Horizon Scanning in Oncology

Ipilimumab (Yervoy®) in the adjuvant therapy for high-risk stage III cutaneous melanoma

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology No. 67
ISSN online 2076-5940

Horizon Scanning in Oncology

Ipilimumab (Yervoy®) in the adjuvant therapy for high-risk stage III cutaneous melanoma

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, March 2017

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft

Author:	Sarah Wolf, MSc
Internal reviewer:	Priv.-Doz. Dr. phil. Claudia Wild
	Nicole Grössmann, MSc
External review:	Univ.-Prof. Dr. Robert Zeiser
	Head of the Section for Tumour Immunology
	Department of Haematology, Oncology and Stem Cell
	University of Freiburg

CONTACT INFORMATION

Publisher:

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

Responsible for Contents:

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

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

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

DSD: Horizon Scanning in Oncology No. 67
ISSN-online: 2076-5940

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

Abstract

Introduction

Melanoma is a malignant tumour derived from neuroectodermal melanomatose cells that primarily involve the skin, referred to as cutaneous melanoma. Recently, ipilimumab (Yervoy®) was approved for the adjuvant treatment of patients with high-risk stage III melanoma by the Food and Drug Administration (FDA) in the U.S. Ipilimumab is a fully human monoclonal immunoglobulin (Ig) G1 antibody that can block the interaction between B7 and CTLA-4 proteins and consequently activates a cytotoxic T-lymphocyte-mediated immune response against cancer cells.

Methodology

On 13 March 2017 a literature search was conducted in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Based on the EUnetHTA internal validity for randomised controlled trials, the methodological quality of the evidence was conducted to assess the risk of bias at the study level. Furthermore, to evaluate the magnitude of clinically meaningful benefit that can be expected from ipilimumab, the original as well as an adapted version of the Magnitude of Clinical Benefit Scale (MCBS) developed by the European Society for Medical Oncology (ESMO) was used.

Results of the EORTC 18071 trial

Between 10 July 2008 and 1 August 2011, 951 patients were randomly assigned to receive either ipilimumab (n = 475) or placebo (n = 476). At a median follow-up of 5.3 years the primary endpoint, recurrence-free survival (RFS) rate at five years, was 40.8% in the ipilimumab group, as compared with 30.3% in the placebo group (hazard ratio for recurrence or death, 0.76; 95% CI, 0.64–0.89; $p < 0.001$). Moreover, the overall survival (OS) rate and the rate of distant metastasis-free survival (DMFS) at five years significantly improved in the ipilimumab group compared to the placebo group. However, there was a 40.0% difference in grade ≥3 immune-related adverse events in the ipilimumab group, and five patients (1.1%) died due to immune-related adverse events before the start of the maintenance therapy. In total, 240 of 471 patients (51.0%) discontinued treatment due to an ipilimumab-induced adverse event. Moreover, no clinically relevant differences in global health status scores were observed during or after induction therapy between the two treatment groups.

Conclusion

Overall, even if the administration of ipilimumab increases the rate of toxicities, no statistically significant differences in health-related quality of life scores between the treatment groups have been observed. In fact, ipilimumab significantly improved the rates of RFS, OS and DMFS at five years. Nevertheless, the identification of predictive biomarkers may be crucial in order to further improve response rates and outcomes, and to reduce severe adverse events. In addition, ongoing studies remain to be seen in order to gain comparable results. Finally, aiming for a reduction of immune therapy costs (annual ipilimumab therapy costs: € 435,850.10) may be a crucial step in the near future.

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.

EUnetHTA HTA Core Model®

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

2 Drug description

Generic/Brand name/ATC code:

Ipilimumab/Yervoy/L01XC11

B0001: What is ipilimumab?

Ipilimumab is a fully human monoclonal immunoglobulin (Ig) G1 antibody that binds to the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Ipilimumab can block the interaction between B7 and CTLA-4 proteins, because natural immune response in the form of a reaction to cancer cells is generated by removing the CTLA-4 inhibitory signal and releasing a brake on the immune system. This process leads to a cytotoxic T-lymphocyte (CTL)-mediated immune response against cancer cells which results in an immune-mediated anti-tumour activity [2-8].

fully human monoclonal Ig G1 antibody against the CTLA-4 protein

The recommended dose of ipilimumab is 10 mg/kg administered intravenously over 90 minutes every three weeks for four times (four doses) as induction therapy followed by 10 mg/kg every 12 weeks for up to three years as maintenance therapy or until disease recurrence, unacceptable level of toxicities, major protocol violation or withdrawal of consent [3, 9].

10 mg/kg every 3 weeks for 4 doses, then every 3 months for up to 3 years

A0022: Who manufactures ipilimumab?

Bristol-Myers Squibb

3 Indication

A0007: What is the target population in this assessment?

Ipilimumab is indicated for the adjuvant therapy in patients with high-risk stage III cutaneous melanoma (CM) after complete regional lymph node dissection (CLND) [3, 9, 10].

adjuvant therapy for high-risk stage III CM

4 Current regulatory status

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

2011: FDA approval for the treatment of metastatic melanoma
2015: FDA approval for adjuvant therapy of high-risk stage III melanoma

In March 2011 ipilimumab was approved by the U.S. Food and Drug Administration (FDA) for the treatment of unresectable or late-stage (metastatic) melanoma. In October 2015 ipilimumab was additionally approved for the adjuvant treatment of patients with high-risk stage III melanoma [9].

2011: EMA approval for metastatic melanoma; no marketing authorisation in Europe for adjuvant therapy of high-risk stage III melanoma

In March 2011 ipilimumab was also approved by the European Medicines Agency (EMA) for the treatment of unresectable or metastatic melanoma in adults who have received prior therapy [11]. However, currently ipilimumab does not have a marketing authorisation in Europe for the adjuvant therapy of patients with high-risk stage III melanoma.

5 Burden of disease

A0002: What is cutaneous melanoma?

CM: malignant tumours derived from neuroectodermal melanomatose cells primarily involved in the skin

various subtypes of CM

Melanoma is a malignant tumour derived from neuroectodermal melanomatose cells that primarily involve the skin, referred to as CM [12, 13]. Furthermore, melanoma cells can also arise in the eyes, meninges and on various mucosal surfaces [14]. There are different subtypes of CM, including superficially spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM) and acral lentiginous melanoma (ALM). In addition, CM can be categorised based on variations in specific genetic alterations, such as non-chronic sun-damage (non-CSD) melanoma, which includes the highest proportion of BRAF mutations compared to other subtypes like chronic sun damage (CSD) melanoma and acral melanoma that mostly appear on the soles, palms, and subungual sites [14-18].

A0004: What is the natural course of melanoma?

stages of melanoma according to TNM and AJCC criteria

Melanoma can be stratified into different disease stages according to the Tumour-Nodes-Metastases (TNM) and the 2009 American Joint Committee on Cancer (AJCC) criteria. Stage I to II includes localised disease with no evidence of metastases, whereas in stage III evidence for nodal and regional disease is given. Stage IV melanoma includes distant-metastasis disease. Detailed information about the different stages and sub-stages is illustrated in Table 1 [14, 16, 17, 19, 20].

