Horizon Scanning in Oncology

Pembrolizumab (Keytruda®) for the treatment of advanced melanoma

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology No. 55
ISSN online 2076-5940

Horizon Scanning in Oncology

Pembrolizumab (Keytruda®) for the treatment of advanced melanoma

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, October 2015

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft

Authors: Dr. med. Eleen Rothschedl

Internal review: Dr. med. Anna Nachtnebel, MSc

External review: Univ.-Prof. Johann Bauer, MBA HCM
Vorstand der Universitätsklinik für Dermatologie
Salzburger Landeskliniken – Universitätsklinikum Salzburg

DISCLAIMER

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

The HTA Core Model ® for Rapid Relative Effectiveness for Pharmaceuticals, developed within EUnetHTA (www.eunethta.eu), has been utilized 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 A working version (unpublished) of V3.0 of the Model was used.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://hta.lbg.ac.at/page/imprint

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 publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

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

DSD: Horizon Scanning in Oncology No. 55
ISSN-online: 2076-5940

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

Table of Contents

List of Tables

1 Research questions

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?
A0020	For which indications has pembrolizumab received marketing authorisation?
A0021	What is the reimbursement status of pembrolizumab?
A0022	Who manufactures pembrolizumab?
Health problem and Current Use	
A0002	What is melanoma?
A0003	What are the known risk factors for melanoma?
A0004	What is the natural course of melanoma?
A0005	What are the symptoms and the burden of melanoma for the patient?
A0006	What are the consequences of melanoma for the society?
A0024	How is melanoma currently diagnosed according to published guidelines and in practice?
A0025	How is melanoma currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
Clinical Effectiveness	
D0001	What is the expected beneficial effect of pembrolizumab on mortality?
D0005	How does pembrolizumab affect symptoms and findings (severity, frequency) of advanced melanoma?
D0006	How does pembrolizumab affect progression (or recurrence) of advanced melanoma?
D0011	What is the effect of pembrolizumab on patients' body functions?
D0012	What is the effect of pembrolizumab on generic health-related quality of life?
D0013	What is the effect of pembrolizumab on disease-specific quality of life?
Safety	
C0008	How safe is pembrolizumab in relation to the comparator?
C0002	Are the harms related to dosage or frequency of applying pembrolizumab?

2 Drug description

Generic/Brand name/ATC code:
Pembrolizumab/Keytruda®/L01XC18

B0001: What is pembrolizumab?

anti-PD-1 antibody

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 to and activation of PD-1 by its ligands, which causes the activation of T-cell-mediated immune responses against tumour cells. The activation of PD-1 negatively regulates the activation of T cells; furthermore it plays an important role in tumour evasion from host immunity [3].

2 mg/kg administered IV every 3 weeks

The recommended dose of pembrolizumab is 2 mg/kg administered as an intravenous (IV) infusion over 30 minutes every three weeks; treatment should be continued until disease progression or unacceptable toxicity. In case of atypical responses, such as 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 for clinically stable patients with initial evidence of disease progression until disease progression gets confirmed [2].

A0022: Who manufactures pembrolizumab?

Merck Sharp & Dohme

3 Indication

A0007: What is the target population in this assessment?

for patients with advanced melanoma

Pembrolizumab monotherapy is indicated for the treatment of adult patients with advanced (unresectable or metastatic) melanoma [2].

4 Current regulatory status

A0020: For which indications has pembrolizumab received marketing authorisation?

approved by the EMA

The EMA granted marketing authorisation for Keytruda® as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults on 17 July 2015.

FDA granted accelerated approval

The FDA initially granted accelerated approval of Keytruda® in September 2014, for patients with advanced or unresectable melanoma no longer responding to other drugs [4]. According to the label approved on 19 June 2015 [5], pembrolizumab is indicated in patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF (proto-oncogene B-Raf) V600 mutation-positive, a BRAF inhibitor. This indication is also approved under accelerated approval and is based on tumour response rate and durability of response, whilst an improvement in survival or disease-related symptoms has not yet been established.

5 Burden of disease

A0002: What is melanoma?

definition of disease

Melanoma is a skin cancer which starts in the melanocytes. In men, it most commonly starts on the trunk (chest and back); in women, most common sites are the legs.

A0004: What is the natural course of melanoma?

outcome depends on the stage at presentation

If melanoma is not detected and cured in early stages, it can spread to other parts of the body [6]. The outcome of melanoma depends on the stage at presentation; it is estimated that 82-85% of patients present with localised disease, 10-13% with regional disease and 2-5% with distant metastatic disease [7].

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

A0023: How many people belong to the target population?

incidence rate in Austria: 12.2 per 100,000 persons per year

In Austria, the incidence of malignant melanoma is 12.2 per 100,000 persons per year; in 2011, 1,551 persons were newly diagnosed with malignant melanoma [8]. However, this number might underestimate the actual incidence due to different reporting structures in Austrian provinces. Age standardised incidence data from other European Countries are for example 26.8 per 100,000 in Switzerland and 26.6 per 100,000 in Norway [9]. In Austria, until 2030, a significant increase in incidence and mortality is expected; the number of newly diagnosed disease is expected to increase by 92% in men and 45% in women [10].

The median age at diagnosis of melanoma is 63 years; it is most frequently diagnosed among patients aged 55 to 64 years. 91.5 % of melanoma patients survive 5 years [11]. In Austria, melanoma mortality rate is 2.2 per 100,000 persons per year [8].

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

warning signs

Warning signs of melanoma are changes in the size, shape or colour of moles or other skin lesions. Furthermore, the appearance of a new growth on the skin or a sore that does not heal represent warning signs [12].

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

diagnosis

In case of suspicious lesions, a biopsy should be performed [13]. Therefore, an excisional biopsy (elliptical, punch or saucerization) with 1-3 mm marginal is preferred and wider marginal should be avoided to permit accurate subsequent lymphatic mapping [7].Microstaging should be conducted by an experienced pathologist [13].

