HRs account for possible non-proportional hazards in the treatment effect.</td></tr>
<tr><td>Analysis population</td><td>Inclusion</td><td colspan="2">❁ Adults (aged ≥ 18 years) with histologically or cytologically-confirmed PD-L1-expressing locally advanced or metastatic NSCLC without sensitizing EGFR or ALK mutations, or previous systemic therapy for advanced or metastatic disease
❁ Life expectancy ≥ 3 months, adequate organ function with ECOG performance-status 0–1, ≥ 1 measurable lesion according to RECIST v1.1, and PD-L1 TPS ≥ 1%
❁ Males with female partners, and females of childbearing potential willing to use adequate contraception up to 180 days post chemotherapy</td></tr>
</table>

Title: Pembrolizumab versus chemotherapy for previously untreated, PD-L1 expressing, locally advanced or metastatic NSCLC (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial [6, 39]

Study identifier	NCT02220894, 3475-042, EudraCT2014-001473-14, JAPIC-CTI152877, MK-3475-042, KEYNOTE-042						
	Exclusion	❁ NSCLC curatively treatable with surgical resection and/or chemoradiation, squamous histology having received adjuvant carboplatin in combination with paclitaxel, or lack of tumour sample for PD-L1 determination ❁ Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 anti-CD137, or CTLA-4 antibody, including ipilimumab or a drug targeting T-cell co-stimulation or checkpoint pathways ❁ Received a study drug, investigational agent, or device within 4 weeks, systemic chemotherapy, biological therapy or major surgery within 3 weeks, or live vaccine within 30 days prior to first dose of study drug ❁ Received systemic steroid therapy or an immunosuppressant ≤ 3 days prior to the first dose of study drug, except for daily steroid replacement therapy ❁ Expected to require antineoplastic therapy during study ❁ History of HIV, hepatitis B or C, malignancy with recurrence within 5 years, substance abuse, non-infectious pneumonitis requiring glucocorticoids, untreated CNS metastases, autoimmune disease or infection requiring systemic treatment, or allogenic tissue/solid organ transplantation ❁ Pregnant, breastfeeding, or expecting to conceive or father children within the study duration					
	Characteristics	Pembrolizumab (n = 637)			Chemotherapy (n = 637)		
		TPS ≥ 50% (n = 299)	TPS ≥ 20% (n = 413)	TPS ≥ 1% (n = 637)	TPS ≥ 50% (n = 300)	TPS ≥ 20% (n = 405)	TPS ≥ 1% (n = 637)
	Median age (range), years <65, n (%)	63.0 (56.0-68.0) 167 (56)	63.0 (56.0-69.0) 228 (55)	63.0 (57.0-69.0) 359 (56)	64.0 (57.0-69.0) 161 (54)	64.0 (57.0-69.0) 212 (52)	63.0 (57.0-69.0) 348 (55)
	Male, n (%)	205 (69)	283 (69)	450 (71)	210 (70)	285 (70)	452 (71)
	Region East Asia Europe Latin America Other	 92 (31) 71 (24) 53 (18) 83 (28)	 128 (31) 96 (23) 78 (19) 111 (27)	 185 (29) 149 (23) 136 (21) 167 (26)	 94 (31) 66 (22) 63 (21) 77 (26)	 121 (30) 95 (23) 82 (20) 107 (26)	 185 (29) 137 (22) 133 (21) 182 (29)
	ECOG performance-status, n (%) 0 1	 96 (32) 203 (68)	 122 (30) 291 (70)	 198 (31) 439 (69)	 91 (30) 209 (70)	 131 (32) 274 (68)	 192 (30) 445 (70)
	Smoking status Current Former Never	 57 (19) 178 (60) 64 (21)	 75 (18) 243 (59) 95 (23)	 125 (20) 370 (58) 142 (22)	 59 (20) 174 (58) 67 (22)	 85 (21) 230 (57) 90 (22)	 146 (23) 351 (55) 140 (22)
	Histology Squamous Non-squamous	 107 (36) 192 (64)	 148 (36) 265 (64)	 243 (38) 394 (62)	 114 (38) 186 (62)	 156 (39) 249 (61)	 249 (39) 388 (61)
	Disease status Locally advanced Metastatic	 27 (9) 272 (91)	 42 (10) 371 (90)	 76 (12) 561 (88)	 35 (12) 265 (88)	 51 (13) 354 (87)	 84 (13) 553 (87)
	BM	19 (6)	23 (6)	35 (5)	15 (5)	22 (5)	35 (5)
	PD-L1 TPS 1–19% 20–49% ≥ 50%	 0 (0) 0 (0) 299 (100)	 0 (0) 114 (28) 299 (72)	 224 (35) 114 (18) 299 (47)	 0 (0) 0 (0) 300 (100)	 0 (0) 105 (26) 300 (74)	 232 (36) 105 (16) 300 (47)
	Previous therapy for non-metastatic Radiotherapy Neoadjuvant therapy Adjuvant therapy	 40 (13) 1 (<1) 8 (3)	 53 (13) 2 (<1) 13 (3)	 75 (12) 3 (<1) 18 (3)	 39 (13) 5 (2) 4 (1)	 51 (13) 7 (2) 8 (2)	 81 (13) 7 (1) 12 (2)