Table 1: Disease stages according to TNM and 2009 AJCC criteria

Stage	Primary tumour	Lymph nodes	Distant metastases
0	Tis (melanoma in situ)	No	Mo
IA	T1a: ≤1.0 mm, no ulceration AND <mitosis rate <1/mm²	No	Mo
IB	T1b: ≤1.0 mm, no ulceration OR <mitosis rate <1/mm² T2a: 1.01-2.0 mm no ulceration	No	Mo
IIA	T2b: 1.01-2.0 mm with ulceration T3a: 2.01-4.0 mm no ulceration	No	Mo
IIB	T3b: 2.01-4.0 mm with ulceration T4a: >4 mm no ulceration	No	Mo
IIC	T4b: >4mm with ulceration	No	Mo
IIIA	T1-4a	N1a: 1 LN with micro metastases N2a: 2-3 LN with micro metastases	Mo
IIIB	T1-4a	N1b: 1 LN with macro metastases N2b: 2-3 LN with macro metastases	Mo
	T1-4b	N1a: 1 LN with macro metastases	
	T1-4a/b	N2a: 2-3 LN with macro metastases N2c: in transit-/satellite lesions no LN infestation	
IIIC	T1-4b	N1b: 1 LN with macro metastases N2c: in transit-/satellite lesions no LN infestation	Mo
	all T	N3: ≥4 LN OR satellite lesions OR in transit metastases with LN infestation	
IV	all T	all	M1a: skin subcutaneous OR LN M1b: lung M1c: all other organ metastases OR increased LDH

Abbreviations: AJCC = American Joint Committee on Cancer, LDH = lactate dehydrogenase, LN = lymph nodes, M0 = no distant metastases, N0 = no metastatic nodes, TNM =Tumour Nodus Metastasis

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

evidence of increasing incidence rate of melanoma

Melanoma, also known as malignant melanoma, is a type of skin cancer that is diagnosed increasingly more often than other malignant diseases [14-16, 19]. Particularly in western countries, the incidence rate has been increasing continuously for young adults since 1980 [16, 19]. One reason for this trend might be the climate change. On the one hand, according to the Montreal Protocol heralded by Kofi Annan, ozone depletion has led to an increase in melanoma and it is still rising. On the other hand, owing to global warming, warmer and drier weather encourage people to spend more time outside and therefore increase their exposure to ultraviolet (UV) light, which poses a high risk factor for melanoma. Consequently, there is an increase in the incidence of melanoma owing to behavioural changes caused by climate change [21].

one reason might be the climate change

A0023: How many people belong to the target population?

incidence rate based on the European Standard Population: 21.1 per 100,000 persons/year

median age at diagnosis: 59 years (women) 66 years (men)

Melanoma is the second most common malign tumour for women and men aged between 15 and 39 years in Germany [22]. The age-standardised incidence rate for the European Standard Population (2013) is 21.1 per 100,000 persons per year. In 2014, 1,794 persons were newly diagnosed with melanoma in Austria, of whom approximately 47.9% were women. Moreover, around 91.4% of female melanoma patients and 85.2% of male melanoma patients (all stages included) are alive at least three years after diagnosis [23]. The median age at diagnosis of melanoma is 59 years for women and 66 years for men. The mortality rate increased by 12.0% (women) and 10.0% (men) during the last ten to fifteen years in Austria [19]. Activating mutations of BRAF are found in about 40.0% to 50.0% of patients with melanoma [24].

A0005: What are the symptoms and the burden of cutaneous melanoma?

main symptoms identified with the ABCDE formula

Symptoms of CM can be very heterogeneous. Most often they include a mole that changes in size, shape or colour, has irregular edges or borders, is asymmetrical or ulcerated and that itches, oozes or bleeds [12, 13]. Guidance is given with the ABCDE formula, which is used for the description of suspicious changes of the skin [13, 19]:

- A: asymmetry of the lesion
- B: border irregularities
- C: colour heterogeneity
- D: diameter (higher than 5 mm or dynamics of morphological changes in the tumour)
- E: elevation or evolution (elevation of surface above the level of surrounding epidermis)

A0003: What are the known risk factors for melanoma?

main risk factors: clinically atypical moles or dysplastic nevi, skin type, personal or family history, weak immune system, exposure to UV light and chemicals

Established high risk factors for developing melanoma are multiple clinically atypical moles or dysplastic nevi, the skin type, a personal history of prior melanoma, as well as a positive family history of melanoma, a weak immune system and prior radiation treatment or chemotherapy. Additionally, the mutation of CDK4 genes and a hereditary retinoblastoma with mutation in the RB1 gene is associated with an increased risk of melanoma. Indeed, environmental factors including excessive sun exposure, UV-based artificial tanning and continuous mechanical or chemical irritancy pose high risk factors for melanoma as well [12, 13, 15-17, 19].

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

local diagnosis: skin exam, dermoscopy, excisional biopsy, SLNB, FNA, full body photography, CLSM, MTP

Local diagnosis of CM includes a physical skin exam as well as a dermoscopy, which can identify differentially pigmented lesions. Currently, dermoscopy is the standard method for the clinical differential diagnosis of CM and for qualifying a lesion for excisional biopsy that can bring further information about major risk factors [12]. Moreover, a sentinel lymph node biopsy (SLNB) or a fine needle aspiration (FNA) represents options of CM biopsies. In particular, a SLNB is important to gather prognostic information and identify patients with nodal metastases, who may benefit from immedi-

ate complete lymphadenectomy [18, 25]. Moreover, a full body photography, a confocal laser scanning microscopy (CLSM) or a multiphoton laser tomography (MPT) can be administered in order to clarify CM moles [15, 19].

molecular diagnosis: CGH, FISH

For the molecular diagnosis of CM, a comparative genomic hybridisation (CGH) and a fluorescence in situ hybridisation (FISH) can be determined in order to detect gene mutations [17]. Especially patients with stage IV CM should be screened for BRAF mutations [12, 14, 15].

disease expansion: sonography, X-ray pictures, ultrasound, PETs, CTs, MRI scans, laboratory tests

Owing to the spread of CM (metastatic disease), a sonography of the lymph nodes, X-ray pictures, ultrasound evaluations of the abdomen and the regional lymph nodes, as well as positron emission tomographies (PETs), computer tomographies (CTs) or magnetic resonance imaging (MRI) scans can be administered. In addition, laboratory tests including complete blood counts (CBCs), liver and kidney parameters, electrolytes, alkaline phosphatase, serum protein S100B and LDH give further information about the diagnosis of CM [12, 14, 16, 17, 19, 20].