AJCC classification system

Melanomas are classified according to the TNM classification system (T = primary tumour, N = regional lymph node, M = distant metastasis). The only internationally accepted classification system for melanoma is the revised American Joint Committee on Cancer (AJCC) staging system, which is based on the TNM system and includes sentinel node staging [14].

A0003: What are the known risk factors for melanoma?

risk factors

Risk factors for the development of melanoma include [15]:

- fair skin (that burns easily)
- high lifetime exposure to natural or artificial sunlight
- a history of blistering sunburns, particularly at a young age
- many common moles
- a history (personal or family) of dysplastic nevi or melanoma
- being white.

6 Current treatment

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

recommendations for treatment

For the treatment of systemic metastatic melanoma (stage IV), the European Society for Medical Oncology (ESMO) recommends [14]:

- In patients with metastatic melanoma, metastasis or the primary tumour should be screened for detection of BRAF V600 mutation. For the first- and second-line setting, different treatment options exist for all patients, including anti-PD-1 antibodies (nivolumab) and ipilimumab, an anti-CTLA4 antibody. Pembrolizumab has already been added to this recommendation as well. For patients with BRAF-mutant melanoma, BRAF inhibitors such as vemurafenib, encorafenib and dabrafenib are available in combination with MEK[1] inhibitors (binimetinib, cobimetinib and trametinib) (II, B).
- Cytotoxic drugs which showed modest activity (i.e. DTIC or temozolomide) may be administered if clinical trials or the approved new targeted compounds are not available (II, C).
- Multi-agent polychemotherapy (containing paclitaxel and carboplatin or cisplatin, vindesine and dacarbazine) may provide mostly short-lived partial responses and/or stabilisation of disease in a meaningful number of patients with aggressive metastatic disease.

For patients with metastatic stage IV melanoma, multidisciplinary tumour board consultation is mandatory [14, 16].

7 Evidence

systematic search in 4 databases

A literature search was conducted on 20 August 2015 in four databases: the Cochrane Library, CRD Database, Embase and Medline. Search terms were “Pembrolizumab”, “Keytruda”, “Lambrolizumab”, “mk-3475” and “Melanoma”. Also, the manufacturer was contacted but did not submit any further evidence.

included:
1 phase III study,
1 dose-comparison study,
1 phase II study

Overall, 199 references were identified. Included in this report are:

- 1 phase III study, assessing pembrolizumab versus ipilimumab in advanced melanoma [17, 18]
- 1 randomised dose-comparison study [19], comparing two different dosages of pembrolizumab in advanced melanoma
- 1 randomised, controlled phase II trial [20], evaluating pembrolizumab versus investigator-choice chemotherapy in patients with advanced melanoma.

[1] MEK = mitogen-activated protein

7.1 Efficacy and safety – Phase III studies

KEYNOTE-006: a randomised phase III study in 834 patients

KEYNOTE-006 [17, 18] is an international, randomised, controlled, open-label phase III study comparing two different dosing regimens of pembrolizumab to ipilimumab in patients with advanced melanoma. A total of 834 patients were randomly assigned in a 1:1:1 ratio to receive pembrolizumab at a dose of 10 mg/kg either every 2 weeks or every 3 weeks, or four cycles of ipilimumab at a dose of 3 mg/kg every 3 weeks. Enrolled patients had histologically confirmed unresectable stage III or IV melanoma and had received no more than one previous systemic therapy for advanced disease; 65.6% (pembrolizumab every 2 weeks), 66.8% (pembrolizumab every 3 weeks) and 65.1% (ipilimumab) of patients had received no prior line of therapy. In patients who had received prior systemic therapy, chemotherapy, immunotherapy or a BRAF or MEK inhibitor (or both) were administered. Patients were excluded if they had received previous therapy with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1) or programmed death ligand (PD-L1) inhibitors. More than two thirds of patients of each group had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and metastasis stage M1c. 80.6%, 79.8% and 80.9% of patients had PD-L1-positive tumour tissue samples and BRAF V600 mutations were detected in 35.1%, 35.0% and 38.5% of patients receiving pembrolizumab every 2 or 3 weeks or ipilimumab respectively. A detailed description of KEYNOTE-006 including patient characteristics can be found in Table 1.

comparison of 2 different dosages of pembrolizumab to ipilimumab

mean duration of exposure: 50–164 days

The median duration of follow-up at the time of data cut-off was 7.9 months, ranging from 6.1 to 11.5 months; the mean duration of exposure was 164 days (pembrolizumab every 2 weeks), 151 days (pembrolizumab every 3 weeks) and 50 days (ipilimumab group). Due to the superior overall survival (OS) results of the two pembrolizumab groups over the ipilimumab group results, the data and safety monitoring committee recommended to stop the study early and give patients of the ipilimumab group the option to receive pembrolizumab.

Table 1: Summary of KEYNOTE-0006 trial and patient characteristics

Study title Pembrolizumab versus ipilimumab in advanced melanoma [17, 18]		
Study identifier	NCT01866319, EudraCT Number 2012-004907-10, KEYNOTE-006	
Design	Randomised, controlled, international phase III study	
	Duration	*Enrolment:* 2013-09-18 to 2014-03-03 *Median follow-up (at the time of data cut-off):* 7.9 months (range: 6.1 to 11.5) *Cut-off dates for analyses:* 2014-09-03 (first interim analysis), 2015-03-03 (second interim analysis)
Hypothesis	Superiority The Kaplan-Meier method was used to calculate estimates of PFS and OS. Treatment differences for PFS and OS were assessed by means of the stratified log-rank test. HRs and associated 95% CIs were assessed with the use of a stratified Cox proportional-hazards model with Efron's method of handling ties. Response rates in the study groups were compared by the stratified Miettinen and Nurminen method.	
Funding	Merck Sharp & Dohme	
Treatment groups	Intervention (n=279)	Pembrolizumab 10 mg/kg (IV during a 30-minute period) every 2 weeks
	Intervention (n=277)	Pembrolizumab 10 mg/kg (IV during a 30-minute period) every 3 weeks
	Control (n=278)	Ipilimumab 3 mg/kg (IV during a 90-minute period) every 3 weeks for 4 cycles

