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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-189 trial

In the phase III, KEYNOTE-189 study, 616 patients with untreated metastatic non-squamous NSCLC without targetable epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) aberrations, regardless of PD-L1 expression, were randomised 2:1 to pemetrexed and platinum-based chemotherapy plus either pembrolizumab or saline placebo every three weeks for four cycles, followed by pembrolizumab or placebo for 35 cycles plus pemetrexed maintenance therapy. Adding pembrolizumab to chemotherapy conferred longer overall survival (OS) than chemotherapy alone (not reached versus 11.3 months). Compared with chemotherapy alone, pembrolizumab increased progression-free survival (PFS) by 3.9 months. Increased PFS was consistent across subgroups except for those with PD-L1 tumour proportion scores (TPS) <1% and those over 65 years of age. Pembrolizumab increased the overall response rate (ORR) by 28.7% and the median duration of response (DOR) by 3.4 months compared with chemotherapy alone. Anaemia and neutropenia were the most frequently reported adverse events (AEs) of grade ≥3 in severity. Common immune-mediated AEs occurring in pembrolizumab combination patients included hypothyroidism (6.7%), hyperthyroidism (4.0%), colitis (2.2%), nephritis (1.7%), and hepatitis (1.2%).

Conclusion

Overall, adding pembrolizumab to platinum-based chemotherapy increases OS, PFS, and ORR, and reduces the risk of death and progression for patients with metastatic NSCLC. While the survival benefit of pembrolizumab combination over chemotherapy alone was observed regardless of PD-L1 tumour expression, the greatest relative benefit was achieved in patients whose tumours exhibited higher PD-L1 levels. Due to cross-over, only relative 12 month OS data are available, absolute OS data are not and will not be available. Data regarding quality of life and central nervous system activity are needed to ensure patients derive a clinically relevant benefit over time despite manageable toxicity. Without direct comparison trials, physicians may need to discuss whether adding pembrolizumab to platinum-based chemotherapy would provide greater individualised efficacy to a patient than pembrolizumab monotherapy.

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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 the NSCLC?
A0004	What is the natural course of NSCLC?
A0006	What are the consequences of NSCLC for the society?
A0023	How many people belong to the target population?
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A0003	What are the known risk factors for NSCLC?
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Clinical effectiveness	
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D0011	What is the effect of pembrolizumab on patients' body functions?
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C0008	How safe is pembrolizumab in relation to the comparator(s)?
C0002	Are the 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 pembrolizumab?

PD-1 inhibitor, immune checkpoint inhibitor

Up-regulation of programmed death 1 (PD-1) ligands 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 + pemetrexed + chemotherapy for 4 cycles, followed by maintenance therapy

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 in combination with pemetrexed and platinum chemotherapy, for four cycles, followed by pembrolizumab (200 mg IV) plus pemetrexed every three weeks until progression or unacceptable toxicity [3, 4]. For melanoma and previously treated NSCLC, the dose depends on the patient's weight and is 2 mg/kg body weight [5].

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, elevated liver enzymes, inability to reduce corticosteroids to ≤10 mg/day within twelve weeks, infusion-related reactions, or intolerance due to adverse events (AEs) [3]. 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 [6].

A0022: Who manufactures pembrolizumab?

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

3 Indication

A0007: What is the target population in this assessment?

previously untreated metastatic non-squamous NSCLC

Pembrolizumab (Keytruda®) is indicated, in combination with pemetrexed and platinum-based chemotherapy, for untreated patients with metastatic non-squamous non-small cell lung cancer (NSCLC) without epidermal

growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements [4].

4 Current regulatory status

A0020: For which indications has pembrolizumab 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 (tumour proportion score [TPS] ≥50%) and overall survival (OS) data from the phase III KEYNOTE-010 study [8-11].

First global approval: FDA licensed for unresectable melanoma in September 2014

FDA: licensed second-line for metastatic NSCLC with PD-L1 expression in October 2015

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 [12, 13]. The combination of pembrolizumab with pemetrexed and carboplatin had 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 [14]. Pembrolizumab is under priority review (expected September 2018) for use in combination with pemetrexed and platinum chemotherapy as first-line treatment for metastatic non-squamous NSCLC based on results from the phase III KEYNOTE-189 study [15].

FDA: licensed first-line for metastatic NSCLC October 2016–May 2017

FDA: priority review first-line in combination with chemotherapy for NSCLC in April 2018

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, and urothelial cancer [5]. 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. A marketing authorisation application (MAA) to extend the use of pembrolizumab in combination with chemotherapy for NSCLC was withdrawn last October as further data were needed to derive conclusions regarding safety and efficacy [16]. However, pembrolizumab is currently under review in combination with pemetrexed and platinum-based chemotherapy as first-line treatment of patients with metastatic NSCLC based on OS data reported in the phase III KEYNOTE-189 trial [17].

EMA approvals: first-line for metastatic NSCLC with high PD-L1 expression without EGFR/ALK aberrations, second-line following progression on platinum-based chemotherapy

MAA: in combination with chemotherapy as first-line for NSCLC

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 [18, 19]. 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 [20]. 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%) [9, 13, 14].

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 [18, 21].

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 [22], leading to a high rate of relapse and early formation of micro-metastases [23].

A0023: How many people belong to the target population?

4,860 Austrians were diagnosed with NSCLC in 2015

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, 2,956 men and 1,904 women were newly diagnosed with lung cancer in 2015; and 2,396 men and 1,493 women died due to lung cancer [24]. 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 1,620 patients in Austria (2015) had metastatic NSCLC at the time of diagnosis. The average age at diagnosis is approximately 70 years [19].

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 [18].

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 [18, 25].

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 or ALK genes. 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 [9].

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 [21]:

- 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 [26, 27]:

- 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, ceritinib or lorlatinib may be effective for crizotinib-resistant cancers. First-line therapy for stage IV patients with BRAF V600E is combination dabrafenib plus trametinib.
- Patients with EGFR mutations may benefit from TKIs such as first generation erlotinib or gefitinib, or second-generation afatinib. 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. Non-squamous NSCLC patients with low PD-L1 expression lacking driver mutations may benefit from pembrolizumab with pemetrexed and carboplatin or cisplatin. Pembrolizumab is currently under review in combination with pemetrexed and platinum-based chemotherapy as first-line treatment for metastatic NSCLC. While combined nivolumab and ipilimumab afforded 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: 248 hits

A literature search was conducted on 18 June 2018 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were "pembrolizumab", "keytruda", "L01XC18", "non small lung cancer", "NSCLC", "lung cancer" and "metastatic". The manufacturer was also contacted and submitted no unpublished data, only information regarding ongoing trials found on clinicaltrials.gov. A manual search identified two statistical reports [19, 24], two FDA approval documents [3, 15], four EMA marketing authorization notifications [5, 6, 16, 17], eight clinical guidance documents [18, 21-23, 25, 26, 28, 29], and six clinical trial articles [10, 11, 14, 30-32] and a cost document [33]. Ongoing trials information was found on www.clinicaltrials.gov.

manual search: 23 additional references

overall: 271 references included: 3 studies

Overall, 271 references were identified. Included in this reported are:

- KEYNOTE-189, phase III [4, 31, 32]
- KEYNOTE-024, phase III [13]
- KEYNOTE-021, phase I/II [14]

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) [34]. 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.

assessment of the external validity based on the EUnetHTA guideline

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 [35].

magnitude of clinically meaningful benefit assessed according to the 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 version 1.1 developed by the European Society for Medical Oncology (ESMO-MCBS v1.1) was used [36]. Additionally, an adapted version (due to perceived limitations) of the ESMO-MCBS was applied [37]. 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-189: pembrolizumab + chemotherapy versus chemotherapy alone as first-line treatment for metastatic NSCLC

KEYNOTE-189 (NCT02578680) is a multicentre, double-blind, randomised, interventional phase III study involving 616 patients with metastatic non-squamous NSCLC without EGFR or ALK mutations and who have not been treated for metastatic disease [4]. The study was designed to evaluate whether adding pembrolizumab to pemetrexed and platinum-based chemotherapy prolongs PFS and OS compared to standard chemotherapy alone. 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; all randomly assigned patients received at least one dose of trial treatment.

ITT (n = 616): stratified by PD-L1 expression, chemotherapy, and smoking history

Eligible patients were 18 years or older, with untreated pathologically confirmed metastatic non-squamous NSCLC without EGFR or ALK mutations, and provided tumour samples for PD-L1 status determination. 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 received more than 30 Gy of radiotherapy to the lung within the previous six months. Study participants were stratified by PD-L1 expression (TPS $\geq$1% versus <1%), choice of platinum-based chemotherapy (cisplatin versus carboplatin), and smoking history (never versus former or current).

Patients were randomised 2:1 to receive pemetrexed (500 mg/m² IV) and platinum-based chemotherapy physicians choice of cisplatin (75 mg/m² IV) or carboplatin (area under the curve [AUC]) 5mg/mL/minute IV) plus either pembrolizumab (200 mg IV) or saline placebo every three weeks for four cycles, followed by pembrolizumab or placebo for up to 35 cycles plus pemetrexed maintenance therapy. Cross-over to pembrolizumab monotherapy was permitted for placebo combination patients with verified disease progression. Dose reductions or interruptions were allowed and one agent alone could be discontinued if it clearly caused toxicity. The mean (± standard deviation [SD]) duration of treatment (DOT) was 7.4 ± 4.7 months for patients receiving pembrolizumab combination and 5.4 ± 4.3 months for those receiving placebo combination.

