IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A12-07

Ipilimumab –

Benefit assessment according to § 35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment ("Ipilimumab – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 27.04.2012). In the present extract, references to Sections 2.7 onwards relate to the full version of the assessment report (hereinafter called the "full dossier assessment"). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Table of contents

List of tables[3]

[3] Table numbers start with “2” as numbering in extract follows that of the full version.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IL-2	interleukin-2
IPI	ipilimumab
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDH	lactate dehydrogenase
M stage	metastasis stage
QLQ-C30	Quality of Life Questionnaire C30
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2. Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book V (SGB), the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ipilimumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 01.02.2012.

Research question

The aim of this report was to assess the added benefit of ipilimumab compared to *best supportive care* (BSC) as appropriate comparator therapy (ACT) in adult patients with advanced (unresectable or metastatic) melanoma, who have received prior therapy.

Given the current therapy situation, all patients need to be treated with *best supportive care*. Studies were therefore included in the benefit assessment that compared ipilimumab in combination with *best supportive care* with treatment consisting of *best supportive care* alone. If available, studies in which ipilimumab as monotherapy was compared with *best supportive care* were also included. The assessment was carried out with respect to patient-relevant outcomes. Randomized controlled trials (RCTs) with a direct comparator were considered in the assessment.

Results

One relevant study (MDX010-20) was available for the benefit assessment. This was an RCT with 3 parallel study arms (randomization ratio: 3:1:1).

- Ipilimumab + gp100 + BSC (1)
- Ipilimumab + placebo + BSC (2)
- Placebo + gp100 + BSC (3)

In 2 of the 3 treatment arms of the study, a non-approved tumour vaccine (gp100) that is supposed to enhance the endogenous immune response specifically to tumour cells was used. The examination by the Institute of possible influences of gp100 on the comparison of ipilimumab and *best supportive care* showed that the administration of gp100 caused no effect that would challenge the basic conclusion of the assessment. Therefore, Arms 1 and 2 are to be considered as arms with ipilimumab in combination with *best supportive care* (ipilimumab/BSC) and Arm 3 as solely *best supportive care* (placebo/BSC). To increase statistical precision, provided it was directly possible for the respective outcomes, the results of both ipilimumab arms (1 and 2) were pooled. For those outcomes for which, on the basis of the available data, a pooling of the results of the two ipilimumab arms was not directly realizable, the results of Arm 1 (because of the higher number of cases in this treatment arm)

were used. For the outcome "overall survival", the comparisons of the two arms that received ipilimumab were then shown in parallel with placebo and qualitatively combined to enable a more accurate estimation of the extent of the added benefit. Arm 3 (placebo + gp100 + BSC) served as comparator arm in all cases.

With one exception (health-related quality of life), the risk of bias of the study included in the assessment was low at study level as well as at outcome level. On the basis of the evidence available from this study, indications (e.g. of an added benefit) could be derived.

Overall survival

With respect to overall survival, there was a statistically significant advantage of ipilimumab/BSC compared to placebo/BSC. There is thus an indication of an added benefit of ipilimumab in combination with *best supportive care* compared to *best supportive care* alone.

Morbidity

No outcomes relating to morbidity (in the sense of morbidity caused by the disease) were investigated in the study. An added benefit of ipilimumab for outcomes relating to morbidity is accordingly not proven.

Quality of life

In the dimensions (global health status, functioning, symptoms) considered in the Quality of Life Questionnaire of the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30), a statistically significant disadvantage of ipilimumab/BSC compared to placebo/BSC was only shown for the symptom "constipation". From this result of a single dimension of the questionnaire, no general advantage or disadvantage of ipilimumab regarding health-related quality of life is derived. There is therefore no proof of added benefit of ipilimumab in combination with *best supportive care* compared to *best supportive care* alone.

Adverse events

The overall rates of adverse events, severe adverse events (Common Terminology Criteria for Adverse Events [CTCAE], Grade ≥ 3) and serious adverse events were comparable between the treatment groups. Therefore greater or lesser harm from ipilimumab in combination with *best supportive care* compared to *best supportive care* alone is not proven for these outcomes.

Adverse events that led to a discontinuation of treatment occurred statistically significantly more often in the ipilimumab /BSC group than in the placebo/BSC group. Despite a statistically significant difference, greater harm from ipilimumab in combination with *best supportive care* compared to *best supportive care* alone is not proven because, due to the low precision, an only marginal effect size cannot be excluded statistically.

The rates of treatment-associated immune-related adverse events (all events, severe [≥ CTCAE Grade 3] and serious adverse events) and of study discontinuations due to

treatment-associated immune-related events were in each case statistically significantly higher under ipilimumab/BSC compared to placebo/BSC. There is thus an indication of greater harm from ipilimumab in combination with *best supportive care* compared to *best supportive care* alone for treatment-associated immune-related adverse events.