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		
	Objective response rate	ORR	Defined as the percentage of patients with complete or partial response according to RECIST		
	Duration of response	DOR	Defined as the time from the first documented response to radiologic progression according to RECIST		
	Safety	-	-		
Results and analysis					
Analysis description	Efficacy was assessed in the intention-to-treat population. Safety was assessed in the as-treated population.				
Analysis population	Inclusion	❖ Age ≥ 18 years ❖ Histologically confirmed, unresectable stage III or IV melanoma ❖ No more than one previous systemic therapy for advanced disease ❖ Known BRAF V600 mutational status; previous BRAF inhibitor therapy was not required for patients with normal LDH levels ❖ No clinically significant tumour-related symptoms or evidence of rapidly progressive disease ❖ ECOG performance status 0 or 1 ❖ Provision of a tumour sample adequate for assessing PD-L1 expression			
	Exclusion	❖ Previous therapy with CTLA-4, PD-1, or PD-L1 inhibitors ❖ Patients who had ocular melanoma, active brain metastases, or a history of serious autoimmune disease			
	Characteristics		Pembrolizumab every 2 weeks	Pembrolizumab every 3 weeks	Ipilimumab
		Median age (range), years	61 (18–89)	63 (22–89)	62 (18–88)
		Male sex, %	57.7	62.8	58.3
		ECOG performance status, % 1 2	 70.3 29.7	 68.2 31.8	 67.6 32.4
		Elevated baseline LDH level, %	29.0	35.4	32.7
		PD-L1-positive tumour, %	80.6	79.8	80.9
		BRAF V600 mutation, %	35.1	35.0	38.5
		Line of previous systemic therapy, % 0 1	 65.6 34.4	 66.8 32.9	 65.1 34.9
		Type of previous systemic therapy, % Chemotherapy Immunotherapy BRAF or MEK inhibitor or both	 12.9 2.9 17.9	 14.8 2.5 16.2	 10.4 4.3 20.1

Abbreviations: BRAF = proto-oncogene B-Raf, CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte-associated protein 4, ECOG = Eastern Cooperative Oncology Group, IV = intravenous, LDH = lactate dehydrogenase, MEK = mitogen-activated protein, NR = not reported, ORR = objective response rate, OS = overall survival, PD-1 = programmed cell death protein 1, PD-L1 = programmed death ligand 1, PFS = progression-free survival, RECIST = Response Evaluation Criteria In Solid Tumours

7.1.1 Efficacy

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

primary endpoint: progression-free survival

The primary endpoint, progression-free survival (PFS), was significantly improved in both pembrolizumab groups compared to the ipilimumab group. The estimated 6-month PFS rates were 47.3% (pembrolizumab every 2 weeks), 46.4% (pembrolizumab every 3 weeks) and 26.5% (ipilimumab group). Median estimates of PFS were 5.5 months (95% CI[2] 3.4-6.9), 4.1 months (95% CI 2.9-6.9) and 2.8 months (95% CI 2.8-2.9) in patients receiving pembrolizumab every 2 weeks, every 3 weeks and in patients receiving ipilimumab respectively. The hazard ratios (HR) for disease progression for pembrolizumab compared to ipilimumab were 0.58 (95% CI 0.46-0.72); $p<0.001$) in patients receiving pembrolizumab every 2 weeks and 0.58 (95% CI 0.47-0.72; $p<0.001$) in patients receiving the 3-week regimen. The PFS improvement in both pembrolizumab groups over the ipilimumab group was reported from all prespecified subgroups and the benefit was also observed in both PD-L1-positive and PD-L1-negative subgroups.

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

OS benefit of pembrolizumab over ipilimumab

Estimated 12-month survival rates were 74.1% (pembrolizumab every 2 weeks), 68.4% (pembrolizumab every 3 weeks) and 58.2% (ipilimumab group); HR for death as compared with the ipilimumab group was 0.63 (95% CI 0.47-0.83; $p<0.0005$) for patients receiving pembrolizumab every 2 weeks and 0.69 (95% CI 0.52-0.90; $p=0.0036$) for patients receiving the 3-week regimen. Median OS was not reached in any of the three groups. The benefit in OS of pembrolizumab over ipilimumab was reported from all subgroups, with the exception of patients with PD-L1-negative tumours (HRs were 0.91 in patients receiving the 2-week regimen and 1.02 in patients receiving the 3-week regimen, as compared with ipilimumab).

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

response rate improved with pembrolizumab

Response rates were 33.7% (pembrolizumab every 2 weeks), 32.9% (pembrolizumab every 3 weeks) and 11.9% (ipilimumab group); patients achieved complete response rates of 5.0%, 6.1% and 1.4% receiving pembrolizumab every 2 or 3 weeks or ipilimumab respectively. The median duration of response was not reached in any group; median times to response were 86 days, 85 days and 87 days in patients receiving the pembrolizumab 2-week regimen, 3-week regimen or receiving ipilimumab respectively.

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?

[2] CI = confidence interval

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

No evidence was found to answer the research questions concerning the body functions and the quality-of-life of patients.

Table 2: Efficacy results for KEYNOTE-006

Descriptive statistics and estimated variability[3]	Treatment group	Pembrolizumab every 2 weeks	Pembrolizumab every 3 weeks	Ipilimumab
	Number of subjects	279	277	278
	PFS median (95% CI), months	5.5 (3.4–6.9)	4.1 (2.9–6.9)	2.8 (2.8–2.9)
	6-month PFS rate, %	47.3	46.4	26.5
	12-month OS rate, %	74.1	68.4	58.2
	Response rate, % CR PR Stable disease	33.7 5.0 28.7 13.3	32.9 6.1 26.7 14.1	11.9 1.4 10.4 16.5
	Ongoing responses, (%)	89.4	96.7	87.9
	Median time to response (range), weeks	86 (32–212)	85 (36–251)	87 (80–250)
	Median duration of response (range), months	25 (42+ to 251)	Not reached (42+ to 246+)	Not reached (33+ to 239+)
Effect estimate per comparison	*Comparison groups*		*2-week regimen vs. ipilimumab*	*3-week regimen vs. ipilimumab*
	PFS	HR	0.58	0.58
		95% CI	0.46–0.72	0.47–0.72
		P value	<0.001	<0.001
	OS	HR	0.63	0.69
		95% CI	0.47–0.83	0.52–0.90
		P value	<0.0005	0.0036
	Response rates	Estimated difference	16.1	17.2
		95% CI	7.8–24.5	9.5–25.6
		P value	<0.001	<0.001

Abbreviations: CI = confidence interval, CR = complete response, HR = hazard ratio, OS = overall survival, PFS = progression-free survival, PR = partial response

[3] All data are taken from the first interim analysis except those for overall survival, which are taken from the second interim analysis.

