Horizon Scanning in Oncology

Pembrolizumab (Keytruda®) in previously treated advanced non-small cell lung cancer (NSCLC)

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology No. 58
ISSN online 2076-5940

Horizon Scanning in Oncology

Pembrolizumab (Keytruda®) in previously treated advanced non-small cell lung cancer (NSCLC)

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, March 2016

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft

Authors: Martina Baumann, BSc, MSc
Nicole Grössmann, BSc, MSc
Internal review: Priv.-Doz. Dr. phil. Claudia Wild
External review: PD Dr. Martin Früh

DISCLAIMER

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

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 A working version (unpublished) of V3.0 of the Model was used.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

CONTACT INFORMATION

Publisher:

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

Responsible for contents:

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

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

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

DSD: Horizon Scanning in Oncology No. 58
ISSN-online: 2076-5940

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

Table of Contents

List of tables

1 Research questions

The EUnetHTA 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.

EUnetHTA HTA Core Model®

Element ID	Research question
Description of the technology	
B0001	What is pembrolizumab?
A0022	Who manufactures pembrolizumab?
A0007	What is the target population in this assessment?
A0020	For which indications has pembrolizumab received marketing authorisation?
Health problem and current use	
A0002	What is NSCLC?
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?
A0005	What are the symptoms and the burden of NSCLC for the patient?
A0003	What are the known risk factors for NSCLC?
A0024	How is NSCLC currently diagnosed according to published guidelines and in practice?
A0025	How is NSCLC managed according to published guidelines and in practice?
Clinical effectiveness	
D0001	What is the expected beneficial effect of pembrolizumab on mortality?
D0005	How does pembrolizumab affect symptoms and findings (severity, frequency) of NSCLC?
D0006	How does pembrolizumab affect progression (or recurrence) of NSCLC?
D0011	What is the effect of pembrolizumab on patients´ body functions?
D0012	What is the effect of pembrolizumab on generic health-related quality of life?
D0013	What is the effect of pembrolizumab on disease-specific quality of life?
Safety	
C0008	How safe is pembrolizumab in relation to docetaxel?
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/MK-3475/Keytruda®/L01XC18

B0001: What is pembrolizumab?

anti-PD-1 antibody, immune checkpoint inhibitor

Pembrolizumab (Keytruda®) is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody (lgG4/kappa isotype with a stabilising sequence alteration in the Fc region), which is produced in Chinese hamster ovary cells by recombinant DNA technology [2]. It binds to an inhibitory signalling receptor (PD-1) on the surface of activated T cells and blocks the binding of ligands which negatively regulate the activation of T cells and thus play an important role in tumour evasion from host immunity [3].

2mg/kg administered IV every 3 weeks

The recommended dose of pembrolizumab is 2mg/kg administered as an intravenous (IV) infusion over 30 minutes every three weeks; treatment should be continued until disease progression or unacceptable toxicity occurs. In case of atypical responses, like an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage, it is recommended to continue treatment in clinically stable patients until disease progression gets confirmed [2].

A0022: Who manufactures pembrolizumab?

Merck Sharp & Dohme

3 Indication

A0007: What is the target population in this assessment?

indicated for pretreated NSCLC patients

Pembrolizumab (Keytruda®) is indicated for metastatic non-small cell lung cancer (NSCLC) in previously treated patients with PD-L1 expressing tumours.

4 Current regulatory status

A0020: For which indications has pembrolizumab received marketing authorisation?

approved for NSCLC by FDA but not by EMA

The European Medicines Agency (EMA) granted a marketing authorisation valid throughout the European Union for pembrolizumab on 17 July 2015 for the indication of unresectable or metastatic melanoma [2].

The US Food and Drug Administration (FDA) granted marketing authorisation for pembrolizumab for the following indications:

advanced or unresectable melanoma

- for the treatment of patients with advanced or unresectable melanoma no longer responding to other drugs (September 2014)[4].

metastatic NSCLC

licensed under the accelerated scheme

- for the treatment of patients with metastatic NSCLC whose tumours express PD-L1 as determined by an FDA-approved test (PD-L1 IHC 22C3 pharmDx assay) and who have disease progression on or after platinum-containing chemotherapy. In addition, pembrolizumab is also approved for pts with EGFR or ALK genomic tumour aberrations in which the disease has progressed under prior therapy (October 2015). Pembrolizumab has been licensed under the accelerated scheme based on tumour response rate and durability of response (based on phase Ib KEYNOTE-001 study), whilst an improvement in survival or disease-related symptoms hast not yet been established [5].

5 Burden of disease

A0002: What is NSCLC?

NSCLC accounts for 85-90% of all lung cancers

subtypes: squamous & non-squamous

NSCLC is the most common type of lung cancer which accounts for about 85%–90% of all lung cancers. Two major types of NSCLC can be distinguished histologically: non-squamous and squamous cell (epidermoid) carcinoma. About 22% of NSCLCs are squamous cell carcinomas which are characterised by the presence of keratin production by tumour cells and/or intercellular desmosomes ("intercellular bridges") [6, 7]. After histological evaluation, the cancer can be staged according to the Tumour Node Metastasis (TNM) to further characterise cancer severity. The TNM system groups lung cancer into 4 stages, based on the size of the tumour and presence or absence of nodal and distant metastases [6]. NSCLC is a heterogeneous group of diseases. Although the initial treatment of localised disease is the same, the molecular characterisation of the disease, also in terms of driver mutations (EGFR, ALK), has become increasingly important for prognosis and choice of therapy in the last few years [8].

various driver mutations are known

A0004: What is the natural course of NSCLC?

late diagnosis and low 5-year survival rate

Patients with lung cancer are usually diagnosed at a late stage of disease since symptoms do not manifest until the tumour is locally advanced or there is metastatic disease. The median age at diagnosis for lung cancer is about 70 years [9]. Besides the stage of the disease, prognostic factors include European Cooperative Oncology Group (ECOG) Performance Status, gender and weight loss, and mutational status [8, 10]. In Germany, only 21% of women and 16% of men with lung cancer are alive 5 years after diagnosis [11]. Patients at early stages survive for a median of 59 months, whereas patients with advanced stage IV disease have a life expectancy of about 4 months. In Austria, of newly diagnosed lung cancer patients, 34% of tumours were disseminated.