200 mg pembrolizumab + chemotherapy versus placebo + chemotherapy

mean DOT: 7.4 months of pembrolizumab combination versus 5.4 months of placebo combination

At data cut-off, 410 events of Response Evaluation Criteria in Solid Tumours (RECIST)-defined disease progression or death and 235 deaths had occurred. In the as-treated population, 33.8% (137/405) of pembrolizumab combination and 17.8% (36/202) placebo combination patients were still receiving assigned treatment. In the ITT population, 30.5% (125/410) of pembrolizumab combination and 46.6% (96/206) of placebo combination patients had received subsequent therapy. In the placebo combination group, 32.5% (67/206) crossed over to pembrolizumab monotherapy following disease progression during the trial and 18 (8.7%) patients received immunotherapy outside of the trial. The cross-over rate was 41.3% in the ITT population and 50.0% in 170 patients who discontinued all trial drugs. The median duration of follow-up for OS was 10.5 months.

death/progression at data cut-off: 410 events

ITT cross-over rate: 42.3%

The two primary endpoints were OS (time from randomisation to all-cause death) and PFS (time from randomisation to RECIST-defined disease progression or all cause death) as assessed by blinded independent central radiologic review (BICR). Secondary endpoints were overall response rate (ORR; percentage of patients with a confirmed complete [CR] or partial response [PR]), duration of response (DOR; time from first CR or PR to disease progression or death), and safety. Exploratory endpoints included the effect of PD-L1 expression on efficacy and patient-reported outcomes (PROs). Tumours were assessed according to RECIST version 1.1 at weeks six and twelve, then every nine weeks through week 48 and every twelve weeks thereafter. Patients were contacted every twelve weeks to assess survival during follow-up. AEs were graded for severity according to the National Cancer Institute Common Terminology Criteria (CTCAE) version 4.0.

primary endpoints: BICR-assessed OS and PFS

secondary endpoints: ORR, DOR, and safety

exploratory endpoints: PD-L1 expression, PROs

The ITT population (n = 616) had a median age of 64 years (range 34–84), 60% were male, 61% were European, 88% were current or former smokers, 18% had brain metastases, 30% had low PD-L1 expression (TPS 1–49%) and 33% had high PD-L1 tumour expression (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: mean age 64 years, 62% European, 88% smokers, 17% brain metastases, 63% low PD-L1 expression, 33% high PD-L1 expression

7.2.1 Clinical efficacy

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

median OS: not reached for pembrolizumab combination vs. 11.3 months for placebo combination

consistent OS benefit regardless of level of PD-L1 expression

The primary endpoint of BICR-assessed median OS was not reached in the pembrolizumab combination group and was 11.3 months (95% confidence interval [CI] 8.7–15.1) in the placebo combination group (HR for death 0.49, 95% CI 0.38–0.64; p < 0.001). Approximately 69.2% (95% CI 64.1–73.8) of the pembrolizumab combination group and 49.4% (95% CI 42.1–56.2) of the placebo combination group reached 12-month survival. The OS benefit of pembrolizumab combination over placebo combination was demonstrated across all subgroups, regardless of the level of PD-L1 tumour expression (n = 190 TPS <1%, HR 0.59, 95% CI 0.38–0.92, p < 0.001; n = 186 TPS 1–49%, HR 0.55, 95% CI 0.34–0.90, p < 0.001; n = 202 TPS ≥50%, HR 0.42, 95% CI 0.26–0.68, p < 0.001). The greatest relative benefit was observed in patients with a PD-L1 TPS ≥50%. While pembrolizumab improved OS for both sexes, women derived a slightly greater benefit than men (n = 253 women HR 0.29, 95% CI 0.19–0.44, p < 0.001; n = 363 men, HR 0.70, 95% CI 0.50–0.99, p < 0.001.) Due to cross-over, only relative 12 month OS data are available, absolute OS data are not and will not be available.

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

median PFS: 8.8 months for pembrolizumab combination vs. 4.9 months for placebo combination

The primary endpoint of BICR-assessed median PFS was 8.8 months (95% CI 7.6–9.2) in pembrolizumab combination patients versus 4.9 months (95% CI 4.7–5.5) in placebo combination patients (HR for progression or death 0.52, 95% CI 0.43–0.64; p < 0.001). Approximately 34.1% (95% CI 28.8–39.5) of the pembrolizumab combination group and 17.3% (95% CI 12.0–23.5) of the placebo combination group reached 12-month PFS.

consistent PFS benefit across subgroups; except for TPS <1% and age >65 years

The PFS benefit of pembrolizumab combination over placebo combination was demonstrated across predefined subgroups with the exceptions of those with a PD-L1 TPS <1% and those older than 65 years of age (n = 190 TPS <1%, HR for progression or death 0.75, 95% CI 0.53–1.05, p = no statistically significant difference between groups; n = 186 TPS 1–49%, HR 0.55, 95% CI 0.37–0.81, p < 0.001; n = 202 TPS ≥50%, HR 0.36, 95% CI 0.25–0.52, p < 0.001; n = 312 age <65 years, HR 0.43, 95% CI 0.32–0.56, p < 0.001; n = 304 age ≥65 years, HR 0.75, 95% CI 0.55–1.02, p = no statistically significant difference between groups).

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

ORR ITT: pembrolizumab combination: 47.6% placebo combination: 18.9%

The secondary endpoint of BICR-assessed ORR in the ITT population was 47.6% (95% CI 42.6–52.5) in the pembrolizumab combination group and 18.9% (95% CI 13.8–25.0) in the placebo combination group (estimated treatment difference [ETD] 28.5, 95% CI 21.1–35.4; p < 0.0001; investigator-assessed ORR ETD 23.2, 95% CI 15.8–30.1; p < 0.0001). The ORR benefit of pembrolizumab combination over placebo combination was consistent across all subgroups regardless of the level of PD-L1 tumour expression (n = 190 TPS <1%, ETD 17.4, 95% CI 4.3–28.6, p < 0.0001; n = 186 TPS 1–49%, ETD 28.5, 95% CI 13.9–41.4, p < 0.0001; n = 202 TPS ≥50%, ETD 38.5, 95% CI

24.6–50.5, p < 0.0001). While the response rate was higher in the pembrolizumab combination group than in the placebo combination group across all categories of PD-L1 TPS, the greatest between-group difference was in patients with a TPS ≥50% (61.4% versus 22.9%). Investigator-assessed ORR was similar (estimated treatment difference [ETD] 28.5, 95% CI 21.1–35.4; p < 0.0001). The disease control rate (DCR), proportion of patients with a confirmed complete or partial response, was 84.6% in the pembrolizumab combination group and 70.4% in the placebo combination group.

The BICR-assessed median time to response (TTR) was 2.2 months (95% CI 1.1–11.1) in the pembrolizumab combination group and 1.4 weeks (95% CI 1.2–11.1) the placebo combination group. The median DOR was 11.2 months (95% CI 1.1–18.0) in pembrolizumab combination patients and 7.8 months (95% CI 2.1–16.4) in placebo combination patients. Ongoing response was observed in 112 (57.4%) of pembrolizumab combination patients versus 18 (46.2%) of placebo combination patients.

median DOR: 11.2 months for pembrolizumab combination vs. 7.8 months for placebo combination patients

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

Pembrolizumab may cause immune-mediated AEs including pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis [3]. In the as-treated population, pneumonitis was reported in 18 (4.4%) of pembrolizumab combination patients versus five (2.5%) of placebo combination patients. Immune-mediated AEs occurring exclusively in the pembrolizumab combination group include colitis (2.2%), nephritis (1.7%), hepatitis (1.2%), hypophysitis (0.7%), pancreatitis (0.7%), myositis (0.2%), thyroiditis (0.2%), and type 1 diabetes mellitus (0.2%). Hypothyroidism, hyperthyroidism, and adrenal insufficiency were more commonly reported in the pembrolizumab combination group than the placebo combination group (27 [6.7%] versus 5 [2.5%], 16 [4.0%] versus 6 [3.0%], and 1 [0.2%] versus 1 [0.5%], respectively). 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 KEYNOTE-189 [4, 31]