Extent and probability of the added benefit, patient groups with therapeutically important added benefit

On the basis of the results presented, the extent and probability of the added benefit of the drug ipilimumab is assessed as follows:

In the global assessment, there are both positive and negative results of equal certainty (indication). On the positive side, the extent "major" was attained for overall survival. On the negative side, the extent "major" was reached for immune-related adverse events. In each case, the extent "considerable" was attained for immune-related adverse events and for discontinuations due to events of this type, while the extent "major" was attained for severe and serious immune-related adverse events. Due to the major risk of harm from severe and serious immune-related adverse events, the Institute decided to downgrade the added benefit of ipilimumab over the ACT *best supportive care* from "major" to "considerable". This does not affect the certainty of results.

In summary, there is a considerable added benefit of ipilimumab over the ACT *best supportive care* for patients with advanced (unresectable or metastatic) melanoma.

The overall conclusion on added benefit is based on the aggregation of the extent of added benefit derived at outcome level.

The procedure for deriving an overall conclusion of the added benefit is a proposal from IQWiG. The decision regarding added benefit is made by the G-BA.

2.2 Research question

The aim of this report was to assess the added benefit of ipilimumab compared to *best supportive care* as ACT in adult patients with advanced (unresectable or metastatic) melanoma, who have received prior therapy.

Given the current therapy situation, all patients need to receive *best supportive care*. Studies were therefore included in the benefit assessment that compared ipilimumab in combination with *best supportive care* with treatment consisting of *best supportive care* alone. If available, studies in which ipilimumab as monotherapy was compared with *best supportive care* were also included.

In the placebo-controlled, three-arm study included in the assessment, the patients of all treatment groups received a concomitant treatment classed as *best supportive care*. The study

compared the administration of ipilimumab in addition to *best supportive care* with *best supportive care* alone.

The assessment was carried out with respect to patient-relevant outcomes. Only RCTs with a direct comparator were considered in the assessment.

Further information about the research question can be found in Module 3, Section 3.1 and Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.1 Information retrieval and study pool

The study pool of the assessment was compiled from the following information:

- Studies on ipilimumab completed by the company up to 13.12.2011 (study list of the company).
- Results of a search in trial registries for studies on ipilimumab (last search on 17.11.2011, company search)
- The Institute's own searches in trial registries for studies on ipilimumab to check the search results of the company (search date: 10.02.2012). The check produced no deviations from the study pool presented in the company's dossier.

The resulting study pool corresponded to that used by the company.

Further information about the inclusion criteria for studies in the present benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.1.1 Studies included

The approval study MDX010-20 listed in Table 2 was included in the assessment.

Table 2: Study pool - RCT with the drug to be assessed; direct comparison ipilimumab/BSC vs. placebo/BSC

Study	**Study category**		
	Study for approval of the drug to be assessed (yes/no)	**Sponsored study[a] (yes/no)**	**Third-party study (yes/no)**
MDX010-20	yes	yes	no
a: Study for which the company was sponsor or in which the company was otherwise financially involved. RCT: randomized controlled trial; BSC: best supportive care			

According to the inclusion criteria, patients with advanced, unresectable melanoma were treated in the study. According to the Summary of Product Characteristics (SPC) [1], ipilimumab is approved for patients with advanced (unresectable or metastatic) melanoma.

The study population does not cover patients with metastatic resectable melanoma and thus does not include the entire therapeutic indication. It is unclear whether the observed effects also apply to these patients. Furthermore, according to the inclusion criteria, the study population covers only patients with genotype HLA-A*0201. Since the submitted documents give no indication of an influence of genotype HLA-A*0201 on the effects of ipilimumab, it is assumed that the observed effects can be applied to HLA-A*0201-negative patients. The following comparator arms were investigated in the study:

- Ipilimumab + gp100 (1)
- Ipilimumab + placebo (2)
- Placebo + gp100 (3)

The following two aspects need to be considered in relation to the study design: in the study, *best supportive care* was not part of the randomization. In addition, in 2 treatment arms, a non-approved substance (gp100) was used, whose interaction with ipilimumab requires investigation. gp100 is an experimental tumour vaccine, studied since 1996, but not yet submitted for approval. It consists of 2 peptide sequences of melanoma cell-specific antigen that can stimulate T-cells and is supposed to potentiate the endogenous immune response specifically to tumour cells. This tumour vaccine was used in the study, in order to investigate whether its administration can enhance the unspecific immune response induced by ipilimumab.

First of all, the study was examined to see whether it enabled conclusions to be drawn on the added benefit of ipilimumab compared to *best supportive care*. Both the randomly allocated treatment and the concomitant treatment were considered. Whether the administration of gp100 has an influence on the effects of ipilimumab was also investigated.

The Institute concluded that the patients of all treatment arms received *best supportive care* as concomitant medication. As regards the administration of gp100, no interaction with ipilimumab that would seriously challenge the assessment was established. Use of the study arms with gp100 was therefore assessed as being acceptable. A detailed explanation can be found in Section 2.7.2.3.2 of the full dossier assessment.

The Institute evaluated the study as relevant for this benefit assessment and agreed on this point with the company.

For the purpose of this assessment, the 3 treatment arms of the study are shown as follows:

- Ipilimumab + (gp100) + BSC (1)
- Ipilimumab + placebo + BSC (2)
- Placebo + (gp100) + BSC (3)

In this assessment, Arms 1 and 2 were considered as treatment group for the investigation of ipilimumab in combination with *best supportive care* (ipilimumab/BSC). Arm 3 was regarded as treatment group for the investigation of a purely *best supportive care* therapy (placebo/BSC).