7.1.2 Safety

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

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

frequency of AEs

Adverse events (AEs) of any grade related to treatment were reported from 79.5% (pembrolizumab every 2 weeks), 72.9% (pembrolizumab every 3 weeks) and 73.0% (ipilimumab group) of patients. Most common in the pembrolizumab groups were fatigue, diarrhoea, rash and pruritus. In the ipilimumab group, pruritus, diarrhoea, fatigue and rash occurred most frequently.

Concerning different dosages, 37.8% of patients receiving pembrolizumab every 2 weeks and 33.2% of patients receiving pembrolizumab every 3 weeks experienced a grade 3, 4 or 5 event. In patients of the ipilimumab group, a grade 3, 4 or 5 event occurred in 36.7% of patients.

treatment-related AEs

Treatment-related grade 3-5 AEs occurred in 13.3% of patients receiving pembrolizumab every 2 weeks, in 10.1% of patients receiving pembrolizumab every 3 weeks and in 19.9% of patients receiving ipilimumab. Median time to onset of first grade 3, 4 or 5 AE was 59.0 days (pembrolizumab every 2 weeks), 64.0 days (pembrolizumab every 3 weeks) and 39.5 days (ipilimumab group). HR was 0.59 (95% CI, 0.43-0.80, $p<0.001$) comparing the 2-week-regimen to ipilimumab and 0.53 (95%CI 0.38-0.72, $p<0.001$) for the 3-week-regimen versus ipilimumab. The similar safety profiles of the two different dosages of pembrolizumab as well as the safety profile of ipilimumab are shown in Table 3. Treatment-related AEs led to permanent discontinuation of a study drug in 4.0% (pembrolizumab every 2 weeks), 6.9% (pembrolizumab every 3 weeks) and 9.4% (ipilimumab group) of patients.

AEs of particular interest

The most common AEs of special interest[4] among the patients of the pembrolizumab groups were hypothyroidism and hyperthyroidism; grade 3 to 4 AEs reported from more than 1% of these patient groups were colitis and hepatitis. In the ipilimumab group, the most frequent AE of special interest was colitis; grade 3 to 4 AEs occurring in more than 1% of these patients were colitis and inflammation of the pituitary gland.

[4] On the basis of the likely autoimmune or immune-related mechanism

Table 3: Adverse events in the as-treated population

Adverse event (according to NCI-CTC version 4.0)	**Pembrolizumab every 2 weeks (n=278)**		**Pembrolizumab every 3 weeks (n=277)**		**Ipilimumab (n=256)**	
	Any grade	Grade 3–5	Any grade	Grade 3–5	Any grade	Grade 3–5
Related to treatment						
Any	221 (79.5)	37 (13.3)	202 (72.9)	28 (10.1)	187 (73.0)	51 (19.9)
Occurring in 10% of patients in any study group						
Fatigue	58 (20.9)	0	53 (19.1)	1 (0.4)	39 (15.2)	3 (1.2)
Diarrhoea	47 (16.9)	7 (2.5)	40 (14.4)	3 (1.1)	58 (22.7)	8 (3.1)
Rash	41 (14.7)	0	37 (13.4)	0	37 (14.5)	2 (0.8)
Pruritus	40 (14.4)	0	39 (14.1)	0	65 (25.4)	1 (0.4)
Asthenia	32 (11.5)	1 (0.4)	31 (11.2)	0	16 (6.3)	2 (0.8)
Nausea	28 (10.1)	0	31 (11.2)	1 (0.4)	22 (8.6)	1 (0.4)
Arthralgia	26 (9.4)	0	32 (11.6)	1 (0.4)	13 (5.1)	2 (0.8)
Vitiligo	25 (9.0)	0	31 (11.2)	0	4 (1.6)	0
Adverse event of special interest						
Hypothyroidism	28 (10.1)	1 (0.4)	24 (8.7)	0	5 (2.0)	0
Hyperthyroidism	18 (6.5)	0	9 (3.2)	0	6 (2.3)	1 (0.4)
Colitis	5 (1.8)	4 (1.4)	10 (3.6)	7 (2.5)	21 (8.2)	18 (7.0)
Hepatitis	3 (1.1)	3 (1.1)	5 (1.8)	5 (1.8)	3 (1.2)	1 (0.4)
Hypophysitis	1 (0.4)	1 (0.4)	2 (0.7)	1 (0.4)	6 (2.3)	4 (1.6)
Pneumonitis	1 (0.4)	0	5 (1.8)	1 (0.4)	1 (0.4)	1 (0.4)
Type 1 diabetes mellitus	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0
Uveitis	1 (0.4)	0	3 (1.1)	0	0	0
Myositis	0	0	2 (0.7)	0	1 (0.4)	0
Nephritis	0	0	1 (0.4)	0	1 (0.4)	1 (0.4)

Abbreviation: NCI-CTC = National Cancer Institute Common Terminology Criteria for Adverse Events