Descriptive statistics and estimate variability	**Treatment group**	**Pembrolizumab combination**	**Placebo combination**
	Number of subjects	410	206
	Progression or death at data cut-off, n Deaths at data cut-off, n	410 235	
	BICR-assessed median OS, m (95% CI) 12 m OS %, (95% CI) 12 m OS, PD-L1 TPS <1%, %, (95% CI) 12 m OS, PD-L1 TPS 1–49%, %, (95% CI) 12 m OS, PD-L1 TPS ≥50%, %, (95% CI)	NE (NE–NE) 69.2 (64.1–73.8) 61.7 (NR–NR) 71.5 (NR–NR) 73.0 (NR–NR)	11.3 (8.7–15.1) 49.4 (42.1–56.2) 52.2 (NR–NR) 50.9 (NR–NR) 48.1 (NR–NR)
	BICR-assessed median PFS, m (95% CI) 12 m PFS, % (95% CI)	8.8 (7.6–9.2) 34.1 (28.8–39.5)	4.9 (4.7–5.5) 17.3 (12.0–23.5)
	BICR-assessed ORR, n, % (95% CI) CR, n (%) PR, n (%) ORR, PD-L1 TPS <1%, %, (95% CI) ORR, PD-L1 TPS 1–49%, %, (95% CI) ORR, PD-L1 TPS ≥50%, %, (95% CI) Investigator-assessed ORR, n, % (95% CI) CP, n (%) PR, n (%)	n = 195; 47.6 (42.6–52.5) 2 (0.5) 193 (47.1) 32.3 (24.3–41.2) 48.4 (39.5–57.4) 61.4 (52.5–69.7) n = 175; 42.7 (37.8–47.6) 2 (0.5) 173 (42.2)	n = 39; 18.9 (13.8–25.0) 1 (0.5) 38 (18.4) 14.3 (6.7–25.4) 20.7 (11.2–33.4) 22.9 (13.7–34.4) n = 40; 19.4 (14.2–25.5) 0 (0.0) 40 (19.4)
	DCR (%)	84.6	70.4
	BICR-assessed median TTR, m, range Investigator-assessed median TTR, m, range	2.2 (1.1–11.1) 1.8 (1.1–11.3)	1.4 (1.2-11.1) 2.6 (1.2–9.0)
	BICR-assessed median DOR, m (range) Investigator-assessed median DOR, m (range) BICR-assessed ongoing response, n (%) Investigator-assessed ongoing response, n (%)	11.2 (1.1–18.0) 12.6 (1.1–18.1) 112 (57.4) 96 (54.9)	7.8 (2.1–16.4) 7.6 (1.6–15.5) 18 (46.2) 18 (45.0)
Effect estimate per comparison	*Comparison groups*		Pembrolizumab combination versus Placebo combination
	OS (primary endpoint)	HR for death	0.49
		95% CI	0.38–0.64
		Log-rank test p-value	<0.001
	OS, PD-L1 TPS <1% (subgroup analysis, n = 190)	HR	0.59
		95% CI	0.38–0.92
		Log-rank test p-value	<0.001
	OS, PD-L1 TPS 1–49% (subgroup analysis, n = 186)	HR	0.55
		95% CI	0.34–0.90
		Log-rank test p-value	<0.001
	OS, PD-L1 TPS ≥50% (subgroup analysis, n = 202)	HR	0.42
		95% CI	0.26–0.68
		Log-rank test p-value	<0.001
	OS, male (subgroup analysis, n = 363)	HR	0.70
		95% CI	0.50–0.99
		Log-rank test p-value	<0.001
	OS, female (subgroup analysis, n = 253)	HR	0.29
		95% CI	0.19–0.44
		Log-rank test p-value	<0.001
	BICR-assessed PFS (primary endpoint)	HR	0.52
		95% CI	0.43–0.64
		Log-rank test p-value	<0.001
	PFS, PD-L1 TPS <1% (subgroup analysis, n = 190)	HR	0.75
		95% CI	0.53–1.05
		Log-rank test p-value	NS
	PFS, PD-L1 TPS 1–49% (subgroup analysis, n = 186)	HR	0.55
		95% CI	0.37–0.81
		Log-rank test p-value	<0.001

Effect estimate per comparison *(continuation)*	PFS, PD-L1 TPS ≥50% (subgroup analysis, n = 202)	HR	0.36
		95% CI	0.25–0.52
		Log-rank test p-value	<0.001
	PFS, age <65 years (subgroup analysis, n = 312)	HR	0.43
		95% CI	0.32-0.56
		Log-rank test p-value	<0.001
	PFS, age ≥65 years (subgroup analysis, n = 304)	HR	0.75
		95% CI	0.55-1.02
		Log-rank test p-value	NS
	BICR-assessed ORR (secondary endpoint)	ETD	28.5
		95% CI	21.1–35.4
		Log-rank test p-value	<0.0001
	ORR, PD-L1 TPS <1% (subgroup analysis, n = 190)	ETD	17.4
		95% CI	4.3–28.6
		Log-rank test p-value	<0.0001
	ORR, PD-L1 TPS 1–49% (subgroup analysis, n = 186)	ETD	28.5
		95% CI	13.9–41.1
		Log-rank test p-value	<0.0001
	ORR, PD-L1 TPS ≥50% (subgroup analysis, n = 202)	ETD	38.5
		95% CI	24.6–50.5
		Log-rank test p-value	<0.0001
	Investigator-assessed ORR (secondary endpoint)	ETD	23.2
		95% CI	15.8–30.1
		Log-rank test p-value	<0.0001

Abbreviations: BICR = blinded independent central review; CI = confidence interval; CR = complete response; DCR = disease control rate; DOR = duration of response; DOFU = duration of follow-up; ETD = estimated treatment difference; m = months; n = number; N = total number; NE = not evaluable; NR = not reported; NS = not 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

7.2.2 Safety

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

In the safety population (n = 607), investigator-assessed AEs commonly reported in the pembrolizumab- and placebo combination groups, respectively, included nausea (55.6% versus 52.0%), fatigue (40.7% versus 38.1%), constipation (34.8% versus 31.7%), diarrhoea (30.9% versus 21.3%), decreased appetite (28.1% versus 30.2%) and vomiting (24.2% versus 23.3%). AEs of grade ≥3 severity observed in at least 10% of patients in the pembrolizumab combination or the placebo combination group were anaemia (16.3% and 15.3%) and neutropenia (15.8% and 11.9%). The only AE of grade ≥3 reported more frequently in pembrolizumab combination patients was febrile neutropenia. Acute kidney injury was more common in the pembrolizumab combination group than in the placebo combination group (5.2% versus 0.5%). AEs that

common AEs: nausea, fatigue, constipation, diarrhoea, decreased appetite and vomiting

common grade ≥3 AEs: anaemia, neutropenia

deaths due to AEs: 6.7% for pembrolizumab combination vs. 5.9% for placebo combination

resulted in death occurred in 27 of 405 (6.7%) pembrolizumab combination patients and in twelve of 202 (5.9%) placebo-combination patients.

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

20% discontinued pembrolizumab due to AEs; 2.0% discontinued all drugs due to acute kidney injury

AEs of grade ≥3 severity were observed in 67.2% and 65.8% of patients in the pembrolizumab- and placebo combination groups, respectively. Approximately 13.8% of pembrolizumab combination patients and 7.9% of placebo combination patients discontinued all trial drugs due to AEs, while 20.2% and 10.4% discontinued pembrolizumab and placebo, respectively. In the pembrolizumab combination group, acute kidney injury of grade ≥3 severity, reported in eight (2.0%) patients, led to the discontinuation of all trial therapies.

infusion reaction: 2.5% for pembrolizumab combination vs. 1.0% for placebo combination

Pembrolizumab may cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis [3]. Infusion-related reactions were reported in 2.5% and 1.0% of patients in the pembrolizumab- and placebo combination groups, respectively.

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

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

Study participants had a median age of 64 years (range 34–84) with a 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 PFS between study groups in patients older than 65 years of age. The clinical specificity of elderly patients with comorbidities, comedication, reduced functional reserve and immunosenescence may affect the efficacy and or toxicity of immune-checkpoint inhibitors [38, 39].

immune-mediated AEs: in 22.7% of pembrolizumab combination and in 11.9% of placebo combination patients

Immune-mediated AEs occurred in 22.7% of pembrolizumab combination patients and 11.9% of placebo combination patients. Events of grade ≥3 severity were reported in 8.9% and 4.5% of the pembrolizumab- and placebo combination groups, respectively. Three deaths incurred due to immune-mediated pneumonitis in the pembrolizumab combination group. While 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 [3].