To increase statistical precision, provided it was directly possible for the outcomes, the data from both ipilimumab arms (1 and 2) were pooled. The comparison of Arm 1 with Arm 3 was used for those outcomes for which, on the basis of the available data, a pooling of the results of the two ipilimumab arms was not directly realizable. This procedure was chosen because, due to the randomization ratio of 3:1:1, Arm 1 included a higher number of cases than Arm 2 and hence led to a higher precision of the results of the comparison.

In relation to the establishment of which comparator arms were to be used for the assessment of added benefit, the procedure of the Institute deviated from that of the company. The latter only included the comparison of the two Arms 2 and 3 in its assessment, although its assessment of the influence of gp100 and of the administration of BSC concurred with that of the Institute. No justification for this procedure was stated.

Section 2.6 contains a list of data sources cited by the company for the studies included in its assessment.

Further information about the results of information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.1.2 Study characteristics

Characteristics of the study and the interventions

Table 3 and Table 4 describe the MDX010-20 study used for the benefit assessment.

Study MDX010-20 was a randomized, double-blind, multicentre, active-controlled trial with 3 parallel study arms. Adult patients with inoperable Stage III or IV malignant melanoma were enrolled in the study. Patients had been previously treated with interleukin-2, dacarbazine, temozolomide, fotemustine and/or carboplatin and had either shown no response under this treatment, had suffered a recurrence or were unable to continue the treatment due to intolerance. The enrolled patients must also have shown genotype HLA-A*0201 in the leucocyte antigen (HLA-A*0201-positive patients). This inclusion criterion was chosen in the study because the tumour vaccine gp100 was used in 2 treatment arms. This vaccine consists of 2 peptide sequences of an antigen specific for melanoma cells and is supposed to enhance the endogenous immune response to tumour cells.

Ipilimumab was administered in a dose of 3 mg/kg every 3 weeks as an intravenous infusion over 90 minutes. Tumour vaccine gp100 was injected subcutaneously in a dose of 1 mg of each peptide immediately after the ipilimumab infusion. The respective placebo was

administered in the same way. Patients of all treatment arms could also receive concomitant medication, which was merely restricted as regards other therapies to treat melanoma. However, in the case of progressive disease, additional treatments for the melanoma could be used at the physician's discretion. There were no other restrictions on the concomitant medication. The Institute classified the concomitant medication available in the study as *best supportive care* (BSC).

The patients were randomly allocated in a ratio of 3:1:1 to the following study arms:

- Ipilimumab + gp100 + BSC (1); 403 patients
- Ipilimumab + placebo + BSC (2); 137 patients
- Placebo + gp100 + BSC (3); 136 patients

With regard to the administration of the tumour vaccine gp100, the Institute considers it has no relevant influence on the effects of ipilimumab measured in the study compared to *best supportive care*.

Overall survival was recorded as the primary outcome of the study. Relevant secondary outcomes were "health-related quality of life" and "adverse events".

Table 3: Characteristics of the included study

Study	Study design	Population	Interventions (number of randomized patients)	Duration of study	Location and period of study	Primary outcome; secondary outcomes[a]
MDX010-20	RCT, double-blind, 3:1:1 randomized, multicentre, parallel	Adult patients with unresectable Stage III or IV melanoma, who had either not responded to previous treatment[b], had suffered a recurrence or showed intolerance and were positive for genotype HLA-A*0201.	IPI + gp100 (N=403) IPI + Plc (N=137) Plc + gp100 (N=136)	Treatment duration of patients was 9 weeks, followed by a follow-up phase of up to 5 years	125 study centres in 15 countries in North and South America, Europe and Africa September 2004 to October 2009	Primary: overall survival (comparison IPI + gp100 and Plc + gp100) Secondary: Health-related quality of life Adverse events

a: Extracted primary outcome criteria contain information without consideration of relevance for this benefit assessment. Extracted secondary criteria contain only information on the available outcomes relevant for this benefit assessment.

b: Previous treatment was defined as administration of at least 1 cycle of one or more of the following therapies: interleukin-2, dacarbazine, temozolomide, fotemustine and/or carboplatin

gp100: glycoprotein 100 (tumour vaccine), IPI: ipilimumab, N: number of patients, Plc: placebo, RCT: randomized controlled trial