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

incidence rate in Austria: 30.5 per 100,000 persons

Primary lung cancer is the leading cause of cancer deaths worldwide. While the mortality of lung cancer is declining in men, increasing rates in women have been observed in Europe [12]. In Austria, 4,573 patients were newly diagnosed with lung cancer in 2012 equalling an incidence rate of 30.5 cases per 100,000 persons. 3,673 patients died from lung cancer in 2012. The age-standardised incidence and mortality rates are about twice as high for men (32.8) than for women (15.8) [13]. On average, patients are aged 70 years at the time of diagnosis of NSCLC [14].

A0023: How many people belong to the target population?

PD-L1 positive patients, 25% of all NSCLC

The target population for the treatment with pembrolizumab is defined as patients with advanced and metastatic NSCLC with positive PD-L1 status. Positive PD-L1 status has an incidence of 25–30% in NSCLC patients [15].

A0005: What are the symptoms and the burden of NSCLC for the patient?

Cough, haemoptysis, chest pain, dyspnoea or hoarseness may be indicative of lung cancer. NSCLC symptoms also include significant weight loss and fatigue [16].

A0003: What are the known risk factors for NSCLC?

main risk factor: smoking

The main risk factor for NSCLC is smoking. Other known risk factors are radiation therapy and environmental toxins such as second-hand smoke, asbestos, arsenic, and polycyclic aromatic hydrocarbons [12].

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

diagnosis: x-ray & CT

IHC for molecular characterisation

For diagnosis and staging, it is recommended to take a first-imaging chest x-ray followed by a computerised tomography (CT) scan. A clinical history including smoking history, a physical exam and laboratory tests are required as well. To further characterise the tumour's pathology, small biopsy samples should be taken and cytology should be performed; immune-histochemical staining (IHC) serves to differentiate the cancer histologically. Since the presence of specific genetic mutations – i.e. mutations in the epidermal growth factor receptor (EGFR) and rearrangements of the anaplastic lymphoma kinase (ALK) genes – enables administration of targeted therapies, patients with non-squamous NSCLC should be tested for EGFR mutations and ALK rearrangements before the initiation of first-line treatment. Due to the low incidence of these mutations in patients with squamous-cell NSCLC, testing of these mutations is not recommended in Europe, the only exception being people who never smoked or people who are former light smokers [10, 12].

diagnosis of PD-L1 status with IHC test

The PD-L1 IHC 22C3 pharmDx assay should be used to identify PD-L1 expression [17].

6 Current treatment

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

most commonly used treatments: radiation therapy, surgery and systematic therapy

The most commonly used treatment modalities for NSCLC are radiation therapy, surgery and systematic therapy. Depending on the tumour stage, histology (non-squamous or squamous), presence or absence of driver mutations and the overall medical condition of a patient, these treatments can be applied alone or in combination [18, 19].

assessing the presence of a driver mutation: EGFR or ALK

Tumour tissue should be assessed for the presence of a driver mutation (EGFR, ALK). If there is no driver mutation present in the tumour of a patient, the initial treatment utilises four to six cycles of cytotoxic chemotherapy with a platinum-based doublet. Supplementary bevacizumab can be used in patients with non-squamous NSCLC. For patients who are responding or stable after initial treatment, maintenance therapy can be considered. Therapy options are bevacizumab, single-agent chemotherapy or an EGFR inhibitor (afatinib or erlotinib) in patients with an activating mutation of EGFR. For patients with the ALK fusion oncogene or ROS1 translocations, crizotinib may be applied [18].

molecular characteristics, performance status & prior treatment have to be taken into account for subsequent therapy

If patients with advanced NSCLC developing a progressive disease after previous treatment, subsequent therapy is required. Therefore, several factors need to be taken into account including molecular characteristics of the tumour, performance status and the type of prior treatment. Immune checkpoint inhibitors such as nivolumab are preferred treatment options for the subsequent therapy of patients with metastatic NSCLC pretreated with a chemotherapy regimen. Osimertinib is a therapy option for patients with an activating mutation of EGRF who have progressed after erlotinib, afatinib or geftinib. Treatment of progressive disease with an ALK rearrangement or sensitising EGFR mutations is dependent on whether the progression is asymptomatic or symptomatic [18, 19].

7 Evidence

systematic search in 5 databases: 223 references

A literature search was conducted on 28 January 2016 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were “Pembrolizumab”, “Keytruda”, “Lambrolizumab”, “mk-3475”, “non-small cell lung cancer” and “NSCLC”. The manufacturer was contacted for additional information on completed and ongoing trials. Manual search identified 15 additional references (web documents and journal articles).

Overall, 223 references were identified. The manufacturer sent no unpublished data, only information about ongoing trials as can be found on clinicaltrials.gov.

Included in this report is one phase III study, KEYNOTE-010.