6 Current treatment

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

factors for treatment decisions

Generally, melanoma can be treated by surgery, radiotherapy and curative adjuvant or palliative therapies. Which treatment strategy is the most suitable for the patient depends on the disease stage (TNM and AJCC criteria), the tumour thickness, the patient's general health, as well as on BRAF and C-KIT mutations.

curative treatment options for stage ≤IV melanoma with solitary metastases

Treatment strategies of stage ≤IV melanoma with solitary metastases have a curative intention. For stage I and IIA melanoma, excision with surgery of the primary tumour including a safety distance, depending on the thickness of the tumour, constitutes the cornerstone of treatment options [17-19, 25, 26]. Particularly for patients with positive SLNB, a complete lymph node dissection (CLND) is recommended [18, 25]. If surgery is not possible due to comorbidity or a cosmetically sensitive tumour location, a topical imiquimod or radiation therapy can be administered, especially in lentigo maligna melanoma [17, 18]. For high-risk stage IIB or IIIA patients, adjuvant immune therapy of interferon alpha or anti-CTLA-4 receptor ipilimumab is given after completed surgery [17, 19, 24, 27-30]. Furthermore, combinations of immune therapies including anti-PD-1/PD-L1 (e.g., pembrolizumab or nivolumab) plus ipilimumab are under investigation [28].

adjuvant treatment options for high-risk stage III melanoma

Commonly, adjuvant treatment strategies for high-risk stage III melanoma can be categorised as followed [17, 24, 29, 31]:

- Local therapy: intralesional injections (talimogene laherparepvec) or laser ablation
- Topical therapies: imiquimod, diphencyprone (DPCP) or radiation therapy

- Regional therapy: isolated limb perfusion (ILP) or isolated limb infusion (ILI) for the administration of cytotoxic chemotherapy, immune therapy with ipilimumab or pembrolizumab, ipilimumab in combination with chemotherapy, like darcabazine, fotemustine or carboplatin/paclitaxel

rehabilitation and follow-up treatment

In fact, surgery or curative adjuvant therapies can cause treatment disorders. Therefore, targeted rehabilitative activities in the somatic and psychosocial area are recommended [19]. Due to the high risk of recurrence, follow-up treatments including physical examination, blood tests, imaging modalities (X-ray, ultrasound, PET/CT, MRI), as well as sonography of the skin and of the lymph nodes, are aimed to improve the prognosis and subsequently prevent recurrence through early detection [19].

7 Evidence

systematic literature search in 5 databases: 234 hints

A literature search was conducted on 13 March 2017 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were “ipilimumab”, “yervoy”, “melanoma”, “adjuvant setting” and “adjuvant therapy”. The manufacturer was also contacted and submitted two references (of which one had already been identified by the literature search). A manual search identified 12 additional references (web documents and journal articles). Overall, 246 references were identified. Included in this report are two publications on the clinical EORTC 18071 trial:

- One publication assessed the efficacy of adjuvant therapy with ipilimumab on all survival endpoints in patients with high-risk stage III CM after CLND [3].
- The other publication assessed secondary outcomes including health-related quality of life (HRQoL) of patients with adjuvant ipilimumab after complete resection of high-risk stage III CM [10].

study level risk of bias assessed based on EUnetHTA internal validity

To assess the risk of bias at the study level, the assessment of the methodological quality of evidence was conducted based on the EUnetHTA internal validity for randomised controlled trials [1]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patient and treating physician, selective outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table 6 of the Appendix.

magnitude of clinically meaningful benefit assessed by the ESMO-MCBS

To evaluate the magnitude of clinically meaningful benefit that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS) was used [32]. Additionally, an adapted version (due to perceived limitations) of the ESMO-MCBS was applied [33]. Further details about the ESMO-MCBS are reported in Table 4.

7.1 Clinical efficacy and safety – phase III studies

EORTC 18071: randomised, double-blind phase III study

EORTC 18071 [3], a randomised double-blind phase III trial, was conducted to assess the efficacy of adjuvant therapy with the human monoclonal antibody ipilimumab on all survival endpoints in patients with high-risk stage III CM after CLND.

10 mg/kg ipilimumab intravenously or placebo

randomisation according to disease stages and geographic regions

A total of 951 patients were enrolled to receive either 10 mg/kg of ipilimumab administered intravenously every three weeks for four times (four doses) as induction therapy, then every 12 weeks for up to three years as maintenance therapy (n = 475) or placebo (n = 476). The randomisation was stratified according to disease stages (stage IIIA vs. stage IIIB vs. stage IIIC with one, two, or three positive nodes vs. stage IIIC with four or more positive nodes) and geographic regions (North America, Europe, or Australia). In order to detect a hazard ratio of 0.76 with a power of 85.0%, a total of 491 deaths would be required. Until now, 506 events of distant metastases or death and 376 deaths have occurred (cut-off date 31 January 2016).

median follow-up duration: 5.3 years; AE-related drug discontinuation: 51.0% ipilimumab group 4.6% placebo group

Four patients in the ipilimumab group and two patients in the placebo group did not start the randomly assigned regimen. The main analyses of the efficacy endpoints include all patients who had undergone randomisation according to the intention-to-treat principle (ipilimumab group: n = 475; placebo group: n = 476). The safety analyses were assessed in patients who had received at least one dose of randomly assigned regimen (n = 471 and n = 474, respectively). Moreover, the overall median follow-up was 5.3 years. Of 471 patients who started ipilimumab, 240 (51.0%) discontinued treatment due to a drug-related adverse event (AE), as compared with 22 of 474 patients (4.6%) of the placebo group who discontinued treatment because of an AE. Overall, a total of 63 patients (13.4%) in the ipilimumab group and 143 patients (30.2%) in the placebo group completed the full treatment period of three years.

median age of 51.5 years

Enrolled patients (~38% women and ~62% men) had a median age of 51.5 years in either treatment group. According to the AJCC criteria, the majority of the patients had stage IIIB (~44%) melanoma in both treatment groups. Detailed patient characteristics with inclusion- and exclusion criteria can be found in Table 5 of the Appendix.

primary endpoint: RFS; main secondary endpoints: OS, DMFS, safety, HRQoL

The primary endpoint of the EORTC 18071 trial was recurrence-free survival (RFS). Secondary outcomes comprised overall survival (OS), distant metastasis-free survival (DMFS), safety and HRQoL.

7.1.1 Clinical efficacy

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

median OS was not reached

Because the number of patients with a follow-up of more than seven years was too small, the estimated median OS was either unreliable or not reached. The OS rate at five years was 65.4% (95% CI 60.8–69.6) in the ipilimumab group, as compared with 54.4% (95% CI 49.7–58.9) in the placebo group. Thus, the OS rate was statistically significantly improved in the

ipilimumab group (hazard ratio for death from any cause, 0.72; 95.1% CI, 0.58–0.88; p = 0.001). Table 2 represents the efficacy of ipilimumab.

D0006: How does ipilimumab affect progression (or recurrence) of cutaneous melanoma?

statistically significant improvement of the 5-year RFS rate

At the time of data cut-off the RFS rate at five years was 40.8% in the ipilimumab group, as compared with 30.3% in the placebo group (hazard ratio for recurrence or death, 0.76; 95% CI, 0.64–0.89; p < 0.001).