Table 2: Most frequent adverse events of KEYNOTE-189 [4]

Adverse Event (according to CTCAE version 4.0)	**Pembrolizumab combination** (n = 405)		**Placebo combination** (n = 202)	
	Any Grade n (%)	Grade 3, 4, or 5 n (%)	Any Grade n (%)	Grade 3, 4, or 5 n (%)
Any event	404 (99.8)	272 (67.2)	200 (99.0)	133 (65.8)
Discontinued all treatment due to AE	56 (13.8)	48 (11.9)	16 (7.9)	14 (6.9)
Discontinued any treatment component due to AE	112 (27.7)	81 (20.0)	30 (14.9)	22 (10.9)
Discontinued pembrolizumab or placebo	82 (20.2)	64 (15.8)	21 (10.4)	17 (8.4)
Discontinued pemetrexed	93 (23.0)	69 (17.0)	23 (11.4)	17 (8.4)
Discontinued platinum-based drug	31 (7.7)	27 (6.7)	12 (5.9)	10 (5.0)
Event leading to death	27 (6.7)	27 (6.7)	12 (5.9)	12 (5.9)
AEs in ≥15% of patients in either group				
Nausea	225 (55.6)	14 (3.5)	105 (52.0)	7 (3.5)
Anaemia	187 (46.2)	66 (16.3)	94 (46.5)	31 (15.3)
Fatigue	165 (40.7)	23 (5.7)	77 (38.1)	5 (2.5)
Constipation	141 (34.8)	4 (1.0)	64 (31.7)	1 (0.5)
Diarrhoea	125 (30.9)	21 (5.2)	43 (21.3)	6 (3.0)
Decreased appetite	114 (28.1)	6 (1.5)	61 (30.2)	1 (0.5)
Neutropenia	110 (27.2)	64 (15.8)	49 (24.3)	24 (11.9)
Vomiting	98 (24.2)	15 (3.7)	47 (23.3)	6 (3.0)
Cough	87 (21.5)	0 (0.0)	57 (28.2)	0 (0.0)
Dyspnoea	86 (21.2)	15 (3.7)	52 (25.7)	11 (5.4)
Asthenia	83 (20.5)	25 (6.2)	49 (24.3)	7 (3.5)
Rash	82 (20.2)	7 (1.7)	23 (11.4)	3 (1.5)
Pyrexia	79 (19.5)	1 (0.2)	30 (14.9)	0 (0.0)
Peripheral oedema	78 (19.3)	1 (0.2)	26 (12.9)	0 (0.0)
Thrombocytopenia	73 (18.0)	32 (7.9)	29 (14.4)	14 (6.9)
Increased lacrimation	69 (17.0)	0 (0.0)	22 (10.9)	0 (0.0)
AEs of interest in the as-treated population				
Any event	92 (22.7)	36 (8.9)	24 (11.9)	9 (4.5)
Hypothyroidism	27 (6.7)	2 (0.5)	5 (2.5)	0 (0.0)
Pneumonitis	18 (4.4)	11 (2.7)	5 (2.5)	4 (2.0)
Hyperthyroidism	16 (4.0)	0 (0.0)	6 (3.0)	0 (0.0)
Infusion reaction	10 (2.5)	1 (0.2)	2 (1.0)	0 (0.0)
Colitis	9 (2.2)	3 (0.7)	0 (0.0)	0 (0.0)
Severe skin reaction	8 (2.0)	8 (2.0)	5 (2.5)	4 (2.0)
Nephritis	7 (1.7)	6 (1.5)	0 (0.0)	0 (0.0)
Hepatitis	5 (1.2)	4 (1.0)	0 (0.0)	0 (0.0)
Hypophysitis	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatitis	3 (0.7)	2 (0.5)	0 (0.0)	0 (0.0)
Adrenal insufficiency	1 (0.2)	1 (0.2)	1 (0.5)	1 (0.5)
Myositis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Thyroiditis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Type 1 diabetes mellitus	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)

Abbreviations: AE = adverse event; CTCAE = common terminology for cancer adverse events

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 metastatic NSCLC patients who were PD-L1-positive without targetable EGFR or ALK aberrations [13]. 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).

KENOTE-021: pembrolizumab + chemotherapy versus chemotherapy alone as first-line for PD-L1-positive NSCLC without EGFR or ALK aberrations

KEYNOTE-021 (NCT02039674) is an ongoing multicentre, randomised, open-label, phase I/II multi-cohort study to assess the safety and efficacy of first-line pembrolizumab in combination with chemotherapy or immunotherapy in patients with metastatic NSCLC. Cohort G, a randomised open-label, phase II study, was designed to evaluate pemetrexed and carboplatin, with or without pembrolizumab, in 123 patients with untreated non-squamous NSCLC without targetable EGFR or ALK aberrations [14]. Stratified by PD-L1 expression (TPS <1% versus ≥1%), patients were randomised 1:1 to four cycles of pemetrexed (500 mg/m^2 IV) and carboplatin (AUC 5 mg/mL/minute IV) with or without pembrolizumab (200 mg IV) every three weeks followed by pembrolizumab for 24 months with pemetrexed maintenance therapy while the chemotherapy arm received pemetrexed and carboplatin alone with pemetrexed maintenance therapy. 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 ORR; secondary endpoints included PFS, DOR, OS, safety, and the correlation between PD-L1 expression and anti-tumour activity. Efficacy was assessed in the ITT population while safety was assessed in the as-treated population. Tumours were evaluated according to RECIST version 1.1 at baseline, every six weeks for 18 weeks, then every nine weeks through the first twelve months and every twelve weeks thereafter. AEs were graded according to the CTCAE version 4.0.

At a median follow-up of 10.6 months, pembrolizumab significantly improved the proportion of patients who achieved an objective response compared with chemotherapy alone (n = 33 [55%, 95% CI 42–68] versus n = 18 [29%, 95% CI 18–41]; ETD 26% [95% CI 9–42]; p = 0.0016). Median time to response was 1.5 months (IQR 1.4–2.8) for pembrolizumab plus chemotherapy versus 2.7 months (IQR 1.4–2.8) for chemotherapy alone. Median DOR was not reached in either group; 29 (88%) of 33 responders in the pembrolizumab combination group and 14 (78%) of 18 responders in the chemotherapy alone group remained alive and progression-free at data cut-off. Analysis of ORR by PD-L1 expression showed consistent ORR benefit of pembrolizumab with chemotherapy over chemotherapy alone (TPS <1%, ETD 57%, 95% CI 34–78 and TPS ≥1% ETD 54%, 95% CI 37–70). Pembrolizumab combination statistically significantly increased PFS compared to chemotherapy alone (HR 0.53, 95% CI 0.31–0.91; p = 0.010). Median PFS was 13.0 months (95% CI 8.3–not reached) for pembrolizumab combination and 8.9 months (95% CI 4.4–10.3) for chemotherapy alone. At the time of data cut-off, 27 patients had died, 22% (13/60) of pembrolizumab plus chemotherapy patients and 22% (14/63) chemotherapy only patients. No difference in OS was noted between groups (HR 0.90, 95% CI 0.42–1.91; p = 0.39).

BICR-assessed ORR: 55% for pembrolizumab + chemotherapy vs. 29% for chemotherapy alone; consistent benefit regardless of level of PD-L1 expression

median PFS: 13.0 months for pembrolizumab + chemotherapy vs. 8.9 months for chemotherapy alone

no difference in OS

The incidence of grade ≥3 treatment-related AEs was similar between groups (39% for pembrolizumab plus chemotherapy versus 25.8% for chemotherapy alone); the rate of discontinuation due to treatment-related AEs was also similar (10.2% versus 12.9%, respectively). The most common grade ≥3 treatment-related AEs in the pembrolizumab plus chemotherapy group were anaemia (12%), decreased neutrophil count (5%), acute kidney injury (3%), decreased lymphocyte count (3%), fatigue (3%), neutropenia (3%), sepsis (3%), and thrombocytopenia (3%). Grade ≥3 immune-mediated AEs were reported in 3.4% and 1.6% of pembrolizumab combination and chemotherapy alone patients, respectively. The most common immune-mediated AEs of any grade in the pembrolizumab combination group were hypothyroidism (15%), hyperthyroidism (15%), and pneumonitis (5%). One treatment-related death occurred in the pembrolizumab plus chemotherapy group due to sepsis.

grade ≥3 AEs: anaemia, acute kidney injury, decreased lymphocytes, fatigue, neutropenia, sepsis, and thrombocytopenia

common immune-related AEs: thyroid disorders and pneumonitis

8 Estimated costs

A0021: What is the reimbursement status of pembrolizumab?

In Austria, single-use vials of 50 mg pembrolizumab powder for reconstitution (25 mg/mL) are available at a cost of € 1,714.00 (ex-factory price) [33]. Administered as an intravenous infusion, a 200 mg dose of pembrolizumab would cost € 6,856.00, every three weeks when used in combination with pemetrexed and platinum therapy, for four cycles, followed by pembrolizumab plus pemetrexed every three weeks for up to 35 cycles. A mean duration of pembrolizumab treatment of 7.4 months would cost approximately € 50,734.40. 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 [9, 13, 14] and approximately

€ 6,856.00 per month, additional cost for pemetrexed + platinum chemotherapy, and molecular testing

7.4 months of pembrolizumab: ~ € 50,734.40

1,620 patients in Austria (2015) had metastatic NSCLC at diagnosis, pembrolizumab would cost approximately € 41,094,864.40 (7.4 month treatment period) annually with additional costs for chemotherapy and molecular testing.

9 Ongoing research

113 registered studies

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 July 2018, searches of www.clinicaltrials.gov and www.clinicaltrialsregister.eu using the search terms "pembrolizumab" and "non-small cell lung cancer" yielded 113 other registered studies (one phase IV, eleven phase III, 100 phase I/II, and one pembrolizumab PET-imaging study). Most studies were industry-sponsored or conducted in collaboration with industry.