7.1 Clinical efficacy and safety – phase III studies

Keynote-010 (phase II/III trial) compared pembrolizumab to docetaxel in previously treated patients with advanced NSCLC

KEYNOTE-010 (NCT01905657) is a randomised, open-label, phase II/III multicentre study with 1,034 previously treated patients with advanced NSCLC. Patients were stratified by ECOG status, region and PD-L1 expression (1-49% vs ≥50% expression) and received either pembrolizumab 2mg/kg or pembrolizumab 10mg/kg or 75mg/m^2 docetaxel intravenously over 1 hour every 3 weeks. Primary endpoints were progression-free survival (PFS) and overall survival (OS), secondary outcomes were response rate (RR) and adverse events (AEs).

All patients had a histologically or cytologically confirmed diagnosis of NSCLC that was PD-L1 positive per central laboratory review. 43% had a PD-L1 expression of at least 50%. Almost all patients had an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 and the median age was 63 years.

median follow-up 13.1 months

discontinuation of treatment:

docetaxel: 40%

pembro. 2mg/10mg: 38%/44%

Histology of tumours was in 70% of cases non-squamous and 8% had an EGFR mutation. Median follow-up at the time of data cut-off (30 September 2015, 2 months after the prespecified second interim analysis) was 13.1 months. 521 of 1,034 patients had died: 50% in the pembrolizumab 2mg/kg group, 45% in the pembrolizumab 10mg/kg group, and 56% in the docetaxel group. After discontinuation of study treatment, additional antineoplastic treatment was received by 40%, 38% and 44% respectively.

For detailed patient characteristics including inclusion and exclusion criteria, please see the appendix, efficacy data can be found in Table 1 and AEs are listed in Table 2.

7.1.1 Clinical efficacy

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

median OS in months
docetaxel: 8.5
PD-L1 ≥50%:
pembro. 2mg[1]: 14.9
pembro. 10mg[2]: 17.3

In patients with a PD-L1 tumour proportion score of 50% or greater[3], the hazard ratio (HR) for overall survival for pembrolizumab 2 (10) mg/kg versus docetaxel was 0.54 (0.50). Median OS was 14.9 months for the pembrolizumab 2mg/kg group, 17.3 months for the pembrolizumab 10mg/kg group, and 8.5 months for the docetaxel group [20].

In the total population, median OS was 10.4 (pembrolizumab 2mg/kg), 12.7 (pembrolizumab 10mg/kg) and 8.5 months (docetaxel). HR of OS was 0.71 for pembrolizumab 2mg/kg vs docetaxel and 0.61 for 10mg/kg pembrolizumab vs docetaxel [20].

---

1 pembro. 2mg = pembrolizumab 2mg/kg

2 pembro. 10mg = pembrolizumab 10mg/kg

3 tumour proportion score of 50% or greater = PD-L1 expression on at least 50% of tumour cells

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

In patients with a PD-L1 tumour proportion score of 50% or greater, pembrolizumab increased median PFS from 4.1 months (docetaxel) to 5.0 (5.2) months (pembrolizumab 2 (10) mg/kg). The HR of PFS for both doses of pembrolizumab vs docetaxel was 0.59 [20]. For the total population, there was no statistically significant difference in PFS between the treatment groups.

median PFS in months
docetaxel: 4.1
pembro. 2mg[1]: 5.0
pembro. 10mg[2]: 5.2

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

All responses were partial responses. Response rates were 30% (pembrolizumab 2 mg/kg), 29% (pembrolizumab 10 mg/kg), and 8% (docetaxel) in patients with a PD-L1 ≥50% score. In the total population, pembrolizumab increased response rates in comparison with docetaxel from 9% to 18%, irrespective of dosage [20].

partial responses increased

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

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

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

No evidence was found for effects of pembrolizumab on body functions and on generic health-related quality of life or disease-specific quality of life.

no evidence: body functions, QoL

Table 1: Efficacy results of KEYNOTE-010

Descriptive statistics and estimated variability[4]	Treatment group	Pembro. 2mg/kg	Pembro. 10mg/kg	Docetaxel 75mg/m²	Pembro. 2mg/kg	Pembro. 10mg/kg	Docetaxel 75mg/m²
		Total population			PD-L1 ≥50%		
	Number of subjects	344	346	343	139	151	152
	OS median (95% CI), months	10.4 (9.4–11.9)	12.7 (10.0–17.3)	8.5 (7.5–9.8)	14.9 (10.4–NR)	17.3 (11.8–NR)	8.2 (6.4–10.7)
	1 year OS,%	43.2	52.3	34.6	NA	NA	NA
	PFS median (95% CI), months	3.9 (3.1–4.1)	4.0 (2.7–4.3)	4.0 (3.1–4.2)	5.0 (4.0–6.5)	5.2 (4.1–8.1)	4.1 (3.6–4.3)
	Grade 3–5 AEs,%	13	16	35	13	16	35
	Median time to response (all partial)	9 weeks	9 weeks	9 weeks	9 weeks	9 weeks	9 weeks
	Response,%	18	18	9	30	29	8
	Median duration of response	NR	NR	6 months	NR	NR	8 months

[4] At the time of data cutoff, which was after the second interim analysis, 521 patients had died.

Effect estimate per comparison	Comparison groups		Pembro. 2mg/kg vs. docetaxel	Pembro. 10mg/kg vs. docetaxel	Pembro. 2mg/kg vs. docetaxel	Pembro. 10mg/kg vs. docetaxel
			Total population		*PD-L1 ≥50%*	
	OS	HR	0.71	0.61	0.54	0.50
		95% CI	0.58–0.88	0.49–0.75	0.38–0.77	0.36–0.70
		p value	0.0008	<0.0001	0.0002	<0.0001
	PFS	HR	*0.88*	*0.79*	*0.59*	*0.59*
		95% CI	*0.74–1.05*	*0.66–0.94*	*0.44–0.78*	*0.45–0.78*
		p value	*0.07*	*0.004*	*0.0001*	*<0.0001*

Abbreviations: AE = adverse event, CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio, NA = not available, NR = not reached, OS = overall survival, PD-L1 = programmed death ligand 1, Pembro. = pembrolizumab, PFS = progression-free survival, RECIST = Response Evaluation Criteria In Solid Tumours

7.1.2 Safety

C0008: How safe is pembrolizumab in relation to docetaxel?