7.2 Efficacy and safety – further studies

dose-comparison study: 2 mg/kg versus 10 mg/kg

pretreated patients

A randomised dose-comparison study [19] was conducted as an expansion cohort of KEYNOTE-001 (a large phase I study evaluating pembrolizumab for the treatment of non-small-cell lung cancer) to assess the clinical benefit of pembrolizumab. Included were 173 patients with ipilimumab-refractory melanoma defined as disease progression after at least 2 doses of ipilimumab (3 mg/kg or higher administered every 3 weeks) and within 24 weeks of the last dose of ipilimumab. The majority of patients (82%) had no BRAF mutation. With 72% of patients having received at least two and with 35% of patients having received more than 3 prior lines of therapy, patients were heavily pretreated. All patients had been treated with ipilimumab but other types of treatment comprised immunotherapy (excluding ipilimumab), chemotherapy, or BRAF or MEK inhibitors (or both). A total of 173 patients were assigned to receive pembrolizumab either at a dose of 2 mg/kg or 10 mg/kg every 3 weeks until disease progression, intolerable toxicity or consent withdrawal. Median follow-up was 8 months; the median number of days from first

to last pembrolizumab dose was 188.0 days in patients who received pembrolizumab 2 mg/kg and 185.5 days in patients of the pembrolizumab 10 mg/kg group. The overall response rate (ORR), which was the primary endpoint of the study, was 26% in both groups. Median PFS was 22 weeks (95% CI 12-36) in the pembrolizumab 2 mg/kg group and 14 weeks (95% CI 12-24) in the pembrolizumab 10 mg/kg group when measured by an independent central review; this differs from the results assessed by the investigator using immune-related response criteria: here, median PFS was 31 weeks (pembrolizumab 2 mg/kg group) versus 35 weeks (10 mg/kg group). The Kaplan-Meier estimated OS at 1 year was 58% (95% CI 47-68) in patients receiving pembrolizumab at a dose of 2 mg/kg and 63% (51-72) in patients of the pembrolizumab 10 mg/kg group. 82% of patients in each group had drug-related AEs but drug-related grade 3 or 4 adverse events occurred in 20 (12%) patients. Serious drug-related AEs were reported from 8% and 1% of patients receiving 2 mg/kg and 10 mg/kg of pembrolizumab respectively. Serious immune-related AEs occurred in 3% and 1% and immune-related grade 3 or 4 AEs in 1% and 2% of patients respectively. The most common grade 3 or 4 drug-related AE occurring in one or more patients was fatigue.

ORR was 26% in both groups

randomised phase II trial comparing pembrolizumab to chemotherapy

KEYNOTE-002 [20] is a randomised, controlled phase II trial, comparing two different doses of pembrolizumab with investigator-choice chemotherapy in overall 540 patients. Enrolled patients had unresectable stage III or IV melanoma not amenable to local therapy, confirmed disease progression within 24 weeks of the last ipilimumab dose and previous BRAF or MEK inhibitor therapy (or both). 77% of patients had BRAF V600 wild-type status. Approximately one third of patients had more than 3 prior lines of therapy, including ipilimumab, interleukin 2, immunotherapy (excluding ipilimumab and interleukin 2), chemotherapy and BRAF or MEK inhibitor. A total of 540 patients were assigned in a 1:1:1 ratio to receive pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg (both administered IV every 3 weeks) or investigator-choice chemotherapy, including paclitaxel plus carboplatin, paclitaxel, carboplatin, dacarbazine or oral temzolomide. Median follow-up duration was 10 months; median time of treatment was 113 days (pembrolizumab 2 mg/kg group), 145 days (pembrolizumab 10 mg/kg group) and 61 days (chemotherapy group).

PFS significantly improved

PFS, the primary endpoint at the second interim analysis, was significantly improved (based on 410 PFS events): HRs, compared to chemotherapy were 0.57 (95% CI 0.45-0.73) in patients receiving 2 mg/kg and 0.50 (95% CI 0.39-0.64) in patients receiving 10 mg/kg. By 6 months, 34% (pembrolizumab 2 mg/kg), 38% (pembrolizumab 10 mg/kg) and 16% (chemotherapy) of patients were progression free. Median PFS was 2.9 (2.8-3.8) months in patients who received pembrolizumab 2 mg/kg, 2.9 (2.8-4.7) months in patients receiving 10 mg/kg and 2.7 (2.5-2.8) months in patients of the chemotherapy group. A response was achieved in 21%, 25% and 4% of patients receiving pembrolizumab 2 mg/kg, 10 mg/kg or chemotherapy respectively. Median duration of response was not reached in both pembrolizumab groups, whereas patients in the chemotherapy group had a median duration of response of 37 weeks. The change from baseline to week 12 in the global health status and quality-of-life score of the EORTC QLQ-30 questionnaire were exploratory endpoints. Between the 2 mg/kg pembrolizumab group and chemotherapy group and the 10 mg/kg pembrolizumab group and the chemotherapy group, the least squares mean change differed significantly (6.53, 95% CI 1.53-11.53, $p = 0.011$ and 6.57, 1.65-11.50, $p = 0.009$ respectively). At week 12, the global health status quality-of-life score deteriorated by 10 points or more in ap-

proximately 7% to 12% fewer patients receiving pembrolizumab than in patients receiving chemotherapy. Treatment-related AEs of grade 3-4 were reported from 11% (pembrolizumab 2 mg/kg), 14% (pembrolizumab 10 mg/kg) and 26% (chemotherapy group) of patients, most common in the pembrolizumab groups was fatigue. The occurrence of serious treatment-related AEs was similar in all 3 treatment groups; most frequent in both pembrolizumab groups were diarrhoea and pneumonitis (1% of patients in each group).

8 Estimated costs

A0021: What is the reimbursement status of pembrolizumab?

estimated costs per treatment: € 5,437.65

In patients with advanced (unresectable or metastatic) melanoma, the recommended dose of pembrolizumab is 2 mg/kg administered every 3 weeks [2]. In Austria, pembrolizumab (Keytruda®) is available as powder for solution for injection 50 mg at € 1,812.55 [21]. Assuming an average body weight of 70 kg, 3 vials of pembrolizumab would be needed, costs would therefore amount to € 5,437.65 per treatment. For one year of pembrolizumab treatment, overall costs of € 92,440 would incur.