6 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 monotherapy (KEYNOTE-042), in combination with carboplatin and paclitaxel or nab-paclitaxel (KEYNOTE-407), epacadostat with platinum-based chemotherapy (KEYNOTE-715-05) and ipilimumab (KEYNOTE-598), in combination with platinum-based therapy for resectable NSCLC (KEYNOTE-671), and after resection with or without standard adjuvant therapy (KEYNOTE-091):

- **NCT02220894:** KEYNOTE-042 is a phase III, randomised, open-label, parallel-group study of OS comparing pembrolizumab versus platinum-based chemotherapy as first-line treatment for PD-L1-positive advanced or metastatic NSCLC. Estimated study completion date is January 2020.
- **NCT02775435:** KEYNOTE-407 is a phase III, randomised, double-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.
- **NCT03322566:** KEYNOTE-715-05 is a phase II, randomised, double-blind study to assess the efficacy and safety of pembrolizumab plus epacadostat with platinum-based chemotherapy versus pembrolizumab plus platinum-based chemotherapy plus placebo as first-line therapy in patients with metastatic NSCLC. Estimated study completion date is October 2021.
- **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.
- **NCT03425643:** KEYNOTE-671 is a phase III, randomised, double-blind trial to evaluate the safety and efficacy of pembrolizumab in

combination with platinum-based chemotherapy before surgery followed by pembrolizumab alone after surgery in patients with resectable NSCLC. Estimated study completion date is June 2026.

- **NCT02504372:** KEYNOTE-091 (PEARLS) is a phase III, randomised, double-blind study to assess the safety and efficacy of pembrolizumab versus placebo in early stage NSCLC after resection and completion of standard adjuvant therapy. Estimated study completion date is August 2021.

10 Discussion

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

first-line: monotherapy for PD-L1-positive NSCLC without EGFR or ALK aberrations; in combination with pemetrexed + carboplatin for NSCLC

under review: first-line for metastatic non-squamous NSCLC

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 (TPS ≥50%), and as second-line therapy for PD-L1-positive NSCLC with progression following platinum-based chemotherapy (TPS >1%). Approved concurrently, PD-L1 ICH 22C3 pharmDx is the only FDA and CE marked companion diagnostic assay for guiding pembrolizumab therapy [9]. First-line monotherapy approval was based on PFS and OS data from KEYNOTE-024 [12, 13]. While accelerated approval of pembrolizumab in previously treated patients was based on ORR correlated with PD-L1 expression in a subset of KEYNOTE-001 patients, full approval was granted based on OS data from KEYNOTE-010 [8-11]. The combination of 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 [14]. Pembrolizumab is under review, by the FDA and EMA, for use in combination with pemetrexed and platinum chemotherapy as first-line treatment for metastatic non-squamous NSCLC based on results from the phase III KEYNOTE-189 study [15].

KEYNOTE-189

OS: pembrolizumab increased OS; reduced risk of progression or death; TPS ≥50% derive greatest relative benefit

KEYNOTE-189, a randomised, double-blind, phase III study compared the efficacy and safety of pembrolizumab (500 mg/m^2 IV) with platinum-based chemotherapy (cisplatin or carboplatin + pemetrexed) versus saline placebo with platinum-based chemotherapy as treatment for 616 patients with metastatic non-squamous NSCLC regardless of PD-L1 expression who have not received any therapy for metastatic disease [4]. Adding pembrolizumab to chemotherapy conferred to a longer OS than chemotherapy alone (not reached versus 11.3 months, respectively), with a HR for death of 0.49. While the survival benefit of pembrolizumab combination over chemotherapy alone was demonstrated across all subgroups, regardless of PD-L1 tumour expression, patients with a PD-L1 TPS ≥50% derived the greatest relative benefit. While cancer immunotherapy generally affords a slightly better OS for males than females based on sex-related dimorphism in immune system response [40], pembrolizumab combination offered a slightly greater survival benefit for women than for men [4]. Due to cross-over, only relative 12 month OS data are available, absolute OS data are not and will not be available.

PFS: pembrolizumab increased PFS by 3.9 months PFS benefit across groups except low PD-L1 expressing and elderly; TPS ≥50% derive greatest relative response

Compared with chemotherapy alone, pembrolizumab increased PFS by 3.9 months and lowered the risk of disease progression or death by 48%. The increase in PFS was consistent across subgroups except for those with PD-L1 expression on less than 1% of tumour cells (TPS <1%) and those older than 65 years of age. Pembrolizumab improved the BICR-assessed response rate (RR) by 28.7% compared with chemotherapy alone, and increased the median DOR by 3.4 months. While the response rate was higher in the pembrolizumab combination group than the placebo combination group across all categories of PD-L1 TPS, patients with TPS ≥50% derived the greatest benefit (61.4% versus 22.9%, respectively). Adding pembrolizumab increased the DCR by 14.2% compared with chemotherapy alone.

common AEs: nausea, fatigue, constipation, diarrhoea, decreased appetite, and vomiting

immune-mediated AEs: colitis, nephritis, hepatitis, hypophysitis, pancreatitis, myositis, thyroid disorders, diabetes mellitus

AEs resulted in death in 6.7% patients

Commonly reported AEs in pembrolizumab combination patients included nausea, fatigue, constipation, diarrhoea, decreased appetite, and vomiting. Anaemia and neutropenia were the most frequently reported AEs of grade ≥3 in severity. Immune-mediated AEs occurring exclusively in pembrolizumab combination patients included colitis (2.2%), nephritis (1.7%), hepatitis (1.2%), hypophysitis (0.7%), pancreatitis (0.7%), myositis (0.2%), thyroiditis (0.2%), and type 1 diabetes mellitus (0.2%). Hypothyroidism (6.7%), hyperthyroidism (4.0%) and adrenal insufficiency (0.2%) were also more commonly reported in pembrolizumab combination patients. Compared with placebo combination, more pembrolizumab combination patients discontinued all trial drugs (13.8% versus 7.9%) or solely the study drug (20.2% versus 10.4%, respectively) due to AEs. Acute kidney injury of grade ≥3 in severity caused 2.0% of patients to discontinue therapy. AEs resulted in death in 6.7% of pembrolizumab combination patients, including three deaths due to immune-mediated pneumonitis.

KEYNOTE-189 limitations: lack of data regarding QoL, CNS activity, and comparison with pembrolizumab monotherapy; clinical specificity in elderly and immune compromised

The results of KEYNOTE-189 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 18% of patients were 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 [41]. Generalizability of the results may be limited in that while study participants had a median age of 64 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. Based on results of the KEYNOTE-024 study in October 2016, pembrolizumab became a first-line monotherapy option for patients with metastatic NSCLC whose tumours express high levels of PD-L1 [12, 13]. Without direct comparison trials, physicians and patients may need to discuss whether adding pembrolizumab to pemetrexed and platinum-based therapy would provide greater individualised efficacy than pembrolizumab monotherapy.

low risk of bias: randomised, double-blind, comparator-matched,

however, industry funded, cross over

KEYNOTE-189 is a phase III trial with few methodological limitations. There was no risk of bias in the generation of randomisation sequence or allocation concealment. Patients were randomly assigned 2:1 to pembrolizumab combination or placebo combination using an interactive voice/web-based response system [32]. Patients, physicians and outcome assessors were blinded as they received ready-to-use blinded pembrolizumab or saline infusion solutions packed identically by an un-blinded pharmacist. The central imaging vendor

was blinded to treatment assignment to minimize bias in response assessments. Selective outcome reporting is unlikely as the primary endpoints of OS and PFS, and secondary endpoints of ORR, DOR, investigator-assessed PFS and safety were reported as specified in the protocol. The risk of bias may be increased by industry involvement in funding the study, assisting with study design, defining immune-mediated AEs, data collection, analysis and interpretation, investigator-assessed safety analysis, as well as due to crossover (67 patients switched to pembrolizumab combination).

ESMO-MCBS: grade 3 (original & adapted scale); no meaningful clinical benefit

Given the non-curative treatment setting of pembrolizumab and the statistically significant co-primary endpoint PFS, we applied Form 2b of the ESMO-MCBS, since median OS was not reached at the time of analysis. We applied the ESMO-MCBS 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. The application of the scale to the KEYNOTE-189 study resulted in a grade 3 in both the original and the adapted version of the ESMO-MCBS, respectively. Therefore, pembrolizumab leads to no "meaningful clinical benefit" according to the original scale or the adapted framework.

consistent efficacy and safety results compared with former studies

The clinical efficacy and safety data from KEYNOTE-189 are consistent with previous studies that suggest pembrolizumab improves OS, PFS, and ORR with manageable toxicity in untreated PD-L1-positive metastatic NSCLC patients lacking EGFR or ALK aberrations. 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 [13]. In cohort G of the phase I/II KEYNOTE-021 study, pembrolizumab plus pemetrexed and carboplatin statistically significantly improved the ORR and PFS compared to chemotherapy alone in non-squamous NSCLC patients [14]. Consistent with existing studies of PD-L1 inhibition, KEYNOTE-001 [10] and KEYNOTE-010 [11], survival benefit was observed across all PD-L1 subgroups; however, the greatest relative benefit was achieved in patients with TPS ≥50%. While outcomes in the placebo-combination group appeared poorer than those reported in patients who had received platinum-based chemotherapy in previous studies, the DCR and PFS were consistent with other studies [13]. Excluding nephritis and acute kidney injury common with platinum-based chemotherapy, the incidence of most immune-mediated AEs was in keeping with those previously observed with pembrolizumab monotherapy [10, 11, 13].