Table 4: Characteristics of the interventions

Study	IPI + gp100 + BSC	IPI + Plc + BSC	Plc + gp100 + BSC
MDX010-20	IPI: 3mg/kg as 90-minute intravenous infusion every 3 weeks up to 4 infusions in the induction regimen [a] gp100 vaccination[b]: subcutaneous injection of 1 mg each of 2 peptides gp100 every 3 weeks up to 4 injections in the induction regimen[a]	IPI: 3mg/kg as 90-minute intravenous infusion every 3 weeks up to 4 infusions in the induction regimen[a] gp100-placebo[c]: subcutaneous injection every 3 weeks up to 4 injections in the induction regimen	IPI-placebo[d]: 3mg/kg as 90-minute intravenous infusion every 3 weeks up to 4 infusions in the induction regimen[a] gp100 vaccination[b]: subcutaneous injection of 1 mg each of 2 peptides gp100 every 3 weeks up to 4 injections in the induction regimen[a]
	Concomitant medication: Non- permitted medications: Interleukin-2, interferon or immunotherapies for the melanoma other than the study medication, cytotoxic chemotherapies, immunosuppressants, other experimental treatments, chronic administration of systemic corticosteroids. Patients with progressive disease, who could not receive further treatment with the study medication, could receive other drugs to treat the melanoma at the investigator's discretion. There were no other restrictions on concomitant medication.		
a: The induction course comprised 4 infusions of the study medication every 3 weeks. Patients were subsequently observed for efficacy and tolerability. If disease progression occurred, patients who had tolerated the study medication well, and who showed stable disease for 3 months or more after Week 12 or an initial objective response (partial response or complete response) during the induction regimen, could receive one or more re-induction regimens of the same treatment. b: gp100 vaccination consisted of Peptide A, a peptide with the sequence YLEPGPVTV (gp100:280-288 [288V]) and Peptide B, a peptide with the sequence IMDQVPFSV (gp100:209-217[210M]). Each of the peptides was prepared with Montanide ISA-51. A gp100 injection consisted of 1 mg of each peptide (A and B) and was given immediately after the infusion of IPI or IPI-placebo. c: gp100-placebo consisted of sterile saline (0.9%). d: IPI-placebo had the same formulation as ipilimumab, produced without the active substance. BSC: best supportive care; IPI: ipilimumab, gp100: glycoprotein 100 (tumour vaccine); Plc: placebo		

Characteristics of the study population

Table 5 shows the characteristics of the patients in the MDX010-20 study.

There were no relevant differences between the treatment arms for the characteristics of age, gender, disease duration, lactate dehydrogenase (LDH) status, M (metastasis) stage or tumour stage (III or IV). The mean age of patients was about 56 years and mean disease duration was approx. 5 years. About 60% of patients were female. The disease had reached the most advanced stage of metastasis (M1c) in about 70% of patients and a further 16 to 19% were in Stage M1b.

Table 5: Characteristics of the study population in the MDX010-20 study

Group	IPI + gp100 + BSC	IPI + Plc + BSC	Plc + gp100 + BSC
N[a]	403	137	136
Age [years] mean (SD)	55.6 (13.2)	56.8 (13.9)	57.4 (13.5)
Gender f /m [%]	39 / 61	31 / 59	31 / 54
Duration of disease [years][b] mean (SD)	5.1 (5.5)	4.3 (5.9)	5.7 (5.8)
LDH [%]			
> ULN	36.7	38.7	39.7
≤ ULN	63.3	61.3	60.3
M stage[c] [%]			
M0	1.2	0.7	2.9
M1a	9.2	10.2	8.1
M1b	18.9	16.1	16.9
M1c	70.7	73	72.1
Tumour stage, n (%)			
III	7 (1.7)	1 (0.7)	4 (2.9)
IV	396 (98)	136 (99)	132 (97)
ECOG Performance Status n			
0	236 (59)	79 (58)	72 (53)
1	167 (41)	58 (42)	63 (46)
unknown	0	0	1 (1)

a: Number of randomized patients.

b: Time from first diagnosis up to randomization.

c: The M classification describes the exclusion (M0) or demonstration (M1) of distant metastases.

BSC: best supportive care, ECOG: Eastern Cooperative Oncology Group, gp100: glycoprotein 100 (tumour vaccine), IPI: ipilimumab, LDH: lactate dehydrogenase, N: number of analysed patients, n: number of patients with characteristic; Plc: placebo, SD: standard deviation, ULN: upper limit of normal

Risk of bias at study level

Table 6 shows the risk of bias at study level.

The risk of bias at study level was rated as low for the MDX010-20 study. This concurs with the company's assessment.

Table 6: Risk of bias at study level

Study	Random sequence generation	Allocation concealment	Blinding		Selective reporting	Other sources of bias	Risk of bias at study level
			Participants	Personnel			
MDX010-20	yes	yes	yes	yes	no	no	low

Further information about the study design, study populations and risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2 of the dossier and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.2 Results concerning added benefit

This assessment covered the following patient-relevant outcomes (for more detailed reasoning, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality (overall survival)
- Morbidity (symptoms and complications of the disease)
- Health-related quality of life
- Adverse events
  - Overall rate of adverse events
  - Overall rate of adverse events of CTCAE Grade ≥ 3
  - Overall rate of serious adverse events
  - Overall rate of adverse events that led to study discontinuation
  - Overall rate of immune-related adverse events
  - Overall rate of immune-related adverse events of CTCAE Grade ≥ 3
  - Overall rate of immune-related serious adverse events
  - Overall rate of immune-related adverse events that led to study discontinuation

The Institute's choice of patient-relevant outcomes deviated from that of the company insofar as in its assessment regarding morbidity, the company only used treatment-related morbidity, i.e., events that occurred in the treatment groups due to the tolerability of the drug. In this benefit assessment, this was recorded under the complex "adverse events". The company's presentation, however, did not cover morbidity (e.g. symptoms) caused by the disease. The Institute includes disease-related morbidity as a patient-relevant outcome in the assessment of the added benefit.