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

improved DMFS at 5 years

The rate of DMFS at five years was higher in the ipilimumab group than in the placebo group (48.3% vs. 38.9%; hazard ratio for distant metastasis or death, 0.76; 95.8% CI, 0.64–0.92; p = 0.002).

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

deterioration in fatigue, insomnia and diarrhoea

Patients receiving ipilimumab showed negative effects on fatigue, insomnia and diarrhoea at week 10 during induction therapy, compared to patients who received a placebo [10].

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

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

no clinically relevant difference in global HRQoL scores between the treatment groups

Patients' mean global health scores during (77.32 [SD 17.36] vs. 72.96 [17.82]; p = 0.00011) and after induction therapy (76.48 [17.52] vs. 72.32 [18.60]; p = 0.00067) were statistically significantly different between the treatment groups, but were not defined as clinically relevant (10 points or more). However, differences in the mean HRQoL score were clinically relevant at week 10 and showed worse HRQoL scores for diarrhoea (7.67 [17.05] vs. 18.17 [28.25]) and for insomnia (15.17 [22.53] vs. 25.60 [29.19]) for the patients receiving ipilimumab. Overall, HRQoL measured by the EORTC QLQ-C30 was similar between the treatment groups, as no clinically relevant differences in global health status scores were observed during or after induction of therapy [10].

Table 2: Efficacy results of EORTC 18071 trial

Descriptive statistics and estimate variability (data cut-off 31st January 2016)	**Treatment group**	**Ipilimumab**	**Placebo**
	Number of subjects	475	476
	Median OS, months	NA	NA
	OS rate at 5 years, %, (95% CI)	65.4 (60.8–69.6)	54.4 (49.7–58.9)
	Median PFS, months	NA	NA
	RFS rate at 5 years,%	40.8	30.3
	DMFS rate at 5 years, %	48.3	38.9
	HRQoL, global health scores during induction therapy, (SD)	77.32 (17.36)	72.96 (17.82)
	HRQoL, global health scores after induction therapy, (SD)	76.48 (17.52)	72.32 (18.60)
Effect estimate per comparison	**Comparison groups**		**Ipilimumab vs. placebo**
	OS rate at 5 years	HR	0.72
		95.1% CI	0.58–0.88
		Two-sided log-rank test p value	p = 0.001
	RFS rate at 5 years	HR	0.76
		95% CI	0.64–0.89
		Two-sided log-rank test p value	p < 0.001
	DMFS rate at 5 years	HR	0.76
		95.8% CI	0.64–0.92
		Two-sided log-rank test p value	p = 0.002
	HRQoL during induction therapy	Two-sided log-rank test p value	p = 0.00011
	HRQoL after induction therapy	Two-sided log-rank test p value	p = 0.00067

Abbreviations: CI = confidence interval, DMFS = distant metastatic-free survival, HR = hazard ratio, HRQoL = health-related quality of life, NA = not applicable, OS = overall survival, PFS = progression-free survival, RFS = recurrence-free survival, SD = standard deviation

7.1.2 Safety

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

471 patients in the ipilimumab group and 474 patients in the placebo group were included in the safety population. AEs of any grade occurred in 465 patients (98.7%) of the ipilimumab group, with grade ≥3 AEs occurring in 225 patients (54.1%). In contrast, 432 patients (91.1%) of the placebo group had an AE of any grade, with grade ≥3 AEs occurring in 124 patients (26.2%). In fact, immune-related AEs of grade ≥3 occurred in 41.6% and in 2.7% of the patients, respectively. In the ipilimumab group the most common grade ≥3 immune-related AEs were gastrointestinal (16.8%), hepatic (10.9%) and endocrine (7.8%). Five patients (1.1%) died due to ipilimumab-induced AEs

grade ≥3 immune-related AEs in 41.6%
most commonly including:
gastrointestinal (16.8%)
hepatic (10.9%)
endocrine (7.8%)

5 AE-related deaths

before the start of the maintenance therapy. Three of these five patients died from colitis (two with intestinal perforation), one patient from myocarditis and one patient from multi-organ failure associated with the Guillain-Barré-Syndrome. All treatment-emergent AEs are illustrated in Table 3.

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

53.3% of the patients receiving ipilimumab discontinued treatment due to an AE; in 51.0% discontinuation was related to ipilimumab administration

In total, 251 of the 471 patients (53.3%) who started ipilimumab treatment discontinued treatment due to an AE. In 240 of the 471 patients (51.0%), the event was considered to be related to ipilimumab administration. In contrast, 22 of 474 patients (4.6%) of the placebo group discontinued treatment owing to an AE. Furthermore, 135 patients (28.7%) and 282 patients (59.5%) in the ipilimumab group and in the placebo group, respectively, discontinued treatment because of disease recurrence. Overall, 63 patients (13.4%) in the ipilimumab group and 143 (30.2%) in the placebo group completed the full three-year treatment period.

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

susceptible patient groups

Patients with an Eastern Cooperative Oncology Group (ECOG) performance-status score of more than 1 indicating greater disability, an autoimmune disease, uncontrolled infection, substantial cardiovascular disease, a lactate dehydrogenase level of more than two times the upper limit of the normal range, and patients who made use of systemic glucocorticoids are more likely to be harmed through the administration of ipilimumab. Hence, these patients were excluded from the study.

Table 3: Most frequent adverse events

Adverse event (according to CTCAE version 3.0)	**Ipilimumab** (n = 471)			**Placebo** (n = 474)		
	Any grade n (%)	Grade 3–4 n (%)	Grade 5 n (%)	Any grade n (%)	Grade 3–4 n (%)	Grade 5 n (%)
Any immune-related adverse event	426 (90.4)	196 (41.6)	5 (1.1)	188 (39.7)	13 (2.7)	0
Any dermatological event	298 (63.3)	20 (4.2)	0	99 (20.9)	0	0
Rash	161 (34.2)	5 (1.1)	0	52 (11.0)	0	0
Any gastrointestinal event	217 (46.1)	76 (16.2)	3 (0.6)	85 (17.9)	4 (0.8)	0
Diarrhoea	194 (41.2)	46 (9.8)	0	80 (16.9)	2 (0.4)	0
Colitis	73 (15.5)	36 (7.6)	3 (0.6)	7 (1.5)	2 (0.4)	0
Any endocrine system event	178 (37.8)	37 (7.8)	0	38 (8.0)	1 (0.2)	0
Hypophysitis	77 (16.3)	21 (4.4)	0	1 (0.2)	0	0
Any hepatic event	115 (24.4)	51 (10.9)	0	20 (4.2)	1 (0.2)	0
Increase in liver enzyme levels	83 (17.6)	20 (4.3)	0	18 (3.8)	0	0
Any neurological event	21 (4.5)	9 (1.9)	0	9 (1.9)	0	0
Other	111 (23.6)	36 (7.6)	2 (0.4)	23 (4.9)	8 (1.7)	0

CTCAE = Common Terminology Criteria for Adverse Events

7.2 Clinical effectiveness and safety – further studies

No further study results on ipilimumab from phase II/III trials in the reviewed indication, including adjuvant therapy in patients with high-risk stage III CM after CLND, are available yet.

no further study results of phase II/III trials available yet

8 Estimated costs

A0021: What is the reimbursement status of ipilimumab?