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

Several studies are underway 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-042 and KEYNOTE-407 are comparing pembrolizumab versus platinum-based chemotherapy, and carboplatin and paclitaxel or nab-paclitaxel with or without pembrolizumab as first-line therapy for metastatic NSCLC, respectively. The efficacy and safety of pembrolizumab in combination with epacadostat and chemotherapy versus pembrolizumab and chemotherapy is under investigation in the phase II KEYNOTE-715-05 study. KEYNOTE-598 is evaluating the efficacy of pembrolizumab in combination with ipilimumab or placebo as first-line treatment for metastatic NSCLC. Phase III trials KEYNOTE-671 and KEYNOTE-091 are investigating pembrolizumab and chemotherapy before surgery followed by pembrolizumab alone after surgery in patients with resectable NSCLC and pembrolizumab versus placebo in early stage NSCLC after resection.

cost: € 6,856.00 per month; € 50,734.40 per 7.4 months with additional costs for chemotherapy and molecular testing

Administered as an intravenous infusion, the recommended dose of 200 mg of pembrolizumab costs € 6,856.00 every three weeks when used in combination with pemetrexed and platinum therapy, for four cycles, followed by pembrolizumab plus pemetrexed every three weeks for up to 35 cycles. A mean duration of treatment of 7.4 months would cost approximately € 50,734.40. Since up to 50% of untreated, advanced NSCLC express PD-L1 and approximately 1,620 patients in Austria (2015) had metastatic NSCLC at diagnosis, pembrolizumab would cost approximately € 41,094,864.40 (7.4 month treatment period) annually with additional costs for chemotherapy and molecular testing.

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 [42]. 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 [43]. In addition to PD-L1 expression, novel biomarkers are needed to identify patients most likely to benefit from pembrolizumab therapy. Total mutation burden [44], 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 [41]. 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.

KEYNOTE-189: phase III RCT demonstrates benefit in OS, PFS and ORR, as initial therapy for metastatic NSCLC

Overall, KEYNOTE-189 is the first phase III, randomized, double-blind study to demonstrate that adding pembrolizumab to platinum-based chemotherapy increases OS, PFS, and ORR, and reduces the risk of death and progression for patients with metastatic NSCLC. While the survival benefit of pembrolizumab combination over chemotherapy alone was observed regardless of PD-L1 tumour expression, the greatest relative benefit was achieved in patients whose tumours exhibited higher PD-L1 levels. Due to cross-over, only relative 12 month OS data are available, absolute OS data are not and will not be available. 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 selection of patients most likely to benefit from treatment and facilitate comparison with other immune checkpoint inhibitors. Without direct comparison trials, physicians may need to discuss whether adding pembrolizumab to platinum-based chemotherapy would provide greater individualised efficacy to a patient than pembrolizumab monotherapy.

optimal therapeutic sequencing of monotherapy vs. combination chemotherapy remains unknown

Table 3: Benefit assessment based on original ESMO-MCBS v1.1 and adapted benefit assessment based on adapted ESMO-MCBS [36, 37]

ESMO-MCBS	Active substance	Indication	Intention	PE	Form	MG standard treatment	Efficacy				Safety		AJ	FM
							MG months	*HR (95% CI)*	*Score calculation*	*PM*	*Toxicity*	*QoL*		
Adapted ESMO-MCBS	Pembrolizumab	NSCLC	NC	OS & **PFS**[1]	2b	≤6 months	+3.9 months	0.52 0.43–0.64	HR ≤0.65 AND Gain ≥1.5 months	3	+1.4% grade 3–4 AEs, +5.9% discontinuation	-	-	**3**
Original ESMO-MCBS	Pembrolizumab	NSCLC	NC	OS & **PFS**[1]	2b	≤6 months	+3.9 months	0.52 0.43–0.64	HR ≤0.65 AND Gain ≥1.5 months	3	-	-	-	**3**

Abbreviations: AJ = Adjustments, CI = confidence interval, FM = final adjusted magnitude of clinical benefit grade, HR = hazard ratio, m = months, MG = median gain, NSCLC = non-small-cell lung cancer, PE = primary endpoint, PM = preliminary magnitude of clinical benefit grade, QoL = quality of life

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.

[1] Progression-free survival was used to evaluate the clinical benefit of pembrolizumab, since median overall survival was not reached at the time of scoring.

11 References

[1] European Network for Health Technology Assessment (EUnetHTA). HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals. Version 3.0. 2013 [cited 2018-06-18]; Available from: http://meka.thl.fi/htacore/model/HTA%20Core%20Model%20for%20Rapid%20REA%20of%20Pharmaceuticals%203.0.pdf.

[2] Medina PJ, Adams VR. PD-1 Pathway Inhibitors: Immuno-Oncology Agents for Restoring Antitumor Immune Responses. Pharmacotherapy. 2016;36(3):317-34. Epub 2016/01/30.

[3] U.S. Food and Drug Administration Drugs@FDA Keytruda® Label Information. 2017 [cited 2018-06-25];Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s014lbl.pdf.

[4] 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.

[5] European Medicines Agency: Keytruda European Public Assessment Report (EPAR) summary 2017 [cited 2018-07-16];Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003820/WC500190993.pdf.

[6] Pembrolizumab label at eMC. UK Electronic Medicines Compendium. 2017;Available from: https://www.medicines.org.uk/emc/medicine/30602.

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

[8] 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.

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

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

[11] 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.

[12] 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. The oncologist. 2017;22(11):1392-9.

[13] 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.

[14] Langer CJ, Gadgeel S, Borghaei H, Papadimitrakopoulou V, Patnaik A, Powell SF, et al. 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. Lancet Oncol. 2016;11:1497-508.

[15] FDA grants priority review to Merk's sBLA for KEYTRUDA® (pembrolizumab) in combination with pemetrexed (ALIMTA®) and platinum chemotherapy based on results from phase 3 KEYNOTE-189 trial as first-line treatment of metastatic nonsquamous NSCLC. 2018 [cited 2018-07-16];Available from: http://investors.merck.com/news/press-release-details/2018/FDA-Grants-Priority-Review-to-Mercks-sBLA-for-KEYTRUDA-pembrolizumab-in-Combination-with-Pemetrexed-ALIMTA-and-Platinum-Chemotherapy-Based-on-Results-fromPhase-3-KEYNOTE-189-Trial-as-First-Line-Treatment-of-Metastatic-Nonsquamous-NSCLC/default.aspx.

[16] European Medicines Agency: Withdrawal of the application for a change to the marketing authorisation for Keytruda (pembrolizumab). 2017 [cited 2018-07-16];Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2017/11/WC500238047.pdf.

[17] European regulators have kicked off a review of MSD's Keytruda/pemetrexed combination for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC). 2018 [cited 2018-07-16];Available from: http://www.pharmatimes.com/news/eu_reviewing_msds_keytrudachemo_combo_1233011.

[18] National Cancer Institute. Non-Small Lung Cancer Treatment. 2018 [cited 2018-07-16];Available from: https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq.

[19] National Cancer Institute. SEER Stat Fact Sheets: Lung and Bronchus Cancer. 2018 [cited 2018-07-16];Available from: https://seer.cancer.gov/statfacts/html/lungb.html.

[20] 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.

[21] Midthun D. Overview of the initial evaluation, treatment and prognosis of lung cancer. 2018 [cited 2018-07-17];UpToDate [Interned] Available from: https://www.uptodate.com Subscription required.

[22] 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.

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

[24] Statistik Austria. Krebserkrankungen-Luftrohre, Bronchien, Lunge. 2015 [cited 2018-07-17];Available from: http://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebserkrankungen/index.html.

[25] Midthun D. Overview of the risk factors, pathology, and clinical manifestations of lung cancer. 2018 [cited 2018-07-17];UpToDate [Interned] Available from: https://www.uptodate.com Subscription required.

[26] Sequist L, Neal JW. Personalized, genotype-directed therapy for advanced non-small cell lung cancer. 2018 [cited 2018-07-17];UpToDate [Interned] Available from: https://www.uptodate.com Subscription required.

[27] 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.

[28] Immunotherapy of advanced non-small cell lung cancer with immune checkpoint inhibition. 2018 [cited 2018-07-17];UpToDate [Internet] Available from: https://www.uptodate.com Subscription required.

[29] Gaettinger S. Immunotherapy of advanced non-small cell lung cancer with immune checkpoint inhibition. 2018 [cited 2018-07-17];UpToDate Available from: https://www.uptodate.com Subscription required.

[30] Brahmer JR, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised open-label phase 3 trial. Lancet Oncol. 2017(12):1600-9.

[31] Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Supplementary Appendix to Gandhi L, Rodriguea-Abreau D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small cell lung cancer. N Engl J Med. 2018;378(22):2078-92. 2018.

[32] Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Protocol to: Gandhi L, Rodriguez-Abreu D, Gadgeel S. et al. Pembroizumab plus chemotherapy in metastatic non-small cell lung cancer. N Engl J Med. 2018;378(22):2078-92.

[33] Grössmann N, Rothschedl E, Wolf S. Horizon Scannning in Oncology 35th Prioritization - 2nd quarter 2018. 2018;Available from: http://eprints.hta.lbg.ac.at/1156/1/HSO_35th_Prioritisation.pdf.

[34] EUnetHTA - European network for Health Technology Assessment. Internal validity of randomized controlled trials. 2013 [cited 2018-06-18]; Available from: http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Internal_Validity.pdf.