Table 7 shows for which outcomes data were available in the studies included in the assessment. Table 8 provides the risk of bias for these outcomes.

Apart from the non-recorded data on disease-related morbidity, a good availability of data could be assumed for the study.

With the exception of the outcome "health-related quality of life", the risk of bias of the outcomes was rated as low. These ratings correspond overall with those of the company, which undertook no assessment at outcome level for the complex "adverse events" (called treatment-related morbidity by the company), but for adverse events as a whole. The high risk

of bias for the outcome "health-related quality of life" arose from the low return rate of the questionnaires. However, it should be pointed out that this can be largely explained by the death of the patients.

Table 7: Matrix of outcomes from the MDX010-20 study

Study	Outcomes							
	Overall survival	Health-related quality of life	Morbidity (symptoms and complications of the disease)	AEs	AEs of CTCAE Grade ≥3	Serious AEs	Study discontinuations due to AEs	Immune-related AEs (including discontinuations, severe and serious AEs)
MDX010-20	yes	yes	–[a]	yes	yes	yes	yes	yes

a: Outcome was not recorded.

AE: adverse event; CTCAE: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events

Table 8: Risk of bias at study and outcome level for the MDX010-20 study

		Outcomes							
Study	Study level	Overall survival	Health-related quality of life	Morbidity (symptoms and complications of the disease)	AEs	AEs of CTCAE Grade ≥ 3	Serious AEs	Study discontinuations due to AEs	Immune-related AEs (including discontinuations, severe and serious AEs)
MDX010-20	low	low	high[b]	–[a]	low	low	low	low	low

a: Outcome was not recorded.

b: Reason: low rate of return of EORTC QLQ-C30 questionnaires at Week 12 and 24 of under 70%

AE: adverse event; CTCAE: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events

Further information about the choice of outcome and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2, 2.7.2.4.3 and 2.7.2.8.1 of the full dossier assessment.

Tables 9 to 11 summarize the results on the comparison of ipilimumab/BSC and placebo/BSC. Where necessary, the data from the manufacturer's dossier were supplemented by the Institute's own calculations.

Pooling of the two ipilimumab arms of the study was not directly possible for the outcomes "overall survival" and "health-related quality of life". To increase precision, the largest ipilimumab/BSC arm was therefore used for the comparison with placebo/BSC. The results of the IPI + placebo + BSC arms can be found in Appendix B of the full dossier assessment (Table 17 and Table 18).

- Ipilimumab + (gp100) + BSC, Arm 1
- Placebo + (gp100) + BSC, Arm 3

Pooling of the two ipilimumab arms of the study was directly possible for the outcome "adverse events". To increase precision, the pooled results from these two ipilimumab/BSC arms were used for the comparison with placebo/BSC (placebo + [gp100] + BSC, Arm 3) (Table 11). The results of the individual arms are shown for information in Appendix B of the full dossier assessment (Table 19).

Table 9: MDX010-20: direct comparison of ipilimumab/BSC vs. placebo/BSC, results on overall survival

Outcome	**Ipilimumab/BSC (IPI + gp100 + BSC)[a]**		**Placebo/BSC (Plc + gp100 + BSC)[b]**		**Group comparison ipilimumab/BSC vs. placebo/BSC**
	N	**Median (95% CI) [months]**	**N**	**Median (95% CI) [months]**	**HR [95% CI] p-value**
Overall survival	403	9.95 [8.48; 11.50]	136	6.44 [5.49; 8.71]	0.68 [0.55; 0.85] p < 0.001

a: Due to lack of effect of gp100, the arm is regarded as IPI/BSC.
b: Due to lack of effect of gp100, the arm is regarded as placebo/BSC.
BSC: best supportive care; CI: confidence interval; gp100: glycoprotein 100 (tumour vaccine); HR: hazard ratio; IPI: ipilimumab; N: number of analysed patients; Plc: placebo

Table 10: MDX010-20: direct comparison of ipilimumab/BSC vs. placebo/BSC, health-related quality of life results