9 Ongoing research

3 phase III trials and 1 expanded access programme were identified

In September 2015, a search in www.clinicaltrials.gov and www.clinicaltrialsregister.eu was conducted. The following phase III trials, evaluating the use of pembrolizumab in melanoma, were identified:

- NCT02506153: A randomised phase III trial comparing high-dose interferon to pembrolizumab in patients with high-risk resected melanoma. The estimated primary completion date is June 2020.
- NCT02362594, EudraCT number 2014-004944-37, MK-3475-054, KEYNOTE-054): A randomised, double-blind phase III trial by the EORTC[5] Melanoma Group, evaluating adjuvant immunotherapy with pembrolizumab versus placebo after complete resection of high-risk stage III melanoma. The estimated study completion date is September 2023.
- NCT02263508, MASTERKEY-265: A multicentre, open-label phase 1b/3 trial of talimogene laherparepvec in combination with pembrolizumab (MK-3475) for the treatment of unresected stage IIIB to IVM1c melanoma. Estimated study completion date is February 2023.
- NCT02083484: An expanded access programme of MK-3475 in metastatic melanoma patients with limited to no treatment options.

[5] EORTC = European Organization for Research and Treatment of Cancer

numerous phase II trials

Pembrolizumab is currently investigated in numerous phase II trials, assessing the use in different treatment lines and combinations with other agents for the treatment of melanoma and in different types of cancer, for example:

- pembrolizumab versus chemotherapy in advanced melanoma
- neoadjuvant pembrolizumab for unresectable stage III and unresectable stage IV melanoma
- double-immune suppression blockade by combining a CSF1R Inhibitor (PLX3397) with pembrolizumab for the treatment of advanced melanoma and other solid tumours
- pembrolizumab in children with advanced melanoma or a PD-L1-positive advanced, relapsed or refractory solid tumour or lymphoma (KEYNOTE-051)
- pembrolizumab with pegylated interferon alfa-2b (PEG-IFN) and pembrolizumab with ipilimumab in patients with advanced melanoma and renal cell carcinoma (KEYNOTE-029)
- pembrolizumab in conjunction with lymphodepletion, TIL (T-cells) and high- or low-dose interleukin-2 in patients with metastatic melanoma
- study of enhancing pembrolizumab responses in melanoma through intratumoural pIL-12 electroporation
- pembrolizumab in combination with trametinib and dabrafenib in patients with advanced melanoma
- combination of pembrolizumab and stereotactic body radiotherapy in patients with metastatic melanoma or NSCLC
- in patients with advanced sarcoma
- pembrolizumab for the treatment of advanced uveal melanoma.

10 Discussion

approved by EMA and FDA for patients with advanced melanoma

Pembrolizumab (Keytruda®) was approved by the EMA in July 2015 as monotherapy for the treatment of adults with advanced (unresectable or metastatic) melanoma [2]. The FDA granted accelerated approval for pembrolizumab in June 2015 for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab (and, if BRAF V600 mutation positive, a BRAF inhibitor) [5].

KEYNOTE-006: improvement in PFS, OS and ORR in patients receiving pembrolizumab

KEYNOTE-006 [17], a randomised, open-label phase III study, was conducted to compare two different dosage regimens of pembrolizumab with ipilimumab in patients with advanced melanoma. Results showed a significant increase in PFS in patients who received pembrolizumab; patients achieved a gain of 2.7 months and 1.3 months in median PFS receiving pembrolizumab every 2 weeks and every 3 weeks compared to ipilimumab respectively. 12-month OS was also improved among patients who received pembrolizumab: 74.1% (pembrolizumab every 2 weeks) and 68.4% (pembrolizumab every 3 weeks) compared to 58.2% of patients in the ipilimumab group. Response rates were also higher among patients who received pembrolizumab: 33.7 (pembrolizumab every 2 weeks) and 32.9% (pembrolizumab every 3 weeks) versus 11.9% in ipilimumab-group patients.

efficacy results of KEYNOTE-006 based on an interim analysis

However, it is notable that efficacy results of the KEYNOTE-006 trial are based on an interim analysis. Generally, the trial provides only results from a short duration of pembrolizumab exposure (ranging from 151-164 days) and, additionally, the trial has been terminated early. In this respect, the results of NCT02083484, an expanded access programme of pembrolizumab in patients with metastatic melanoma with limited to no treatment options, will be of interest. Furthermore, PFS and response rates are surrogate parameters and OS results from KEYNOTE-006 were estimates from interim analyses.

grade 3-5 treatment-related AEs more frequent in ipilimumab group

Treatment-related AEs of grade 3-5 were more frequent in ipilimumab-group patients compared to patients in the pembrolizumab groups. In terms of AEs of special interest (autoimmune and immune-related), hypothyroidism and hyperthyroidism were most frequent in the pembrolizumab groups. However, these side-effects are easier to be treated than immune-related gastrointestinal reactions such as colitis which are associated with ipilimumab therapy [22].

are significant study results clinically meaningful too?

Generally, pembrolizumab provides a new option for the treatment of patients with advanced melanoma, showing higher response rates as compared to the standard treatment options ipilimumab and chemotherapy. In KEYNOTE-006 and KEYNOTE-002, a significant improvement in PFS was observed among patients who had received pembrolizumab compared to patients in the control group receiving ipilimumab and chemotherapy respectively [17, 19]. Although these improvements were statistically significant, it does not necessarily follow that they are clinically meaningful too.

different dosages and schedules were used among pembrolizumab studies

In the KEYNOTE-006 trial [17], two different schedules of pembrolizumab were assessed: 10 mg/kg, administered either every 2 or every 3 weeks; in the KEYNOTE-002 study [20], pembrolizumab was administered at a dose of 2 mg/kg or 10 mg/kg every 3 weeks. In the dose-comparison cohort of KEYNOTE-001 [19], pembrolizumab 2 mg/kg was compared to 10 mg/kg every 3 weeks. Among these three trials, the results were similar in efficacy and safety between the pembrolizumab groups. Both the EMA and the FDA recommend the administration of pembrolizumab at a dose of 2 mg/kg every 3 weeks [2, 5]. This raises the question if, using the recommended (lower) dose, a comparative study of pembrolizumab and ipilimumab would show the same efficacy and safety results as reported from KEYNOTE-006. Nevertheless, there is no phase III data for a direct comparison of pembrolizumab 2 mg/kg or 10 mg/kg administered every 3 weeks. In trials evaluating pembrolizumab for other types of cancer including non-small-cell lung cancer, genitourinary cancers or head and neck squamous-cell carcinoma, different dosages (ranging from 1 mg/kg to 10 mg/kg) were administered in different schedules [23]. However, pembrolizumab is not licensed for any of these cancers and no conclusions can be drawn from these trials. At any rate, the administration of a higher dose (>2 mg/kg every 3 weeks) of pembrolizumab would significantly increase the costs of pembrolizumab treatment.