AEs grade 3–5
docetaxel: 35%
pembro. 2mg[1]: 13%
pembro. 10mg[2]: 16%

Grade 3–5 treatment-related adverse events were less common in the pembrolizumab groups than in the docetaxel group. In the KEYNOTE-010 study, 13% of patients given 2 mg/kg and 16% of patients given 10 mg/kg pembrolizumab vs 35% of patients given docetaxel showed these high-grade AEs [20]. A detailed list of all AEs related to treatment in the KEYNOTE-010 study is shown in Table 2.

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

Higher dosage of pembrolizumab (10 mg/kg) increased the frequency of AEs grade 3–5 from 13% to 16% [20].

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

patient groups older and comorbid patients

Older and frailer patients with more severe symptoms and comorbidities may be assumed to have more severe side effects than reported in the studies, which only included patients with an ECOG status of 0 or 1 [21].

Pembrolizumab belongs to the new class of immune targeting therapies which have a unique side-effect profile due to off-target effects on the immune system function [22]. Patients with a compromised immune system or autoimmune diseases have been excluded from the study population, probably because more severe side effects may be expected in this group.

Table 2: Safety result of KEYNOTE-010 – most frequent adverse events

Adverse event (according to NCI-CTC version 4.0)	**Pembrolizumab 2mg/kg** (n = 339)		**Pembrolizumab 10mg/kg** (n = 343)		**Docetaxel** (n = 309)	
	Any grade	Grade 3–5	Any grade	Grade 3–5	Any grade	Grade 3–5
Related to treatment, %[5]						
Any	63	13	66	16	81	35
Occurring in ≥ 10% of patients in any study group, %						
Decreased appetite	14	1	10	<1	16	1
Fatigue	14	1	14	2	25	4
Nausea	11	<1	9	1	15	<1
Rash	9	<1	13	<1	5	0
Diarrhoea	7	1	6	0	18	2
Asthenia	6	<1	6	1	11	2
Stomatitis	4	0	2	<1	14	1
Anaemia	3	1	4	<1	13	2
Alopecia	1	0	1	0	33	1
Neutropenia	<1	0	<1	0	14	12
Adverse event of special interest, % (occurring in ≥ 2 patients in the pembrolizumab groups)						
Hypothyroidism	8	0	8	0	<1	0
Pneumonitis	5	2	4	2	2	1
Hyperthyroidism	4	0	6	<1	1	0
Colitis	1	1	1	<1	0	0
Severe skin reactions	1	1	2	2	1	1
Pancreatitis	1	1	0	0	0	0
Adrenal insufficiency	1	0	1	<1	0	0
Myositis	1	0	<1	0	<1	0
Thyroiditis	1	0	0	0	0	0
Autoimmune hepatitis	<1	<1	1	0	0	0
Hypophysitis	<1	<1	<1	<1	0	0
Type 1 diabetes	<1	<1	1	<1	0	0

7.2 Clinical effectiveness and safety – further studies

approval of pembrolizumab for NSCLC based on KEYNOTE-001 (phase Ib trial)

NCT01295827 (P07990/MK-3475-001/KEYNOTE-001) [23] is a phase I study of pembrolizumab in participants with progressive, locally advanced or metastatic carcinoma, melanoma, or NSCLC and will be completed in July 2016. It led to the FDA approval of pembrolizumab for NSCLC. 80% of the 495 patients had received prior therapy. They received varying doses of pembrolizumab IV, every two or three weeks, until disease progression.

safety and efficacy in KEYNOTE-001 ORR 19.4%

Across doses, schedules, and degrees of PD-L1 expression, the overall response rate (ORR, assessed per RECIST v1.1) was 19.4%, median duration of response was 12.5 months and median OS was 12 months. Patients with previous treatment had lower duration of median response and response rates (10 vs. 23 months and 18 vs. 25%) and lower median OS (9.3 vs. 16 months) [23].

[5] Assessed by the investigator

A relationship between the degree of PD-L1 expression and efficacy outcomes was found. Patients with PD-L1 expression in ≥50% of tumour cells had higher ORR and longer PFS and OS compared with patients who had PD-L1 expression in <50% of tumour cells. PD-L1 prevalence was established by screening patients with advanced NSCLC. 23.2% of 824 patients had ≥50% expression. The trial was amended after the first NSCLC cohort to require tumour PD-L1 expression by immunohistochemistry (≥1% of tumour cells staining for PD-L1 using the Dako 22C3 PD-L1 assay) for all, but one of the subsequent NSCLC expansion cohorts. Thus, the majority of patients treated had some degree of tumour PD-L1 expression.

Another result was that previous or current smokers had an ORR of 22.5% compared with 10.3% in non-smokers.

grade 3–5 toxicities in 10% of patients

The most common low-grade toxicities were fatigue, pruritus and decreased appetite. Grade 3 or higher toxicities occurred in 10% of patients [23, 24].