Subscales Intervention	N[a]	Value at start of study mean (SD)	Value at Week 12 mean (SD)	Change after 12 weeks mean[b] [95% CI]	Group difference[b] [95% CI]	p-value
Health-related quality of life: EORTC QLQ-C30						
Global health status						
IPI/BSC[c]	226	65.0 (23.5)	61.4 (24.1)	-7.4 [-10.4; 4.3]	3.0 [-2.5; 8.6]	0.281
Placebo/BSC[d]	77	60.6 (23.3)	55.4 (25.9)	-10.4 [-15.3; -5.5]		
Physical functioning						
IPI/BSC[c]	226	78.2 (21.5)	75.0 (24.7)	-6.2 [-8.9; -3.4]	3.9 [-1.1; 8.9]	0.122
Placebo/BSC[d]	78	74.4 (23.1)	66.7 (25.9)	-10.1 [-14.5; -5.7]		
Role functioning						
IPI/BSC[c]	226	70.8 (31.5)	67.3 (32.6)	-9.3 [-13.4; -5.3]	4.3 [-3.0; 11.7]	0.248
Placebo/BSC[d]	78	67.6 (30.2)	60.1 (35.9)	-13.7 [-20.2; -7.2]		
Cognitive functioning						
IPI/BSC[c]	227	84.2 (19.5)	81.1 (22.8)	-3.1 [-5.8; -0.3]	0.3 [-4.7; 5.2]	0.912
Placebo/BSC[d]	78	83.1 (22.1)	80.0 (23.5)	-3.4 [-7.8; 1.0]		
Emotional functioning						
IPI/BSC[c]	227	73.6 (21.8)	73.2 (22.5)	-1.5 [-4.2; 1.1]	0.0 [-4.8; 4.8]	0.998
Placebo/BSC[d]	78	72.0 (22.2)	71.2 (22.5)	-1.5 [-5.8; 2.7]		
Social functioning						
IPI/BSC[c]	227	73.2 (27.7)	72.6 (29.9)	-5.6 [-9.2; -2.0]	-1.4 [-8.1; 5.2]	0.670
Placebo/BSC[d]	78	71.4 (26.9)	71.0 (30.6)	-4.2 [-10.1; 1.8]		
Fatigue						
IPI/BSC[c]	226	34.43 (25.3)	40.2 (28.0)	10.6 [7.0; 14.1]	-3.9 [-10.3; 2.4]	0.226
Placebo/BSC[d]	78	38.3 (26.4)	47.3 (34.0)	14.5 [8.8; 20.2]		
Nausea and vomiting						
IPI/BSC[c]	226	10.7 (20.5)	12.9 (21.3)	4.6 [1.9; 7.3]	0.2 [-4.7; 5.1]	0.940
Placebo/BSC[d]	78	10.5 (18.3)	14.0 (20.2)	4.4 [0.1; 8.7]		
Pain						
IPI/BSC[c]	227	28.2 (29.4)	29.1 (29.0)	5.6 [2.0; 9.3]	-6.3 [-12.8; 0.3]	0.063
Placebo/BSC[d]	78	30.7 (28.7)	36.6 (32.4)	11.9 [6.0; 17.7]		
Dyspnoea/respiratory complaints						
IPI/BSC[c]	222	18.1 (25.9)	19.5 (25.6)	3.5 [0.0; 6.9]	-5.6 [-11.8; 0.6]	0.076
Placebo/BSC[d]	77	20.2 (25.8)	27.2 (31.2)	9.1 [3.6; 14.6]		
Insomnia						
IPI/BSC[c]	225	27.4 (29.6)	30.2 (31.5)	6.5 [2.3; 10.7]	-4.5 [-12.1; 3.1]	0.245
Placebo/BSC[d]	76	30.4 (32.4)	37.5 (35.3)	11 [4.3; 17.8]		

(continued on next page)

Table 10: MDX010-20: direct comparison of ipilimumab/BSC vs. placebo/BSC, health-related quality of life results (continued)

Subscales Intervention	N[a]	Value at start of study mean (SD)	Value at Week 12 mean (SD)	Change after 12 weeks mean[b] [95% CI]	Group difference[b] [95% CI]	p-value
Health-related quality of life: EORTC QLQ-C30						
Loss of appetite						
IPI/BSC[c]	225	20.0 (30.4)	22.9 (31.4)	8.5 [4.4; 12.5]	-1.8 [-9.1; 5.5]	0.629
Placebo/BSC[d]	78	20.8 (29.5)	26.7 (33.9)	10.3 [3.8; 16.8]		
Constipation						
IPI/BSC[c]	225	13.5 (24.8)	13.6 (25.7)	5.2 [91.7; 8.7]	-6.5 [-12.9; -0.2]	0.043
Placebo/BSC[d]	77	17.9 (28.3)	25.0 (33.3)	11.8 [6.2; 17.4]		
Diarrhoea						
IPI/BSC[c]	223	7.7 (17.4)	14.7 (26.9)	6.4 [2.8; 10.1]	4.3 [-2.2; 10.8]	0.194
Placebo/BSC[d]	78	5.9 (13.4)	9.5 (17.7)	2.1 [-3.7; 7.9]		
Financial difficulties						
IPI/BSC[c]	265	20.7 (29.7)	19.0 (28.5)	0 [-3.2; 3.2]	-1.7 [-7.5; 4.2]	0.572
Placebo/BSC[d]	76	23.0 (30.2)	23.0 (32.8)	1.7 [-3.5; 6.9]		

a: Number of patients analysed for the group comparisons at Week 12; mean and standard deviations (at start of study and Week 12) based on sometimes higher numbers of cases.
b: Adjusted values (LS Mean).
c: Ipilimumab + gp100 + BSC.
d: Placebo + gp100 + BSC.