Ipilimumab is available as 0.3, 3 and 10 mg/kg intravenous doses. At the recommended dose of 10 mg/kg every three weeks four times (four doses) (induction therapy), and thereafter every three months for up to three years (maintenance therapy), ipilimumab costs approximately € 62,264.30 per 21-day cycle, assuming an average body weight of 70 kg. Therefore, the costs are € 249,057.20 and € 435,850.10 for the induction therapy and for a one-year treatment cycle, respectively.

€ 62,264.30 per 21-day cycle

€ 435,850.10 per year

9 Ongoing research

3 ongoing phase III studies are investigating ipilimumab in patients with high-risk stage III melanoma after CLND

In March 2017 a search in the databases www.clinicaltrials.gov and www.chlinicaltrialsregister.com was conducted. The following three ongoing phase III trials are investigating ipilimumab in patients with high-risk stage III melanoma after CLND:

- NCT02506153: A randomised phase III clinical trial is comparing high-dose recombinant interferon alfa-2B or ipilimumab to pembrolizumab in high risk patients with stage III-IV melanoma that has been removed by surgery. Estimated primary completion date is June 2020.

- NCT02388906: A randomised, placebo-controlled, double-blind phase III study is comparing nivolumab to ipilimumab in high risk patients with stage IIIB/C-IV melanoma that has been removed by surgery. Estimated primary completion date is November 2018 [34].

- NCT01274338: A randomised phase III trial is comparing ipilimumab to high-dose interferon alfa-2b in treating high risk patients with stage III-IV melanoma that has been removed by surgery. Estimated primary completion date is May 2018 [35].

5 ongoing phase III studies in different treatment lines and regimes

ipilimumab investigated in other indications

Currently, five additional studies are ongoing in different treatment lines and regimens in patients after complete resection with stage IIIB/C or stage IV melanoma (NCT03068455, NCT02599402, NCT02905266, NCT02278887, NCT02224781). Besides, ipilimumab is also being investigated for other indications like non-small cell lung cancer (NSCLC), squamous cell lung cancer, stomach cancer, renal cell cancer, urothelial cancer and squamous cell carcinoma of the head and neck.

10 Discussion

2015: U.S. approval for adjuvant treatment in high-risk stage III melanoma

In March 2011 the anti-CTLA-4 receptor ipilimumab was approved by the FDA and by the EMA for the treatment of unresectable or late-stage (metastatic) melanoma in adults who have received prior therapy [9, 11]. For the adjuvant treatment in patients with high-risk stage III melanoma, ipilimumab is only approved in the U.S. (October 2015), but not yet in Europe [9].

The randomised, double-blind, phase III study EORTC 18071 was aimed to assess the efficacy of adjuvant therapy with the human monoclonal antibody ipilimumab on all survival endpoints in patients with high-risk stage III CM after CLND. Owing to the fact that the number of patients with a follow-up of more than seven years was too small, the estimated median OS was either unreliable or not reached. Additionally, no data on PFS were available. However, ipilimumab monotherapy showed a significant improvement in the primary endpoint, the RFS rate at five years by 10.5% compared to the placebo group (hazard ratio for recurrence or death, 0.76; 95% CI, 0.64–0.89; $p < 0.001$). Moreover, the OS rate and the rate of DMFS at five years both statistically significantly improved by 11.0% and 9.4%, respectively, in the ipilimumab group (hazard ratio for death from any cause, 0.72; 95.1% CI, 0.58–0.88; $p = 0.001$, and hazard ratio for distant metastases or death, 0.76; 95.8% CI, 0.64–0.92; $p = 0.002$, respectively). In total, 240 of the 471 patients (51.0%) discontinued treatment due to an ipilimumab-induced adverse event. Furthermore, global HRQoL measured by the EORTC QLQ-C30 was similar between the two treatment groups, as no clinically relevant differences in global health status scores were observed during or after the induction of ipilimumab treatment [10]. However, the validity of these scores might be weak owing to the high discontinuation rate in the study. In fact, compliance with completing the HRQoL questionnaire was 893 (94.0%) of 951 patients at baseline, 693 (75.0%) of 924 at week 24, and 354 (51.0%) of 697 at week 108.

no OS and PFS data available

significantly improved RFS, OS and DMFS rates at 5 years in the ipilimumab group

51.0% of the patients discontinued therapy due to ipilimumab-related AE

no significant difference in HRQoL between treatment groups

Regarding the safety outcomes, 465 patients (98.7%) who received ipilimumab had all grade AEs, with grade ≥3 AEs occurring in 225 patients (54.1%). In contrast, 432 patients (91.1%) of the placebo group had an AE of any grade, with grade ≥3 AEs occurring in 124 patients (26.2%). In fact, there was a difference of 40.0% in grade ≥3 immune-related AEs between the treatment groups, including gastrointestinal (16.8% ipilimumab group vs. 0.8% placebo group), hepatic (10.9% vs. 0.2%) and endocrine (7.8% vs. 0.2) AEs. Additionally, five patients (1.1%) died due to ipilimumab-induced AEs before the start of the maintenance therapy.

significantly increased AEs;
most common grade ≥3 immune-related AEs: gastrointestinal, hepatic, endocrine;

5 AE-related deaths

In general, the study had a low risk of bias according to the assessment of the methodological quality of evidence based on the EUnetHTA internal validity for randomised controlled trials, as the allocation concealment was adequate, the study was double-blinded, and selective outcome reporting was unlikely.

low risk of bias of the EORTC 18071 study

Given the adjuvant therapy setting of ipilimumab, we applied Form 1 of the ESMO-MCBS in order to assess whether ipilimumab satisfies the criteria for a "meaningful clinical benefit" (score A or B). Both the original as well as the adapted version of the MCBS were applied [32, 33]. Because the endpoints disease-free survival (DFS) and RFS do not differ in their definitions, we used the primary endpoint RFS to generate a score. The application of the ESMO-MCBS to the EORTC 18071 study resulted in a grade A and C in the original and the adapted version of the ESMO-MCBS, respectively. Therefore, ipilimumab only leads to a meaningful clinical benefit in the original scale, but not in the adapted framework. This difference occurs due to the use of the point estimate of the HR and the higher implication of toxicities in the adapted ESMO-MCBS.