8 Estimated costs

A0021: What is the reimbursement status of pembrolizumab?

estimated costs € 5,075.14 every 3 weeks

The recommended dose of pembrolizumab is 2 mg/kg administered every 3 weeks [2]. Pembrolizumab (Keytruda®) is available as a powder for injection solutions, 50 mg cost € 1,812.55 [25]. Assuming an average body weight of 70 kg, 140 mg pembrolizumab would be needed, costing € 5,075.14 every three weeks.

9 Ongoing research

47 ongoing trials registered in clinicaltrial.gov

Numerous trials (47 registered in clinicaltrials.gov, search terms "pembrolizumab" and "NSCLC") in patients with NSCLC are ongoing, which evaluate pembrolizumab as a single agent or in combination and as first-line or second-line treatment. Comparators are either placebo or docetaxel and PD-L1-expression is an inclusion criterion in several the studies. All KEYNOTE studies and all phase III studies are sponsored by Merck.

Selection of phase I and II studies:

MSD-sponsored phase I/II trials

- **NCT01840579 (MK-3475-011/KEYNOTE-011):** A phase I study of pembrolizumab alone in subjects with advanced solid tumours and in combination with cisplatin/pemetrexed or carboplatin/paclitaxel in subjects with advanced NSCLC, estimated completion June 2016.
- **NCT02039674 (MK-3475-021/KEYNOTE-021):** A Phase I/II study of pembrolizumab in combination with chemotherapy or immunotherapy in patients with locally advanced or metastatic NSCLC, estimated completion June 2019.

- **NCT02007070 (MK-3475-025/KEYNOTE-025):** An open-label, non-randomised, multicentre phase Ib study of pembrolizumab in subjects with PD-L1 positive advanced NSCLC, estimated completion September 2016.
- **NCT02564380:** A phase II randomised, double-blind, placebo-controlled study of pembrolizumab maintenance following first-line platinum-based chemotherapy in patients with metastatic squamous NSCLC, estimated completion September 2019.
- **NCT02343952:** An open-label, multi-institutional, single-arm phase II trial of consolidation therapy with pembrolizumab, following initial treatment with concurrent chemoradiation in patients with inoperable or unresectable stage IIIA or IIIB NSCLC. No randomisation or blinding, estimated completion January 2017.
- **NCT02574598** (sponsored by Instituto Nacional de Cancerologia de Mexico): A phase II open-label randomised clinical trial of pembrolizumab in combination with docetaxel vs docetaxel alone on previously treated PD-L1 positive NSCLC patients, estimated completion October 2020.

1 independent trial comparing pembrolizumab + docetaxel vs docetaxel

Selection of phase III studies:

- **MK-3475-042/KEYNOTE-042:** A randomised, open-label phase III study comparing overall survival of pembrolizumab versus platinum-based chemotherapy in treatment-naive subjects with PD-L1 positive advanced or metastatic non-small cell lung cancer, estimated completion July 2019.
- **MK-3475-024/KEYNOTE-024:** A randomised open-label phase III trial of pembrolizumab versus platinum-based chemotherapy in 1L subjects with PD-L1 strong metastatic non-small cell lung cancer, estimated completion May 2018.
- **MK-3475-091/KEYNOTE-091:** A randomised phase III trial with pembrolizumab versus placebo for patients with early-stage NSCLC after resection and completion of standard adjuvant therapy (PEARLS), estimated completion April 2024.
- **MK-3475-189/KEYNOTE-189:** A randomised, double-blind phase III study of platinum + pemetrexed chemotherapy with or without pembrolizumab in first-line metastatic non-squamous NSCLC subjects, estimated completion March 2019.

4 RCTs sponsored by MSD

10 Discussion

FDA accelerated approval pembrolizumab for NSCLC in October 2015, but not EMA

Pembrolizumab 2 mg/kg given once every 3 weeks was granted accelerated approval in the USA for the treatment of patients with metastatic NSCLC, whose tumours express PD-L1 (tested by means of PD-L1 IHC 22C3 pharmDx assay) with disease progression during or after platinum-containing chemotherapy. This approval was based on a multicohort, phase Ib study, KEYNOTE-001. Up to now, data from only one further study, the phase III KEYNOTE-010 study, is available. The EMA granted marketing authorisation to pembrolizumab, but so far the sole indication is for patients with unresectable or metastatic melanoma [2].

KEYNOTE-010: superior OS results & reduced AEs of pembrolizumab compared to docetaxel +6.7 (2mg)/ + 9.1 (10mg) months PFS: +0.9 (2mg)/ +1.1 (10mg) months

KEYNOTE-010 [20], a randomised, open-label phase II/III study, was conducted to compare two different dosages of pembrolizumab with docetaxel in a total of 1,034 previously treated patients with PD-L1 positive, advanced NSCLC. The efficacy results showed an improvement in median OS in all patients treated with pembrolizumab compared to docetaxel; whereas the highest gains in median OS were achieved by patients with a tumour proportion score of ≥50% (median OS gain: 6.7 (2mg) and 9.1 (10mg) months). PFS with pembrolizumab was superior to that of docetaxel in patients with a tumour proportion score of ≥50% (median PFS gain: 0.9 (2mg) and 1.1 (10mg) months) but not in the total population. AEs related to pembrolizumab were lower than for docetaxel.

higher improvement of mOS in patients with a TPS[6] of ≥50%

Although there was a statistically significant improvement in median OS in the total population, it was much smaller (median OS gain: 2.1 months for the recommended dosage 2 mg/kg; 4.2 months for dosage 10 mg) than in the subpopulation of patients with a tumour proportion score ≥50%. The identification of PD-L1 positive patients will thus be crucial for meaningful benefits in an average clinical setting.