[35] EUnetHTA - European network for Health Technology Assessment. EUnetHTA guidelines. Levels of evidence. Applicability of evidence in the context of a relative effectiveness

assessment of pharmaceuticals. 2013 [cited 2018-06-18]; Available from: http://www.eunethta.eu/sites/default/files/sites/5026.fedimbo.belgium.be/files/Applicability.pdf.

[36] Cherny NI, Dafni U, Bogaerts J, Latino NJ, Pentheroudakis G, Douillard JY, 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.

[37] 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.

[38] 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.

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

[40] Conforti F, Pala L, Bagnardi V, De Pas T, Martinetti M, Viale G, et al. Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis. Lancet Oncol. 2018;Available from: http://dx.doi.org/10.1016/S1470-2045(18)30261-4.

[41] 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.

[42] Hirsh V. Checkpoint inhibitors anti PD1/PDL1 in metastatic NSCLC. Journal of translational medicine Conference: 2nd annual immunotherapy bridge and melanoma bridge 2016 Italy [Internet]. 2017; 15(Supplement 1):[1 p.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/275/CN-01432275/frame.html.

[43] 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. Ther Adv Respir Dis. 2017;11(9):353-73.

[44] Rizvi N, Garon E, Leighl N, Hellmann M, Patnaik A, Gandhi L, et al. Optimizing PDL1 as a biomarker of response with pembrolizumab (pembro; MK-3475) as first-line therapy for PDL1-positive metastatic non-small cell lung cancer (NSCLC): updated data from KEYNOTE-001. Journal of clinical oncology [Internet]. 2015; 33(15 suppl. 1). Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/470/CN-01471470/frame.html.

12 Appendix

Table 4: Administration and dosing of pembrolizumab combination or placebo combination [3, 4, 6, 32]

	Pembrolizumab combination	Placebo combination
Administration mode	Pembrolizumab IV over 30 minutes, prior to same day chemotherapy [3]	Matching saline placebo [4]
Description of packaging	50 mg white lyophilized powder in a single-dose vial for reconstitution using 2.3 mL of sterile water (resulting concentration 25 mg/mL); 100 mg/4mL (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) [3]	Ready-to-use blinded matching saline placebo infusion solution packaged identically to maintain blinding [32]
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 [3]	Matching saline placebo [4]
Dosing	Pemetrexed + PC platinum-based chemotherapy + pembrolizumab (200 mg IV) every 3 weeks for 4 cycles, followed by pembrolizumab for up to 35 cycles + pemetrexed maintenance therapy [4]. Discontinue pembrolizumab in patients with life-threatening AEs, grade 3/4 or recurrent pneumonitis, grade 3/4 nephritis, AST or ALT >5xULN or bilirubin >3xULN, grade 3/4 infusion reactions, inability to reduce corticosteroid dose to ≤10 mg/day within 12 weeks, or persistent grade 2/3 AE; withhold for grade 2 pneumonitis, grade 2/3 colitis, grade 3/4 endocrinopathies, grade 2 nephritis, AST/ALT>3-5xULN or bilirubin >1.5-3xULN, or grade 3 treatment-related AEs [3]. If toxicity was attributed to one agent, that drug alone could be discontinued [4].	Pemetrexed + PC platinum-based chemotherapy + matching saline placebo (IV) every 3 weeks for 4 cycles, followed by saline placebo for up to 35 cycles + pemetrexed maintenance therapy. If progression occurs, participants may receive pembrolizumab every 3 weeks for the remainder of the study or until DP [4]. If toxicity was attributed to one agent, that drug alone could be discontinued [4].
Median treatment duration	Until DP, unacceptable toxicity, investigator decision, patient withdrawal or up to 24 months in patients without DP; mean DOT was 7.4±4.7 months [4].	Until DP, unacceptable toxicity, investigator decision, patient withdrawal, or up to 24 months without DP. Participants with progression may receive pembrolizumab every 3 weeks for the remainder of the study or until DP; mean DOT was 5.4±4.3 months [4].
Contraindications	None [3]	None
Drug interactions	Avoid systemic corticosteroids or immunosuppressants prior to starting pembrolizumab [6]	Matching saline placebo [4]

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DOT = duration of treatment; DP = disease progression; IV = intravenous; PC = physicians' choice; ULN = upper limit of normal; USP = United States Pharmacopeia

Table 5: Characteristics of the KEYNOTE-189 trial [35]

Title: Pembrolizumab plus chemotherapy in metastatic NSCLC (KEYNOTE-189) [4, 31]			
Study identifier	NCT02578680, EUDRACT2015-003694-15, 3475-189, JAPIC-CTI 163421, MK-3475-189, KEYNOTE-189		
Design	International (16 countries), multicentre (126 sites), randomised, double-blind, interventional, phase III		
	Duration of main phase:		February 2016 – March 2017, 965 patients were screened; 616 patients randomized 2:1 to receive SoC chemotherapy plus pembrolizumab (n = 405, pembrolizumab combination) or saline placebo (n = 202, placebo combination) Data cut-off: November 8, 2017; 410 events of progression or death and 235 deaths; results reviewed by external monitoring committee January 10, 2018 Median duration of follow-up: 10 months (range 0.2-20.4) Mean duration of treatment: 7.4±4.7 months for pembrolizumab combination, 5.4±4.3 months for placebo combination
	Duration of run-in phase:		Not applicable
	Duration of extension phase:		At data cut-off, as-treated population, 137 (34%) of pembrolizumab combination and 36 (18%) of placebo combination patients were still receiving assigned treatment. In the ITT population, 125 (31%) of pembrolizumab combination and 96 (47%) of placebo combination patients received ≥ 1 subsequent therapy during or outside of the trial. In the placebo combination group, 67 (33%) had crossed over during the trial to receive pembrolizumab monotherapy after progression; an additional 18 (9%) had received immunotherapy outside the trial resulting in a 41% cross-over rate in the ITT population and 50% in the 170 patients who discontinued all trial drugs.
Hypothesis	Superiority The primary hypothesis is that pembrolizumab in combination with pemetrexed/platinum chemotherapy prolongs PFS and OS compared to pemetrexed/platinum chemotherapy alone.		
Funding	Merck, Eli Lilly		
Treatments groups	Pembrolizumab combination *(n= 405 efficacy; n=405 safety; n=137 ongoing at data cut-off; n=82 treatment post-discontinuation of pembrolizumab)*		Pembrolizumab (200 mg IV) + pemetrexed (500 mg/m² IV + folic acid (300-1000 µg), vitamin B12 (1000 µg) + PC cisplatin (75 mg/m² IV) or carboplatin (AUC 5 IV) on day 1 every 3 weeks for 4 cycles, followed by pembrolizumab (200 mg IV) + pemetrexed (500 mg/m² IV) every 3 weeks until progression
	Placebo combination *(n= 202 efficacy; n=202 safety; n=36 ongoing at data cut-off; n=67 crossed over to pembrolizumab monotherapy post progression)*		Saline placebo (IV) + pemetrexed (500 mg/m² IV + folic acid (300-1000 µg), vitamin B12 (1000 µg) + PC cisplatin (75 mg/m² IV) or carboplatin (AUC 5 IV) on day 1 every 3 weeks for 4 cycles, followed by saline placebo (IV) + pemetrexed (500 mg/m² IV) every 3 weeks until progression. If progression occurs, participants may receive pembrolizumab every 3 weeks until progression or the remainder of the study.
	Notes		Treatment continued until radiographic progression, unacceptable toxicity, investigator's decision or patient withdrawal. If toxicity was clearly attributed to one agent, that drug alone could be discontinued. Placebo + chemotherapy patients were permitted to cross-over to pembrolizumab monotherapy after BICR-assessed progression.
Endpoints and definitions	Progression-free survival Primary endpoint	PFS	Time from randomization until progression (RECIST v1.1) or all-cause death as assessed by BICR (up to 24 months)
	Overall survival Primary endpoint	OS	Time from randomization until all-cause death (up to 24 months)
	Overall response rate Secondary endpoint	ORR	The number (%) of patients with confirmed CR or PR (RECIST v1.1) as assessed by BICR (up to 24 months)
	Duration of response Secondary endpoint	DOR	Time from first response until progression or death (RECIST v1.1) as assessed by BICR (up to 24 months)
	Adverse events Secondary endpoint	AEs	AEs graded by CTCAE version 4.0 (up to 27 months)
	Discontinued due to adverse events Secondary endpoint	—	The number of patients who discontinue study treatment due to an AE (up to 24 months)