treatment landscape for melanoma patients fundamentally changed over the past decade

In the past decade, various targeted therapies, including kinase inhibitors, immune activators and, subsequent combination regimens, have become available for melanoma patients [24, 25]. Several targeted agents have been approved by the EMA and the FDA in the past few years for melanoma treatment: vemurafenib, dabrafenib as monotherapy (EMA and FDA) and in combination with trametinib (FDA only), ipilimumab and, most recently, nivolumab and pembrolizumab. It is notable that both nivolumab and pembrolizumab are PD-1-blocking antibodies approved for the same melanoma indication: the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation

positive, a BRAF inhibitor [5, 26]. Due to this short clinical experience (as compared to standard – chemotherapeutical – treatment options, e.g. dacarbazine), there is a lack of long-term data on these new agents; even the KEYNOTE-006 trial has been stopped earlier than planned. A central tenet of immunotherapy, the long-lasting benefit, is as yet unproven for pembrolizumab [27]. Especially regarding the impact of pembrolizumab on the immune system and the associated immune-related AEs, long-term data is required.

appropriate line of therapy remains unclear

Another unresolved issue of pembrolizumab treatment relates to the appropriate line of therapy: in the KEYNOTE-006 trial, more than two thirds of patients did not receive any prior line of therapy and pembrolizumab was their first-line therapy for advanced disease [17]. While the EMA approved pembrolizumab as monotherapy for advanced melanoma without any restrictions,

FDA approved pembrolizumab for pretreated patients

the FDA granted marketing authorisation for patients with advanced disease and disease progression following ipilimumab and, if appropriate, a BRAF inhibitor. The approvals are based on different trials: the EMA approval is supported by evidence from KEYNOTE-002, KEYNOTE-006 and KEYNOTE-001 [28]; the FDA only refers to phase II data from the dose-comparison cohort and a subgroup of KEYNOTE-001 [5]. This raises the question whether pembrolizumab should be administered as first- or second-line treatment of advanced melanoma. According to the ESMO [14], the recommendations for the first-line treatment of metastatic melanoma are "under debate". Ipilimumab has been the standard treatment in patients with BRAF wild-type disease; however, the results of KEYNOTE-006 indicate that anti-PD-1 antibody therapy is the preferred first-line treatment for patients with BRAF wild-type disease [17]. However, anti-PD-1 antibody therapies are also recommended as second-line treatment of advanced disease after ipilimumab failure [14]. This recommendation is supported by the results of the KEYNOTE-002 trial [20] where all patients had received prior ipilimumab, and PFS and overall response were improved in patients receiving pembrolizumab compared those who received chemotherapy. Robert et al. [19] showed that pembrolizumab is an effective treatment option in patients who are refractory to ipilimumab, providing an option for patients without other therapeutic options. However, the decision for the appropriate first-line therapy of advanced melanoma patients, regarding the use of either BRAF/MEK combination therapy or a PD-1/PD-L1 antibody is influenced by disease burden, the presence of symptoms and serum lactate dehydrogenase (LDH) until predictive biomarkers (e.g. PD-1 expression on the tumour) are identified and integrated into clinical practice [27].

BRAF V600 mutations

Furthermore, BRAF V600 mutation status needs to be clarified: in the KEYNOTE-006 study, BRAF V600 mutation status (mutations were observed in 36.2% of patients) did not seem to influence the benefit of pembrolizumab over ipilimumab [17]. Results from an expanded access programme with 855 participating patients also suggest the effectiveness and safety of immunotherapy (ipilimumab) in pretreated melanoma patients regardless of their BRAF status [29]. Since vemurafenib (Zelboraf®), a kinase inhibitor, is approved by both the EMA and the FDA for the treatment of BRAF V600 mutation-positive, unresectable or metastatic melanoma [30, 31], it may be an appropriate comparator to pembrolizumab in patients with BRAF V600 mutation. However, the role of BRAF V600 mutation status and the optimal sequence of BRAF/MEK therapy and immunotherapy need to be defined.

identification of biomarkers

With regard to the high costs of available immunotherapeutic agents, it is important to identify predictive biomarkers to select appropriate patients [32]; and it is necessary to explore the use of biomarkers to identify the patients most likely responding to monotherapy [33]. In this context, PD-L1 expression is currently under investigation. Merelli et al. [34] point out that most of the published data regarding PD-L1 expression, variability in the assays, cell immunolocalisation and cut-off values for positive vs. negative PD-L1 immunohistochemical expression are heterogeneous. They also report that PD-L1 expression has been evaluated in primary tumours and metastatic tissue samples but that there is conflicting data concerning the PD-L1 and PD-1 expression in tissues from primary melanomas and respective metastases [34].

treatment costs

An important issue to be discussed are the high costs of immunotherapies, especially considering that not all patients respond to the therapy. According to expert information, pembrolizumab – in clinical practice – is administered for 2 years in patients who respond to the therapy. In the KEYNOTE-006 trial, the longest possible pembrolizumab treatment duration was 2 years [17]. For one year of treatment, the costs of the comparators used in KEYNOTE-006, pembrolizumab and ipilimumab are similar (about € 90,000). However, depending on the treatment duration of pembrolizumab and foremost depending on the actual dosage delivered, the costs for pembrolizumab can be considerably higher.

effective treatment option for ipilimumab-refractory patients

As a large number of patients is refractory to ipilimumab, pembrolizumab offers a new therapeutic option for these patients based on phase II studies. For these patients, chemotherapy is the only currently available option and fewer AEs were observed with pembrolizumab by comparison with chemotherapy. However, for patients who were previously untreated, the situation is less clear, especially since relevant issues including the role of BRAF status und the optimal dosage and schedule of pembrolizumab administration remain unclear. However, phase III long-term data is required to confirm the effectiveness and safety of pembrolizumab. Furthermore, biomarkers must be identified to define the appropriate patient population, not least in light of the high costs of pembrolizumab therapy.

long-term data required

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 2015-10-30]; Available from: http://meka.thl.fi/htacore/model/HTA%20Core%20Model%20for%20Rapid%20REA%20of%20Pharmaceuticals%203.0.pdf.