limitations for generalisability: low patient age ECOG status <2

It should be noted that there was no significant difference in OS results for the EGFR-mutant subgroup (86 patients) between the study groups. In addition, concerning the PFS results, a trend favouring docetaxel over pembrolizumab treatment could be observed for this group. Since these results are based on a relatively small patient sample, the best choice of treatment for patients with EGFR mutations cannot be concluded from these results.

trend for higher efficacy of docetaxel in the subgroup of patients with EGFR-mutations

Limitations of the study may exist in regard to generalizability, as median patient age was 63 and almost all patients had an ECOG score of <2. Patients are aged about 70 years at the time of diagnosis of NSCLC and the target population includes also patients with a higher ECOG score [14]. For these excluded patient groups side-effects and efficacy might be different.

benefit to risk profile compared to other immunotherapies not known

Another concern is that there is no quality of life (QoL) data available. Pembrolizumab causes fewer side effects than docetaxel, but without an assessment of the general or disease-specific quality of life, it is problematic to state that pembrolizumab has a favourable benefit for patients compared to existing therapies, especially as other immunotherapies against NSCLC, like nivolumab, are not considered in the study.

patients and clinicians were not blinded to AE

One methodological limitation of the KEYNOTE-010 study is that it is an open-label trial, so neither patients nor clinicians have been blinded. How-

[6] TPS = tumour proportion score

ever, PFS was the only reported outcome dependent on subjective evaluation, and it was assessed by an independent central review. Bias may, however, have been introduced in the safety assessment, as this was carried out by the non-blinded investigator.

high discontinuation of treatment rate and following treatments may introduce bias to OS results

After discontinuation of treatment, additional antineoplastic treatment was received by 40%/38% in the two pembrolizumab groups and 44% in the docetaxel group, but it was not reported for what reasons and at which time point [26]. It has been argued that a discontinuation number should be included in the Kaplan-Meier analysis, which was not done in this study. A bias could have been introduced, if discontinuation and ensuing censoring differed in the study groups. For example, discontinuation in the docetaxel group could have been primarily due to side effects and in the pembrolizumab group due to missing response, leading to an overestimation of response to pembrolizumab. Also, OS results may have been influenced by therapies that followed after discontinuation [27].

challenge of PD-L1 positive subgroup definition & patient identification

another predictive marker: smoking status

Furthermore, the utility of PD-L1 as a biomarker of response is compromised by technical issues and the dynamic, inducible expression of PD-L1, which may also differ between solid tumours and metastatic sites [28]. Taking other studies into account, RR is clearly higher in the PD-L1 expressing patients, but the predictive and prognostic value of PD-L1 expression for OS is less clear [15]. Questions also remain in regard to the exact cut-off value of PD-L1-expression, its clinical implementation and alternative or additional subgroup markers. Quantifying smoking history by number of pack-years of consumption may prove to be just as sensitive an indicator of benefit as PD-L1 expression since there is a significant difference in response rate between smokers and non-smokers (27% vs 9%) [15]. To identify the patients that benefit from pembrolizumab, a biopsy of the patient's tumour has to be available and a standardised, validated test has to be applied.

cost effectiveness of pembrolizumab is difficult to estimate

Costs are difficult to estimate, as they depend not only on the cost of pembrolizumab dosage and treatment duration. Treatment of side-effects, savings of costs for symptomatic treatment in case of better overall constitution of patients, costs for screening/testing of PD-L1 expression and costs for alternative treatments have to be additionally taken into account. No estimates exist for the overall cost-effectiveness of pembrolizumab yet.

FDA approval based on preliminary data

Long term data needed

Targeting of the PD-L1 checkpoint blockade is a potential new option for previously treated, advanced NSCLC patients. However, it should be noted that approval by the FDA is based on preliminary results from a phase Ib trial. The new findings from the phase III KEYNOTE-010 trial have to be considered for decisions about the future application of pembrolizumab in NSCLC patients, and more studies with long-term data are needed.

improved efficacy and better AE result, but missing QoL data

PD-L1 testing issues

limited generalisability

KEYNOTE-010 reports superior efficacy (OS, PFS and RR) with fewer side effects for PD-L1 positive patients, defined as an expression of ≥50% by means of an FDA-specified test compared to docetaxel. Besides the challenge of defining a PD-L1 expression cut-off value or other predictive biomarkers for response, and technical issues in regard to PD-L1 testing, generalisability is unclear as only relatively young patients with an ECOG of 0 or 1 have been included in the KEYNOTE-010 trial. Additionally, the benefit for patients with an EGFR mutation has to be further examined. Patient-relevant outcomes (such as QoL) are still missing but shall be measured in an ongoing trial. Also, the evaluation of safety and efficacy of combination therapies is ongoing.

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 2015-01-28]; Available from: http://meka.thl.fi/htacore/model/HTA%20Core%20Model%20for%20Rapid%20REA%20of%20Pharmaceuticals%203.0.pdf.

[2] European Medicine Agency. Keytruda: EPAR – Product Information. [cited 2016-01-28]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003820/WC500190990.pdf.

[3] National Cancer Institute. NCI Drug Dictionary. Pembrolizumab. [cited 2016-01-29]; Available from: http://www.cancer.gov/publications/dictionaries/cancer-drug?CdrID=695789.

[4] U.S. Food and Drug Administration. FDA New Release: FDA approves Keytruda for advanced melanoma. [cited 2016-03-02]; Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm412802.htm .

[5] U.S. Food and Drug Administration. Drugs@FDA.Keytruda.Label information. [cited 2016-02-24]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125514s005lbl.pdf.

[6] Thomas KW, Gould MK. Overview of the initial evaluation, diagnosis, and staging of patients with suspected lung cancer. 2015 [01.07.2015]; Available from: http://www.uptodate.com/contents/overview-of-the-initial-evaluation-diagnosis-and-staging-of-patients-with-suspected-lung-cancer?source=see_link#H98205022.