<table>
<tr><td colspan="5">Title: Pembrolizumab plus chemotherapy in metastatic NSCLC (KEYNOTE-189) [4, 31]</td></tr>
<tr><td>Study identifier</td><td colspan="4">NCT02578680, EUDRACT2015-003694-15, 3475-189, JAPIC-CTI 163421, MK-3475-189, KEYNOTE-189</td></tr>
<tr><td>Database lock</td><td colspan="4">Last update posted May 22, 2018</td></tr>
<tr><td colspan="5">Results and Analysis</td></tr>
<tr><td>Analysis description</td><td colspan="4">Primary Analysis
ITT: efficacy analyses included all patients randomized. Safety analysis included all patients who received at least one dose of study drug.
OS and PFS were estimated using Kaplan-Meier method. Data OS data were censored at the time, except patients who crossed over. Between-group differences were assessed by stratified log-rank test. HRs and 95% CIs were calculated using a stratified Cox proportional-hazards model and Efron's method for handling tied events to assess the magnitude of the treatment difference. Differences in RR were assessed with the stratified method of Miettinen and Nurminen. Randomization stratification factors were applied to all stratified efficacy analyses.
Two interim analyses and a final analysis were planned. Family-wise type I error rate was controlled at a one-sided alpha of 0.025 using Maurer and Bretz. If a significant benefit in primary endpoints was found in the pembrolizumab-combination group, corresponding alpha level was rolled over for testing of other primary endpoints. Lan-DeMets O'Brien-Fleming spending function was used to control type I error in interim and final analyses.
A power of 90% was needed to show a HR for progression or death of 0.70 at a one-sided alpha of 0.0095 (based on 468 events) and a HR of 0.70 for death at a one-sided alpha of 0.0155 (based on 416 deaths) for comparison between pembrolizumab-combination versus placebo-combination; planned enrolment of n = 570. First interim analysis was performed at complete enrolment when 370 events of progression or death had occurred; approximately 242 deaths would have occurred. As of November 8, 2017, there were 410 events of progression or death and 235 deaths. Multiplicity-adjusted, one-sided alphas at first interim analysis were 0.00559 for PFS and 0.00128 for OS.</td></tr>
<tr><td rowspan="4">Analysis population</td><td>Inclusion</td><td colspan="3">✲ Adults (aged ≥18 years) with pathologically confirmed metastatic non-squamous NSCLC without sensitizing EGFR or ALK mutations without previous systemic therapy
✲ Provide tumour sample to determine PD-L1 status
✲ Life expectancy ≥ 3 months, adequate organ function with ECOG performance-status 0–1 and ≥ 1 measurable lesion according to RECIST v1.1
✲ Males with female partners, and females of childbearing potential willing to use adequate contraception up to 180 days post chemotherapy</td></tr>
<tr><td>Exclusion</td><td colspan="3">✲ Received study drug investigational agent, device, antineoplastic biological therapy, or had major surgery <3 weeks prior to first pembrolizumab dose
✲ Received a live-virus vaccination within 30 days of starting study
✲ Is expected to require antineoplastic therapy during the study
✲ History of HIV, hepatitis B or C, psychiatric or substance abuse disorder, non-infectious pneumonitis requiring glucocorticoids, clinically active diverticulitis, intra-abdominal abscess, symptomatic CNS metastases, gastrointestinal obstruction or peritoneal carcinomatosis
✲ Active autoimmune disease, receiving systemic immunosuppressive treatment or having received ≥ 30 Gy of radiotherapy to the lung within previous 6 months
✲ Known hypersensitivity to monoclonal antibody, cisplatin, carboplatin or pemetrexed
✲ Pregnant, breastfeeding, or expecting to conceive or father children prior to 120 days after last dose of study medication through 180 days after last dose of chemotherapy</td></tr>
<tr><td>Characteristics</td><td>Pembrolizumab combination (n = 410)</td><td>Placebo combination (n = 206)</td><td>Total (n = 616)</td></tr>
<tr><td>Age
Median age (range), years
<65 years, n (%)</td><td>
65.0 (34.0-84.0)
197 (48.0)</td><td>
63.5 (34.0-84.0)
115 (55.8)</td><td>
64.3 (34.0-84.0)
312 (50.6)</td></tr>
<tr><td>Male, n (%)</td><td>254 (62.0)</td><td>109 (52.9)</td><td>363 (58.9)</td></tr>
<tr><td>Region of enrolment, n (%)
Europe
North America
East Asia
Other region</td><td>
243 (59.3)
111 (27.1)
4 (1.0)
52 (12.7)</td><td>
131 (63.6)
46 (22.3)
6 (2.9)
23 (11.2)</td><td>
374 (60.7)
157 (25.5)
10 (1.6)
75 (12.2)</td></tr>
</table>

Title: Pembrolizumab plus chemotherapy in metastatic NSCLC (KEYNOTE-189) [4, 31]				
Study identifier	NCT02578680, EUDRACT2015-003694-15, 3475-189, JAPIC-CTI 163421, MK-3475-189, KEYNOTE-189			
	ECOG performance-status, n (%) 0 1 2	 186 (45.4) 221 (53.9) 1 (0.2)	 80 (38.8) 125 (60.7) 0 (0.0)	 266 (43.2) 346 (56.2) 1 (0.2)
	Smoking status, n (%) Current or former Never	 362 (88.3) 48 (11.7)	 181 (87.9) 25 (12.1)	 543 (88.1) 73 (11.9)
	Histological features, n (%) Adenocarcinoma Unspecified NSCLC Other	 394 (96.1) 10 (2.4) 6 (1.5)	 198 (96.1) 4 (1.9) 4 (1.9)	 592 (96.1) 14 (2.3) 10 (1.6)
	Brain metastases, n (%)	73 (17.8)	35 (17.0)	108 (17.5)
	PD-L1 tumour score, n (%) <1% ≥1% 1–49% ≥50% Not evaluable	 127 (31.0) 260 (63.4) 128 (31.2) 132 (32.2) 23 (5.6)	 63 (30.6) 128 (62.1) 58 (28.2) 70 (34.0) 15 (7.3)	 190 (30.8) 388 (63.0) 186 (30.2) 202 (32.8) 38 (6.2)
	Previous therapy for non-metastatic disease Thoracic radiotherapy Neoadjuvant therapy Adjuvant therapy	 28 (6.8) 5 (1.2) 25 (6.1)	 20 (9.7) 6 (2.9) 14 (6.8)	 48 (7.8) 11 (1.8) 39 (6.3)
Applicability of evidence				
Population	KEYNOTE-189 was conducted in patients with PD-L1-positive metastatic non-squamous 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-189 is consistent with that recommended for the treatment of NSCLC [3]. Dose reductions or interruptions were allowed and one agent alone could be discontinued if it caused toxicity. Cross-over to pembrolizumab monotherapy was permitted for placebo combination patients with verified disease progressions.			
Comparators	Based on results of the KEYNOTE-024 study pembrolizumab became a first-line monotherapy option for patients with metastatic NSCLC whose tumours express high levels of PD-L1. Without direct comparison trials, physicians and patients may need to discuss whether adding pembrolizumab to pemetrexed and platinum-based therapy 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-189 was a multination, multicentre study where approximately 61% of patients were European, 26% were North American, 2% were East Asian, and 12% were from other regions.			

Abbreviations: ALK = anaplastic lymphoma kinase; AUC = area under the curve; BICR = blinded independent central review; CI = confidence interval; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; EGFR = Epidermal Growth Factor Receptor; Gy = gray; HIV = Human Immunodeficiency Virus; HR = hazard ratio; IV = intravenous; ITT = intention-to-treat; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PC = physician's choice; PD-L1 = programmed death ligand 1; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; RR = response rate; SoC = standard of care

Table 6: Risk of bias assessment on study level is based on EUnetHTA [32, 34]

Criteria for judging risk of bias		Risk of bias
Adequate generation of randomisation sequence: randomised 2:1 to pembrolizumab combination or placebo combination using the IVRS/IWRS system. Randomization was stratified according to PD-L1 expression (TPS, ≥1% versus <1%), choice of platinum-based drug (cisplatin versus carboplatin), and smoking history (never versus former or current).		yes
Adequate allocation concealment: Study site's unblinded pharmacist obtained each subject's study identification number and study drug assignment from the IVRS/IWRS and prepared ready-to use blinded pembrolizumab/saline solutions for infusion.		yes
Blinding:	**Patient:** Study identification numbers and drug assignments were obtained from the IVRS/IWRS by an unblinded pharmacist who prepared blinded solutions packaged identically to maintain blinding.	yes
	Treating physician: The unblinded pharmacist provided investigative staff with ready-to-use blinded pembrolizumab/saline infusion solutions packaged identically to maintain blinding.	yes
	Outcome assessor: centralised randomisation and allocation; central imaging vendor blinded to treatment assignment to minimize bias in response assessments; BICR assessed efficacy and safety at pre-specified interim analyses; sensitivity analysis was planned to assess OS, PFS and ORR by predefined subgroups. AEs and safety data were investigator-assessed and immune-mediated AEs were defined on the basis of a list of terms specified by the sponsor.	yes
Selective outcome reporting unlikely: primary endpoints include BICR-assessed PFS, OS, ORR, DOR, investigator-assessed PFS and safety. Other endpoints that are not included in this analysis are PROs, biomarker research and pharmacokinetics, as per protocol.		yes
No other aspects which increase the risk of bias: industry funded the study, assisted with study design, data collection, analysis, interpretation, manuscript preparation and review. Placebo combination patients (n = 67) crossed over to pembrolizumab monotherapy post progression.		no
Risk of bias – study level		low-risk

Abbreviations: BICR = blinded independent central review; DOR = duration of response; IVRS/IWRS = interactive web response system; interactive web response system; OS = overall survival; ORR = overall response rate; PD-L1 = programmed death ligand 1; PFS = progression-free survival; PROs = patient reported outcomes; TPS = tumour proportion score