[2] European Medicines Agency. Keytruda: EPAR – Product Information. [cited 2015-09-03]; 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 2015-09-04]; Available from: http://www.cancer.gov/publications/dictionaries/cancer-drug?CdrID=695789.

[4] U.S. Food and Drug Administration. FDA News Release: FDA approves Keytruda for advanced melanoma. [cited 2015-09-03]; Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm412802.htm.

[5] U.S. Food and Drug Administration. Drugs@FDA. Keytruda. Label information [cited 2015-09-03]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf.

[6] American Cancer Society. Melanoma Skin Cancer Overview. [cited 2015-09-08]; Available from: http://www.cancer.org/cancer/skincancer-melanoma/overviewguide/melanoma-skin-cancer-overview-what-is-melanoma.

[7] National Comprehensive Cancer Network. NCCN Guidelines Version 1.16. Melanoma. [cited 2015-11-02]; Available from: http://www.nccn.org.

[8] Statistik Austria. Malignes Melanom – Krebsinzidenz. [cited 2015-09-08]; Available from: http://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebserkrankungen/haut/021736.html.

[9] International Agency for Research on Cancer. Cancer factsheet. Malignant melanoma of skin. [cited 2015-11-05]; Available from: http://eco.iarc.fr/eucan/Cancer.aspx?Cancer=20 .

[10] Bundesministerium für Gesundheit. Trends der Entwicklung von Krebserkrankungen in Österreich. Eine Prognose bis 2030. [cited 2015-10-19]; Available from: http://bmg.gv.at/cms/home/attachments/0/6/3/CH1480/CMS1422957020341/bericht_krebsprognose_3_2_2015.pdf.

[11] National Cancer Institute. Surveillance, Epidemiology, and End Results Program. SEER Stat Fact Sheets: Melanoma of the Skin. [cited 2015-09-08]; Available from: http://seer.cancer.gov/statfacts/html/melan.html.

[12] American Cancer Society. Cancer Facts & Figures 2015. [cited 2015-09-08]; Available from: http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf.

[13] National Cancer Institute. Melanoma treatment. [cited 2015-11-02]; Available from: http://www.cancer.gov/types/skin/hp/melanoma-treatment-pdq#link/_22_toc.

[14] Dummer R, Hauschild A, Lindenblatt N, Pentheroudakis G, Keilholz U, on behalf of the ESMO Guidelines Committee. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 26 (Supplement 5): v126–v132, 2015 doi:101093/annonc/mdv297. 2015.

[15] National Cancer Institute. A snapshot of melanoma. [cited 2015-09-08]; Available from: http://www.cancer.gov/research/progress/snapshots/melanoma.

[16] National Comprehensive Cancer Network. NCCN Guidelines Version 3.2015. Melanoma. [cited 2015-09-10]; Available from: www.nccn.org.

[17] Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015;372(26):2521-32.

[18] Robert C, et al. Supplementary Appendix. Supplement to: Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015;372:2521-32. DOI: 10.1056/NEJMoa1503093.

[19] Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet. 2014;384(9948):1109-17.

[20] Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol. 2015;16(8):908-18.

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

[22] European Medicines Agency. Yervoy: EPAR – Product Information. [cited 2015-11-02]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002213/human_med_001465.jsp&mid=WC0b01ac058001d124.

[23] Gangadhar TC, Salama AK. Clinical applications of PD-1-based therapy: a focus on pembrolizumab (MK-3475) in the management of melanoma and other tumor types. Onco Targets Ther. 2015;8:929-37.

[24] Hao M, Song F, Du X, Wang G, Yang Y, Chen K, et al. Advances in targeted therapy for unresectable melanoma: New drugs and combinations. Cancer Letters. 2015;359(1):1-8.

[25] Maverakis E, Cornelius LA, Bowen GM, Phan T, Patel FB, Fitzmaurice S, et al. Metastatic melanoma – a review of current and future treatment options. Acta Derm Venereol. 2015;95(5):516-24.

[26] U.S. Food and Drug Administration. Drugs@FDA. Opdivo. Label information. [cited 2015-10-02]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125527s000lbl.pdf.

[27] Sullivan RJ, Flaherty KT. Pembrolizumab for Treatment of Patients with Advanced or Unresectable Melanoma. Clin Cancer Res. 2015;21(13):2892-7.

[28] European Medicines Agency. Keytruda: EPAR – Public assessment report. [cited 2015-10-07]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003820/WC500190992.pdf.

[29] Ascierto PA, Simeone E, Sileni VC, Pigozzo J, Maio M, M A, et al. Clinical experience with ipilimumab 3 mg/kg: real-world efficacy and safety data from an expanded access programme cohort. [cited 2015-09-26]; Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030525/.

[30] European Medicines Agency. Zelboraf: EPAR-Product information. [cited 2015-10-05]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002409/WC500124317.pdf.

[31] U.S. Food and Drug Administration. Drugs@FDA. Zelboraf. Label information. [cited 2015-10-05]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/202429s008lbl.pdf.

[32] Bhatia S, Tykodi SS, Lee SM, Thompson JA. Systemic therapy of metastatic melanoma: on the road to cure. Oncology (Williston). 2015;29(2):126-35.

[33] Martin-Liberal J, Kordbacheh T, Larkin J. Safety of pembrolizumab for the treatment of melanoma. Expert Opin Drug Saf. 2015;14(6):957-64.

[34] Merelli B, Massi D, Cattaneo L, Mandalà M. Targeting the PD1/PD-L1 axis in melanoma: Biological rationale, clinical challenges and opportunities. Critical Reviews in Oncology/Hematology. 2014;89(1):140-65.