[7] Surveillance E, and End Results Program,. SEER Cancer Statistics Review 1975-2012. 2012 [01.07.2015]; Available from: http://seer.cancer.gov/csr/1975_2012/browse_csr.php?sectionSEL=15&pageSEL=sect_15_table.28.html.

[8] David E Midthun M. Overview of the initial evaluation, treatment and prognosis of lung cancer. [cited 2016-02-24]; Available from: http://www.uptodate.com/contents/overview-of-the-initial-evaluation-treatment-and-prognosis-of-lung-cancer?source=see_link.

[9] National Cancer Institute. SEER Stat Fact Sheets: Lung and Bronchus Cancer. [cited 2016-02-24]; Available from: http://seer.cancer.gov/statfacts/html/lungb.html.

[10] National Comprehensive Cancer Network. NCCN – Clinical Practice Guidelines in Oncology – Non-Small Cell Lung Cancer V7. 2015.

[11] Krebsregisterdaten Zf. Lungenkrebs (Bronchialkarzinom). [cited 2016-02-24]; Available from: http://www.krebsdaten.de/Krebs/DE/Content/Krebsarten/Lungenkrebs/lungenkrebs.html.

[12] Reck M, Popat S, Reinmuth N, De Ruysscher D, Kerr KM, Peters S. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii27-39.

[13] Statistik Austria. 2012 [cited 01.07.2015]; Available from: http://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebserkrankungen/index.html.

[14] National Cancer Institute. SEER Stat Fact Sheets: Lung and Bronchus. [cited 2016-03-02]; Available from: http://seer.cancer.gov/statfacts/html/lungb.html.

[15] González-Cao M, Karachaliou N, Viteri S, Morales-Espinosa D, Teixidó C, Ruiz JS, et al. Targeting PD-I/PD-LI in lung cancer: Current perspectives. Lung Cancer: Targets and Therapy. 2015;6((González-Cao M., mgonzalezcao@oncorosell.com; Karachaliou N.; Viteri S.; Morales-Espinosa D.; Rosell R.) Translational Cancer Research Unit, Instituto Oncológico Dr Rosell, Quirón Dexeus University Hospital, Barcelona, Spain):55-70.

[16] National Cancer Institute. Non-Small Cell Lung Cancer Treatment (PDQ®). [cited 2016-02-24]; Available from: http://www.cancer.gov/types/lung/patient/non-small-cell-lung-treatment-pdq.

[17] Jørgensen JT. Companion diagnostic assays for PD-1/PD-L1 checkpoint inhibitors in NSCLC. Expert Review of Molecular Diagnostics. 2015((Jørgensen J.T., jan.trost@dx-rx.dk) Dx-Rx Institute, Fredensborg, Denmark):1-3.

[18] Lilenbaum R. M, FACP,. UptoDate-Overview of the treatment of advanced non-small cell lung cancer. 2015 [cited 2016-03-02]; Available from: http://www.uptodate.com/contents/overview-of-the-treatment-of-advanced-non-small-cell-lung-cancer?detectedLanguage=en&source=search_result&search=therapy+nsclc&selectedTitle=3~150&provider=noProvider.

[19] National Comprehensive Cancer Network® (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) – Non-Small Cell Lung Cancer. 2016 [cited 2016-03-02]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

[20] Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. The Lancet. 2015((Herbst R.S., roy.herbst@yale.edu) Yale School of Medicine, Yale Cancer Center, and Smilow Cancer Hospital, New Haven, CT, USA).

[21] Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. British journal of cancer. 2014;110(3):551-5. Epub 2014/02/06.

[22] Gangadhar TC, Vonderheide RH. Mitigating the toxic effects of anticancer immunotherapy. Nature reviews Clinical oncology. 2014;11(2):91-9. Epub 2014/01/22.

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

[24] Gettinger S. Immunotherapy of non-small cell lung cancer with immune checkpoint inhibition. [cited 2016-0224]; Available from: http://www.uptodate.com/contents/immunotherapy-of-non-small-cell-lung-cancer-with-immune-checkpoint-inhibition?source=search_result&search=keynote+001&selectedTitle=1~24.

[25] Warenverzeichnis Apothekerverlag Online. [cited 2015-09-15]; Available from: http://warenverzeichnis.apoverlag.at/.

[26] Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, et al. Supplementary appendix. Supplement to: Herbst et al.,Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer(KEYNOTE-010): a randomised controlled trial. 2015.

[27] Prasad V, Bilal U. The role of censoring on progression free survival: oncologist discretion advised. European journal of cancer (Oxford, England: 1990). 2015;51(16):2269-71. Epub 2015/08/12.

[28] Bagley SJ, Bauml JM, Langer CJ. PD-1/PD-l1 immune checkpoint blockade in non-small cell lung cancer. Clinical Advances in Hematology and Oncology. 2015;13(10):676-83.