ESMO-MCBS:
grade A in the original scale
grade C in the adapted framework

improved efficacy of ipilimumab at the cost of higher toxicity profile

Various studies have shown that immune therapies, especially ipilimumab, have been praised because of their improved impact on survival rates in advanced stages of melanoma, albeit at the cost of a higher frequency of toxic effects. Most commonly these effects include gastrointestinal disturbances, which in a few cases even led to death [36-39]. These findings were in line with the EORTC 18071 trial results presenting a difference in grade ≥3 immune-related AEs of 40.0% and five drug-related deaths in the ipilimumab group. Nevertheless, Bouwhuis et al. showed that these autoimmunity- and immune-related AEs were associated with response to ipilimumab and favourable outcomes [37]. However, the success of ipilimumab is dependent partly on the patient's immune system, as well as on his/her ability to generate an active, tumour-specific response. Additionally, psychological stress factors, such as financial-, familial-, and sleep-related problems, which are likely to occur after the diagnosis of melanoma, are known to alter hormone levels and are deemed to affect both innate and adoptive immune response pathways. Therefore, these factors need to be considered during the management of melanoma with immune-based drugs [36].

responsiveness of ipilimumab is influenced by several factors

long-term consequences of ipilimumab administration in survivors

Given the fact that the half-life of ipilimumab is 15 days, a prolonged activity can be expected [40]. Indeed, Johnson et al. investigated chronic immune toxicities and health outcomes of long-term survivors who received ipilimumab approximately two years ago [39]. Few patients suffered from ipilimumab-associated chronic toxicities after two years of administration, including colitis, hypophysitis, pruritus, skin rashes and neurological events (e.g., memory loss). Moreover, no other AEs like cardiac, pulmonary, renal, hematologic, neoplastic or hepatic events were observed in most of the patients. Overall, ipilimumab was associated with good functional outcomes in patients with extended survival with only a few exceptions [39]. Nevertheless, only a subset of melanoma patients with advanced or metastatic disease still seems to generally benefit from the therapy. Hence, predictive biomarkers identifying these patients need to be investigated in order to further improve response rates and outcomes, as well as to spare patients the increased risk of severe AEs [28, 37].

predictive biomarkers to improve response rates, outcomes and to reduce the risk of severe AEs

improved efficacy with both ipilimumab and interferon alpha

Long-term effects of ipilimumab have shown to be sound in most cases [39]. On top of ipilimumab, both high-dose interferon alpha-2b and pegylated interferon alpha-2b have also demonstrated significantly improved relapse-free-, disease-free- and overall survival in randomised clinical trials for adjuvant systemic therapy in high-risk CM [41]. Currently, an ongoing study (ECOG E-1609) is investigating ipilimumab compared to high-dose interferon alfa-2b in treating patients with high-risk stage III-IV melanoma that have been removed by surgery [35]. These results should give further implications about which therapy patients benefit the most, since ipilimumab is only compared to placebo and not to the standard therapy, interferon alpha, in this indication. Furthermore, combining CTLA-4 receptors and PD-1 blockades could result in increased anti-tumour activity compared to either strategy alone. In fact, the combination of ipilimumab and nivolumab increased the degree of tumour response and was associated with greater numbers of effector T cells of CM. The results from two studies, Checkmate-067 and -069, confirmed this, however, at the cost of clearly increased severe treatment-related AEs. Therefore, once more predictive biomarkers will likely be needed to identify patients who will require combination treatment regimens despite the higher toxicity rates in order to maximise anti-tumour responses [28]. Moreover, several ongoing studies are investigating ipilimumab in combination with radiotherapy for melanoma, as there might be a

possible improved outcomes due to combination therapy at the cost of increased severe AEs

predictive biomarkers may be crucial for combination treatments

synergy of cancer immunotherapy and radiotherapy [42]. Therefore, ongoing studies remain to be seen in order to possess comparable results.

costs of immune therapies huge barrier

One of the biggest hurdles of immune-based therapies is the cost [36]. At the recommended dose of 10 mg/kg every three weeks for four times (four doses) (induction therapy) and thereafter every three months for up to three years (maintenance therapy), ipilimumab costs approximately € 435,850.10 per year (induction: € 249,057.20 + maintenance: € 186,792.90). Moreover, the high percentage of severe immune-related AEs, as well as long-term consequences due to ipilimumab administration, lead to additional costs in the present, as well as in the future. Therefore, it is crucial to make immune therapies like ipilimumab more affordable by decreasing the costs of immune-based treatment approaches [36, 39].

€ 435,850.10 per year

increased toxicity rates, but maintained HRQoL

improved efficacy outcomes

identify predictive biomarkers and reduce immune therapy costs

Overall, even if the administration of ipilimumab increases the rate of toxicities, no statistically significant differences in HRQoL between the treatment groups have been investigated. However, these results should be seen with caution because of the high discontinuation rate. In fact, ipilimumab statistically significantly improved the RFS rate by 10.5% compared to the placebo group. Additionally, the OS rate and the rate of DMFS at five years statistically significantly increased. In long-term survivors, too, ipilimumab was associated with good functional outcomes with only a few exceptions. Nevertheless, the identification of predictive biomarkers may be crucial in order to further improve response rates and outcomes, and to reduce severe AEs. In addition, ongoing studies remain to be seen in order to possess comparable results. Finally, the costs of the immune therapies are a big hurdle, partly because AEs and long-term consequences can lead to additional costs. Hence, aiming for a reduction of immune therapy costs (annual ipilimumab therapy costs: € 435,850.10) may be a crucial step in the near future.

Table 4: Benefit assessment based on original ESMO-MCBS and adapted benefit assessment based on adapted ESMO-MCBS [34, 35]

ESMO-MCBS	Active substance	Indication	Intention	PE	Form	Efficacy				Safety		AJ	FM
						RFS rate	*HR (95% CI)*	*Score calculation*	*PM*	*Toxicity*	*QoL*		
adapted ESMO-MCBS	ipilimumab	stage III CM	adjuvant therapy	RFS	1	intervention: 40.8% control: 30.3%	0.76 0.64-0.89	improvement in RFS alone: HR 0.65–0.80, without mature OS data	B	+86.7% grade 3–4 AEs (-1)[1]	ND	-1	C
ESMO-MCBS	ipilimumab	stage III CM	adjuvant therapy	RFS	1	intervention: 40.8% control: 30.3%	0.76 0.64–0.89	improvement in RFS alone: HR <0.65, without mature OS data	A	+86.7% grade 3–4 AEs	ND	-	A

Abbreviations: AJ = Adjustments, CM = cutaneous melanoma, FM = final adjusted magnitude of clinical benefit grade, HR = hazard ratio, m = months, MG = median gain, ND = no difference, PE = primary endpoint, PM = preliminary magnitude of clinical benefit grade, QoL = quality of life, RFS = recurrence-free survival

DISCLAIMER

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

[1] One level downgrade because >10% grade ≥3 adverse events.

References

[1] European Network for Health Technology Assessment (eunethta). HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals (Version 3.0). 2013.

[2] Ascierto PA, Marincola FM, Ribas A. Anti-CTLA4 monoclonal antibodies: The past and the future in clinical application. Journal of Translational Medicine. 2011;9(1).