BSC: best supportive care; CI: confidence interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30; IPI: ipilimumab; gp100: glycoprotein 100 (tumour vaccine); LS: least square; Plc: placebo; SD: standard deviation

Table 11: MDX010-20: direct comparison of ipilimumab/BSC (pooled data of arms IPI + gp100 + BSC and IPI + Plc + BSC) vs. placebo/BSC, adverse events results

Adverse events	Ipilimumab / BSC (IPI + gp100 + BSC and IPI + Plc + BSC)[a]		Placebo/BSC (Plc + gp100 + BSC)		Group difference[b]	
	N	Patients with events n (%)	N	Patients with events n (%)	RR[c] [95% CI]	p-value[d]
AEs	511	502 (98.2)	132	128 (97.0)	1.01 [0.98; 1.05]	0.402
CTCAE Grade ≥ 3	511	267 (52.3)	132	69 (52.3)	1.00 [0.83; 1.20]	1.000
SAEs	511	212 (41.5)	132	52 (39.4)	1.05 [0.83; 1.33]	0.678
Study discontinuation due to AEs	511	52 (10.2)	132	5 (3.8)	2.69 [1.09; 6.59]	0.022
Immune-related AEs						
Overall rate	511	301 (58.9)	132	42 (31.8)	1.85 [1.43; 2.40]	< 0.001
Severe AEs (CTCAE Grade ≥3)	511	65 (12.7)	132	4 (3.0)	4.20 [1.56; 11.31]	0.004
SAEs	511	59 (11.5)	132	1 (0.8)	3.57 [1.85; 6.89][e]	< 0.001
Study discontinuation due to AEs	511	33 (6.5)	132	1 (0.8)	3.12 [1.33; 7.32][e]	0.014

a: Pooled data of arms IPI + gp100 + BSC and IPI + Plc + BSC (for results of the individual arms, see Appendix B of the full dossier assessment).

b: Comparison of groups IPI/BSC (pooled) and placebo/BSC.

c: Institute's calculation, asymptotic.

d: Institute's calculation, unconditional exact test (CSZ method according to [2]).

e: Peto Odds ratio, because the rates for immune-related SAEs and discontinuations under placebo/BSC was below 1%.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CSZ: convex, symmetry, z-score; CTCAE: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events; gp100: glycoprotein 100 (tumour vaccine), N: number of analysed patients, n: patients with event, Plc: placebo; RR: relative risk; SAE: serious adverse event

Only one study was available for the assessment of ipilimumab. In the Institute's view, the present study did not meet the particular requirements placed on the derivation of proof from a single study. Hence, at most indications - e.g. of an added benefit - could be inferred from the data, provided that there were no other aspects that weakened the informative value.

Overall survival

The median overall survival of patients in the ipilimumab/BSC group (IPI + gp100 + BSC) was longer than in the placebo/BSC group (Plc + gp100 + BSC) and the group difference was

statistically significant. There is an indication of an added benefit of ipilimumab in combination with *best supportive care* compared to *best supportive care* alone.

The company also derived an added benefit for overall survival, but its conclusions were based on the analysis of the smaller ipilimumab + placebo + BSC arm compared to the placebo + gp100 + BSC arm. A detailed explanation can be found in Section 2.7.2.8.2 of the full dossier assessment.

Morbidity

No outcomes relating to morbidity (in the sense of morbidity caused by the disease) were investigated in the study. An added benefit of ipilimumab for outcomes relating to morbidity is not proven.

Health-related quality of life

In the dimensions (global health status, functioning, symptoms) considered in the EORTC QLQ-C30 questionnaire, a statistically significant difference to the disadvantage of ipilimumab/BSC was only shown for the symptom "constipation". From this result of a single dimension of the questionnaire, no general advantage or disadvantage of ipilimumab regarding health-related quality of life is derived. There is therefore no proof of added benefit of ipilimumab in combination with *best supportive care* compared to *best supportive care* alone. The results of the study arms IPI + placebo + BSC and the related group comparisons are shown in Appendix B of the full dossier assessment.

The company also derived no added benefit for health-related quality of life, but its conclusions were based on the analysis of other comparator arms. A detailed explanation can be found in Section 2.7.2.8.2 of the full dossier assessment.

Adverse events

The overall rates of adverse events, severe adverse events (CTCAE Grade ≥ 3) and serious adverse events were comparable between the treatment options. The group difference was not statistically significant. Greater or lesser harm from ipilimumab in combination with *best supportive care* compared to *best supportive care* alone is thus not proven for these outcomes.

Adverse events that led to discontinuation of treatment occurred more frequently in the ipilimumab/BSC group (pooled arms IPI + gp100 + BSC and IPI + Plc + BSC) than in the placebo/BSC group. The difference was statistically significant. Despite a statistically significant difference, greater harm from ipilimumab in combination with *best supportive care* compared to *best supportive care* alone for this outcome is not proven because, due to the low precision, an only marginal effect size cannot be excluded statistically (see Table 12).

In addition, the Institute investigated the rates of treatment-associated immune-related adverse events (all events, severe [≥ CTCAE Grade 3] and serious events) as well as study discontinuations due to treatment-associated immune-related adverse events. There was a

statistically significantly higher occurrence under ipilimumab/BSC compared to placebo/BSC for each of these 4 outcomes. There is thus an indication of greater harm from ipilimumab in combination with *best supportive care* compared to *best supportive care* alone for these 4 outcomes.

The company stated that there was no added benefit of ipilimumab for these outcomes regarding immune-related adverse events, but described – albeit not explicitly – greater harm. It should also be noted that the company's conclusions were based on the analysis of other comparator arms.