12 Appendix

Table 3: Characteristics of the KEYNOTE-010 trial

Title: Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer [20]			
Study identifier	NCT01905657, 2012-004391-19, KEYNOTE-010		
Design	Randomised, open-label, international phase II/III study		
	Duration		Enrolment: 2013-08-28 to 2015-02-27 Median follow-up (at the time of data cut-off 2015-09-30): 13.1 months (IQR 8.6–17.7) Cut-off dates for analyses: first interim analysis: Nov 2014, second interim analysis: Jul 2015
Hypothesis	With 140 deaths between one MK-3475 arm and control, the study has over 81% power to detect a 0.55/0.70 hazard ratio for overall survival in the population of patients with a tumour proportion score of 50% or greater/in the total population at the final analysis, where 0.825% alpha is allocated to the two MK-3475 vs. docetaxel comparisons using the Hochberg procedure.		
Funding	Merck Sharp & Dohme		
Treatments groups	Intervention (n = 345)		Pembrolizumab 2 mg/kg every 3 weeks
	Intervention (n = 346)		Pembrolizumab 10 mg/kg every 3 weeks
	Control (n = 343)		Docetaxel 75 mg/m² every 3 weeks
Endpoints and definitions	Progression-free survival (primary endpoint)	PFS	Defined as the time from randomisation to documented disease progression according to RECIST or death from any cause
	Overall survival (primary endpoint)	OS	Defined as the time from randomisation to death from any cause
	Response rate	RR	Percentage of patients with complete or partial response according to RECIST (version 1.1)
	Safety	-	-
Results and analysis			
Analysis description	Efficacy was assessed in the intention-to-treat-population. Safety was assessed in patients who received at least one dose of study treatment		
Analysis population	Inclusion		❁ Life expectancy of at least 3 months ❁ Age ≥ 18 years ❁ Histologically or cytologically confirmed diagnosis of NSCLC that is PD-L1 positive (≥ 1% of tumour cells) per central laboratory review ❁ At least one bi-dimensional measurable lesion ❁ Radiographic progression after treatment with at least 2 or more cycles of a platinum-containing doublet ❁ Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
	Exclusion		❁ Prior therapy with PD-1 checkpoint inhibitors or docetaxel ❁ Receiving systemic steroid therapy within three days prior to the first dose of study treatment or receiving any other form of immunosuppressive medication ❁ Currently participating or having participated in a study using an investigational antineoplastic agent or device within 30 days of first dose ❁ Expected to require any other form of systemic or localised antineoplastic therapy while on trial ❁ History of allogeneic tissue/solid organ transplant ❁ Prior systemic cytotoxic chemotherapy, antineoplastic biological therapy (e.g. cetuximab), major surgery within 3 weeks of the first dose of study drug; received thoracic radiation therapy of >30 Gray within 6 months of the first dose of study drug; received prior tyrosine kinase inhibitor therapy or completed palliative radiotherapy within 7 days of the first dose of study drug ❁ Prior therapy with an anti-programmed cell death (PD)-1, anti-PD-L1, anti-PD-L2, anti-tumour necrosis factor CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways or participation in a previous pembrolizumab trial

Title: Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer [20]

Study identifier | NCT01905657, 2012-004391-19, KEYNOTE-010

Analysis population *(continuation)*

Exclusion

- Known history of prior malignancy, with the exception of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, or in situ cervical cancer, and has undergone potentially curative therapy with no evidence of disease recurrence for 5 years since initiation of that therapy
- Known active central nervous system (CNS) metastases and/or carcinomatous meningitis
- Active autoimmune disease, or a documented history of autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents
- Interstitial lung disease, or history of pneumonitis requiring systemic steroids for treatment
- Known history or active human immunodeficiency virus (HIV), hepatitis B or hepatitis C
- Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial through 120 days after last dose of pembrolizumab or 180 days after last dose of docetaxel

Characteristics	Pembro-lizumab 2mg/kg (n = 344)	Pembro-lizumab 2mg/kg (n = 346)	Docetaxel 75mg/m² (n = 343)	Pembro-lizumab 2mg/kg PD-L1 ≥50% (n = 139)	Pembro-lizumab 10mg/kg PD-L1 ≥50% (n = 151)	Docetaxel PD-L1 ≥50% (n = 152)
Median age (range), years	63 (56–69)	63 (56–69)	62 (56–69)	62 (56–69)	64 (58–70)	60 (54–69.5)
Male sex, %	62	62	61	58	59	61
Histology, %						
Squamous	22	23	19	21	27	17
Non-squamous	70	71	70	68	65	73
Other	3	2	3	3	3	3
Unknown	6	5	8	8	5	7
Smoking status						
Former or current	81	82	78	81	81	74
Never	18	17	20	19	19	22
Unknown	1	<1	2	1	0	3
Stable brain metastases	16	14	14	23	15	15
ECOG performance status[1], %						
0	33	35	34	34	31	32
1	67	65	65	65	69	67
2	1	<1	<1	1	0	1
EGFR status						
Wild-type	85	83	86	86	84	86
Mutant	8	9	8	6	9	8
Unknown	7	8	6	8	7	6
PD-L1-TPS ≥50%, %	40	44	44	100	100	100
ALK translocation						
No	89	88	90	86	87	90
Yes	1	1	1	1	1	1
Unknown	10	11	9	13	12	9
Line of previous systemic therapy, %						
1	71	68	69	70	69	72
2	19	20	22	22	17	16
≥3	8	10	8	7	11	10

Title: Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer [20]							
Study identifier	NCT01905657, 2012-004391-19, KEYNOTE-010						
	Type of previous systemic therapy, %						
	Chemo[2]	97	97	99	99	97	98
	Immuno	1	<1	<1	1	1	0
	EGFR tyrosine kinase	12	16	14	10	13	14
	ALK inhibitor	1	1	1	2	2	1

Data are median (IQR) or n (%).

Abbreviations: EGFR = epidermal growth factor receptor, ALK = anaplastic lymphoma kinase, ECOG = Eastern Cooperative Oncology Group, TPS = tumour proportion score.

[1] *For five of the six patients who had an ECOG performance status ≥2 during screening, the score improved to 1 by the time the patients were randomly allocated to treatment.*

[2] *Patients whose disease progressed within 1 year of completing platinum-based therapy were also eligible.*