[3] Eggermont AM, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, Schmidt H, et al. Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. New England Journal of Medicine. 2016;375(19):1845-55.

[4] Eggermont AM, Testori A, Maio M, Robert C. Anti-CTLA-4 antibody adjuvant therapy in melanoma. Seminars in oncology. 2010;37(5):455-9.

[5] Graziani G, Tentori L, Navarra P. Ipilimumab: A novel immunostimulatory monoclonal antibody for the treatment of cancer. Pharmacological research. 2012;65(1):9-22.

[6] Trinh VA, Hagen B. Ipilimumab for advanced melanoma: A pharmacologic perspective. Journal of Oncology Pharmacy Practice. 2013;19(3):195-201.

[7] Natonal Cancer Institute (NIH). Ipilimumab. 2017 [2017/16/03]; Available from: https://ncit.nci.nih.gov/ncitbrowser/pages/message.jsf.

[8] Callahan MK, Postow MA, Wolchok JD. Immunomodulatory therapy for melanoma: Ipilimumab and beyond. Clinics in dermatology. 2013;31(2):191-9.

[9] U.S. Food and Drug Administration (FDA). Label information Yervoy. 2017 [2017/16/03]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125377s073lbl.pdf.

[10] Coens C, Suciu S, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, et al. Health-related quality of life with adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): secondary outcomes of a multinational, randomised, double-blind, phase 3 trial. The Lancet Oncology. 2017;18(3):393-403.

[11] European Mecicines Agency (EMA). Medicines. [2017/16/03]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp.

[12] Rutkowski P, Wysocki PJ, Nowecki ZI, Rudnicka L, Nasierowska-Guttmejer A, Fijuth J, et al. Recommendations for diagnostics and therapy of cutaneous melanoma. Nowotwory. 2013;63(2):157-70.

[13] National Cancer Institute (NIH). Skin Cancer. 2017 [2017/17/03]; Available from: https://www.cancer.gov/types/skin.

[14] Garbe C, Peris K, Hauschild A, Saiag P, Middleton M, Spatz A, et al. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline-Update 2012. European journal of cancer (Oxford, England : 1990).48(15):2375-90.

[15] Eggermont AM, Spatz A, Robert C. Cutaneous melanoma. Lancet (London, England). 2014;383(9919):816-27.

[16] Davar D, Kirkwood JM. Adjuvant Therapy of Melanoma. Cancer treatment and research. 2016;167:181-208.

[17] National Comprehensive Cancer Network (NCCN). NCCN Guidelines Version 1.2017 Staging Melanoma. 2017 [2017/17/03]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf.

[18] Dummer R, Siano M, Hunger RE, Lindenblatt N, Braun R, Michielin O, et al. The updated Swiss guidelines 2016 for the treatment and follow-up of cutaneous melanoma. Swiss medical weekly. 2016;146:14279.

[19] Keilholz U, Brossart P, Mackensen A, Peschel C, Pritzkuleit R, Schadendorf D, et al. Melanom. 2014 [2017/17/03]; Available from: https://www.onkopedia.com/de/onkopedia/guidelines/melanom/@@view/html/index.html.

[20] Pflugfelder A, Kochs C, Blum A, Capellaro M, Czeschik C, Dettenborn T, et al. Malignant melanoma S3-guideline "diagnosis, therapy and follow-up of melanoma". Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG. 2013;11 Suppl 6:1-116, 1-26.

[21] Bharath AJ, Turner RJ. Impact of climate change on skin cancer. JRSM Journal of the Royal Society of Medicine. 2009;102(6):215–8.

[22] Hilgendorf I, Borchmann P, Engel J, Heußner P, Katalinic A, Neubauer A, et al. Adolescents and Young Adults (AYA). 2016 [2017/10/04]; Available from: https://www.onkopedia.com/de/onkopedian/guidelines/heranwachsende-und-junge-erwachsene-aya-adolescents-and-young-adults/@@view/html/index.html.

[23] Statistik Austria. Krebserkrankungen - Haut. 2017 [2017/10/01]; Available from: http://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebserkrankungen/haut/index.html.

[24] Tarhini AA, Thalanayar PM. Adjuvant Therapy for High-Risk Melanoma. Hematology/oncology clinics of North America. 2014;28(3):471-89.

[25] van Akkooi AC, Atkins MB, Agarwala SS, Lorigan P. Surgical Management and Adjuvant Therapy for High-Risk and Metastatic Melanoma. American Society of Clinical Oncology educational book American Society of Clinical Oncology Meeting. 2016;35:e505-14.

[26] Zeijl MCT, Eertwegh AJ, Haanen JB, Wouters M. (Neo)adjuvant systemic therapy for melanoma. European Journal of Surgical Oncology. 2017;43(3):534-43.

[27] Palumbo G, Di Lorenzo G, Ottaviano M, Damiano V. The future of melanoma therapy: Developing new drugs and improving the use of old ones. Future oncology (London, England). 2016;12(22):2531-4.

[28] Redman JM, Gibney GT, Atkins MB. Advances in immunotherapy for melanoma. BMC medicine. 2016;14:20.

[29] Thalanayar PM, Agarwala SS, Tarhini AA. Melanoma adjuvant therapy. Chinese clinical oncology. 2014;3(3):26.

[30] Weise AM, Flaherty LE. New Options for the Adjuvant Treatment of Cutaneous Melanoma? Current oncology reports. 2014;16(11):1-6.

[31] Eggermont AM, Maio M, Robert C. Immune checkpoint inhibitors in melanoma provide the cornerstones for curative therapies. Seminars in oncology. 2015;42(3):429-35.

[32] Cherny NI, Sullivan R, Dafni U, Kerst JM, Sobrero A, Zielinski C, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Annals of Oncology. 2015;26(8):1547-73.

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

[34] Weber J, Grob JJ, Margolin KA, Ascierto PA, Sznol M, Ott PA, et al. A Phase III study (CheckMate 238) of adjuvant immunotherapy with nivolumab (NIVO) versus ipilimumab (IPI) after complete resection of stage IIIb/c or stage IV melanoma (MEL) in patients (pts) at high risk for recurrence. Journal for

ImmunoTherapy of Cancer [Internet]. 2015. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/991/CN-01162991/frame.html.

[35] Minutilli E, Feliciani C. Adjuvant therapy for resected stage III melanoma patients: High-dose interferon-alpha versus ipilimumab combined with kinases inhibitors. Tumori. 2012;98(2):185-90.

[36] Rotte A, Bhandaru M, Zhou Y, McElwee KJ. Immunotherapy of melanoma: present options and future promises. Cancer metastasis reviews. 2015;34(1):115-28.

[37] Bouwhuis MG, Ten Hagen TLM, Suciu S, Eggermont AM. Autoimmunity and treatment outcome in melanoma. Current Opinion in Oncology. 2011;23(2):170-6.

[38] Ianiro G, Gasbarrini A, Cammarota G. Ipilimumab adjuvant therapy in melanoma. New England Journal of Medicine. 2017;376(4):398.