Title: Pembrolizumab versus chemotherapy for previously untreated, PD-L1 expressing, locally advanced or metastatic NSCLC (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial [6, 39]	
Study identifier	NCT02220894, 3475-042, EudraCT2014-001473-14, JAPIC-CTI152877, MK-3475-042, KEYNOTE-042
Applicability of evidence	
Population	KEYNOTE-042 was conducted in patients with PD-L1-expressing metastatic NSCLC without EGFR or ALK mutations. Generalizability of the results may be limited in that while study participants were a median age of 64 years with good performance status, the average age at diagnosis is 70 years. The clinical specificity in elderly patients with comorbidities, reduced functional reserve, and immunosenescence may affect the efficacy and or toxicity of pembrolizumab.
Intervention	The dosage and administration of pembrolizumab used in KEYNOTE-042 is consistent with that recommended for the treatment of NSCLC [4]. Pembrolizumab was withheld for drug-related toxicities and severe or life-threatening AEs. Cross-over from chemotherapy to pembrolizumab was not permitted.
Comparators	The comparator arm may be suboptimal as cross-over is desirable in settings where a drug has proven benefit in a subsequent line of therapy and attempts are being made to advance it to an earlier line. Without direct comparison trials, physicians and patients may need to discuss whether adding pembrolizumab to chemotherapy would provide greater individualised efficacy than pembrolizumab monotherapy.
Outcomes	No evidence was reported regarding the effect of pembrolizumab on generic or disease-specific QoL of CNS activity. QoL measures are needed to ensure patients achieve a clinically relevant benefit over time despite favourable tolerability, especially as other immunotherapies are not considered for comparison. NSCLC patients frequently present with brain metastases; there is concern regarding the ability of pembrolizumab to penetrate the blood brain barrier.
Setting	KEYNOTE-042 was a multinational, multicentre study where approximately 63% of patients were East Asian, 48% were European, 43% were Latin American, and 57% were from other regions.

Abbreviations: AE = adverse events; ALK = anaplastic lymphoma kinase; AUC = area under the curve; BICR = blinded independent central review; BM = brain metastases; CI = confidence interval; CNS = central nervous system; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; CTLA-4 = anti-cytotoxic T-lymphocyte-associated antigen-4; ECOG = Eastern Cooperative Oncology Group; HIV = Human Immunodeficiency Virus; HR = hazard ratio; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-1 = programmed cell death protein 1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; TPS = tumour proportion score

Table 6: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomised controlled trials) [6, 40]

Criteria for judging risk of bias		Risk of bias
Adequate generation of randomisation sequence: randomisation schedule generated by a computerised randomised list generator held centrally; randomised 1:1 to pembrolizumab or chemotherapy using the IVRS/IWRS system. Randomisation was stratified by region of enrolment (Asia versus rest of world), ECOG performance status score (0 versus 1), histology (squamous versus non-squamous), PD-L1 TPS (≥ 50% versus 1–49%) and treatment was allocated in blocks of four in each stratum.		yes
Adequate allocation concealment:		no
Blinding:	**Patient:** due to differences in infusion durations, administration schedules, and premedication requirements, patients were not masked.	no
	Treating physician: due to differences in infusion durations, administration schedules, and premedication requirements, investigators, members of the external data monitoring committee, and select representatives of the sponsor were not masked.	no
	Outcome assessor: central radiological reviewers (BICR) were unaware of treatment assignment.	yes
Selective outcome reporting unlikely: primary outcomes include OS, PFS, ORR, AEs and discontinuation due to AEs, as per clinical trial report. Response and DP were assessed by BICR according to RECIST v1.1.		yes
No other aspects which increase the risk of bias: industry funded the study, assisted with study design, data collection, analysis, interpretation and writing of the report.		no
Risk of bias – study level		high

Abbreviations: BICR = blinded independent central review; DP = disease progression; ECOG = Eastern Cooperative Oncology Group; IVRS/IWRS – interactive web response system/interactive web response system; PD-L1 = programmed death ligand 1; TPS = tumour proportion score