[39] Johnson DB, Friedman DL, Berry E, Decker I, Ye F, Zhao S, et al. Survivorship in immune therapy: Assessing chronic immune toxicities, health outcomes, and functional status among long-term ipilimumab survivors at a single referral center. Cancer immunology research. 2015;3(5):464-9.

[40] Burdine L, Lai K, Laryea JA. Ipilimumab-induced colonic perforation. Journal of surgical case reports. 2014;2014(3).

[41] Mocellin S, Lens MB, Pasquali S, Pilati P, Chiarion SV. Interferon alpha for the adjuvant treatment of cutaneous melanoma. 2013(6).

[42] Mansfield AS, Park SS, Dong H. Synergy of cancer immunotherapy and radiotherapy. Aging (Albany NY). 2015.

[43] European Network for Health Technology Assessment (eunethta). Internal validity of randomized controlled trials 2013.

11 Appendix

Table 5: Characteristics of EORTC 18071 trial

Title: Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy			
Study identifier	*NCT00636168, EudraCT 2007-001974-10, EORTC 18071*		
Design	Randomised, double-blind, multinational, phase III trial		
	Duration of main phase:		10 July 2008 to 1 August 2011 + median follow-up of 5.3 years
	Duration of Run-in phase:		NA
	Duration of Extension phase:		NA
Hypothesis	Superiority The study was designed to assess the efficacy of adjuvant therapy with the human monoclonal antibody ipilimumab on all survival endpoints in patients with high-risk stage III CM after CLND. Prespecified criteria for superiority required a total of 491 deaths in order to detect a hazard ratio of 0.76 with a power of 85.0%.		
Funding	Bristol-Myers Squibb		
Treatments groups	Ipilimumab group (n = 475)		10 mg/kg (intravenously) every three weeks for four doses, then every 12 weeks of up to three years
	Placebo group (n = 476)		10 mg/kg (intravenously) every three weeks for four doses, then every 12 weeks of up to three years
Endpoints and definitions	Recurrence-free survival	RFS	The time from randomisation until the date of first recurrence (local, regional or distant metastasis) or death from any cause
	Overall survival	OS	The time from randomisation until death from any cause
	Distant metastasis-free survival	DMFS	The time from randomisation until the date of the first distant metastasis or death from any cause
	Health-related quality of life	HRQoL	-
Database lock	Last verified: June 2016		
Results and analysis			
Analysis description	**Primary Analysis** Data were collected and computerised at the EORTC headquarters. The trial was conducted in accordance with the Declaration of Helsinki and with Good Clinical Practice guidelines as defined by the International Conference on Harmonisation. All patients provided written informed consent. A total of 491 deaths were required in order to provide the trial with 85.0% power to detect a superiority of ipilimumab, corresponding to a hazard ratio for death of 0.76. Efficacy analyses (primary and secondary endpoints) were performed in the intention-to-treat population, which was defined as all randomly assigned patients. The safety profile was assessed in patients who have received at least one dose of the randomly assigned regimen. Given the 506 events of distant metastasis or death and 376 deaths at the clinical cut-off date, it was computed (with the use of a Lan-DeMets Alpha-Spending Function) that the final analyses of OS and DMFS is performed at two-sided alpha levels of 0.049 and 0.042, respectively, so the confidence interval for the hazard ratio of the group comparison regarding these endpoints was set at 95.1% and 95.8%, respectively; the statistical power was 75.8% and 89.4%, respectively.		

Title: Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy			
Study identifier	*NCT00636168, EudraCT 2007-001974-10, EORTC 18071*		
Analysis population	Inclusion	❁ minimum age of 18 years ❁ histologically confirmed CM that was metastatic to regional lymph nodes ❁ stage IIIA melanoma according to AJCC 2009 classification ❁ patients with N1a cancer need at least one metastasis measuring >1 mm in the greatest dimension ❁ stage IIIB or IIIC CM with no in-transit metastases according to AJCC 2009 classification ❁ complete regional lymphadenectomy within 12 weeks before randomisation	
	Exclusion	❁ ECOG performance-status score of more than 1 ❁ autoimmune disease ❁ uncontrolled infection ❁ substantial cardiovascular disease (New York Heart Association functional class III or IV) ❁ lactate dehydrogenase level of more than two times the upper limit of the normal range ❁ use of systemic glucocorticoids ❁ previous systemic therapy for CM	
	Characteristics	Ipilimumab	Placebo
	Sex, no. (%)		
	Male	296 (62.3)	293 (61.6)
	Female	179 (37.7)	183 (38.4)
	Median age, years (range)	51 (20-84)	52 (18-78)
	Distribution, no (%)		
	<50 years	214 (45.1)	211 (44.3)
	51 to <65 years	180 (37.9)	178 (37.4)
	≥65 years	81 (17.1)	87 (18.3)
	Disease stage, no. (%)		
	At randomisation		
	IIIA	98 (20.6)	88 (18.5)
	IIIB	182 (38.3)	182 (38.2)
	IIIC with 1-3 positive lymph nodes	122 (25.7)	121 (25.4)
	IIIC with ≥4 positive lymph nodes	73 (15.4)	75 (15.8)
	According to AJCC 2002 criteria		
	IIIA	98 (20.6)	88 (18.5)
	IIIB	213 (44.8)	207 (43.5)
	IIIC with 1-3 positive lymph nodes	69 (14.5)	83 (17.4)
	IIIC with ≥4 positive lymph nodes	95 (20.0)	98 (20.6)

Title: Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy			
Study identifier	*NCT00636168, EudraCT 2007-001974-10, EORTC 18071*		
	Type of lymph-node involvement, no. (%)		
	Microscopic	210 (44.2)	193 (40.5)
	Macroscopic	265 (55.8)	283 (59.5)
	No. of positive lymph nodes on pathological testing, no. (%)		
	1	217 (45.7)	220 (46.2)
	2 or 3	163 (34.3)	158 (33.2)
	≥4	95 (20.0)	98 (20.6)
	Ulceration, no. (%)		
	Yes	197 (41.5)	203 (42.6)
	No	257 (54.1)	244 (51.3)
	Unknown	21 (4.4)	29 (6.1)

Abbreviations: AJCC = American Joint Committee on Cancer, CLND = complete lymph node dissection, CM = cutaneous melanoma, DMFS = distant metastasis-free survival, ECOG = Eastern Cooperative Oncology Group, HRQoL = health-related quality of life, OS = overall survival, RFS = recurrence-free survival

Table 6: Risk of bias assessment on study level based on EUnetHTA (Internal validity of randomised controlled trials) [43]

Criteria for judging risk of bias		**Risk of bias**
Adequate generation of randomisation sequence: randomisation stratified according to disease stages and geographic regions		unclear
Adequate allocation concealment: centrally interactive voice-response system		yes
Blinding: double-blinded	**Patient**	yes
	Treating physician	yes
Selective outcome reporting unlikely		yes
No other aspects which increase the risk of bias: industry funded		no
Risk of bias – study level		low