Subgroup analyses

For the outcome "overall survival", the company presented subgroup analyses of the following factors: age, gender, M stage, LDH status at the start of the study, and pre-treatment with IL-2. Since interaction tests showed no interactions between the named factors and the treatment effect, the subgroup analyses are not shown separately here.

Further information about the choice of outcome, the risk of bias at outcome level and outcome results can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2., 2.7.2.4.3 and 2.7.2.8.1 of the full dossier assessment.

2.3 Extent and probability of the added benefit

The derivation of extent and probability of the added benefit at outcome level is shown below, taking into account the various outcome categories and effect sizes. The methods used are explained in Appendix A of Benefit Assessment A11-02 [3].

The procedure for deriving an overall conclusion regarding added benefit based on the aggregation of the conclusions derived at outcome level is a proposal from IQWiG. The decision regarding added benefit is made by the G-BA.

2.3.1 Evaluation of added benefit at outcome level

The data presented in Section 2.4 produced an indication of an added benefit for overall survival and an indication of greater harm for immune-related adverse events (including severe adverse events and serious adverse events as well as immune-related adverse events that led to study discontinuation). The extent of the respective added benefit at outcome level was estimated from these results.

Results of the comparison of the two ipilimumab arms with placebo for the outcome "overall survival" could not be directly pooled in a quantitative manner. Therefore the precise position of the upper limit of the confidence interval for the effect (hazard ratio), based on the comparison of the two pooled ipilimumab arms with placebo, remains unclear. It is, however, certain that this unknown upper limit must lie below 0.85 because the comparison of the larger ipilimumab arm with placebo already showed an upper limit of 0.85. Through the additional inclusion of the results of the smaller ipilimumab arm, which, compared to placebo,

showed an even somewhat stronger effect (see Table 17, Appendix B of the full dossier assessment), a higher precision and hence a narrower confidence interval would be produced.

Table 12: MDX010-20: ipilimumab/BSC vs. placebo/BSC – extent of added benefit at outcome level

	Effect estimator [95% CI][a] / quantile of the time to event and/or proportion of events: ipilimumab/BSC vs. placebo/BSC / p-value probability[b]	**Derivation of extent[c]**
Mortality		
Overall survival	IPI + gp100 vs. placebo: HR: 0.68 [0.55; 0.85] p < 0.001 median: 10.0 months vs. 6.4 months IPI + placebo vs. placebo: HR 0.66 [0.51; 0.87] p = 0.003 median: 10.1 months vs. 6.4 months Probability: "indication"	Outcome category: survival period $CI_o < 0.85$[d] Added benefit, extent: "major"
Morbidity[e]		
	Not recorded as separate outcome.	Added benefit not proven.
Health-related quality of life		
EORTC QLQ-C30	No statistically significant difference apart for 1 of 15 subscales (constipation, p = 0.043)	Added benefit not proven.
Adverse events[f]		
AEs	RR 1.01 [0.98; 1.05] 98.2% vs. 97.0% p = 0.402	Greater/lesser harm not proven.
Severe AEs (CTCAE Grade ≥ 3)	RR 1.00 [0.83; 1.20] 52.3% vs. 52.3% p = 0.999	Greater/lesser harm not proven.
SAEs	RR 1.05 [0.83; 1.33] 41.5% vs. 39.4% p = 0.678	Greater/lesser harm not proven.
Discontinuation due to AEs	RR 2.69 [1.09; 6.59] RR: 0.37 [0.15; 0.91][g] 10.2% vs. 3.8% p = 0.022	Outcome category: non-serious/non-severe adverse events $CI_o \geq 0.90$ Greater/lesser harm not proven.
Immune-related AEs	RR 1.85 [1.43; 2.40] RR: 0.54 [0.42; 0.70][g] 58.9% vs. 31.8% p < 0.001 Probability: "indication"	Outcome category: non-serious/non-severe adverse events $CI_o < 0.80$ Greater risk of harm, extent: "considerable".

(continued on next page)

Table 12: MDX010-20: ipilimumab/BSC vs. placebo/BSC – extent of added benefit at outcome level (continued)

	Effect estimator [95% CI][a] / quantile of the time to event and/or proportion of events: ipilimumab/BSC vs. placebo/BSC / p-value probability[b]	**Derivation of extent[c]**
Severe immune-related AEs (CTCAE Grade ≥ 3)	RR 4.20 [1.56; 11.31] RR: 0.24 [0.09; 0.64][g] 12.7% vs. 3.0% p = 0.004 Probability:" indication"	Outcome category: serious/severe adverse events CI_o < 0.75 Greater harm, extent: "major"
Immune-related SAEs	Peto OR: 3.75 [1.85; 6.89] Peto OR: 0.28 [0.15; 0.54][g] 11.5% vs. 0.8% p < 0.001 Probability: "indication"	Outcome category: serious/severe adverse events CI_o < 0.75 Greater harm, extent: "major"
Discontinuation due to immune-related AEs	Peto OR: 3.12 [1.33; 7.32] Peto OR: 0.32 [0.14; 0.75][g] 6.5% vs. 0.8% P = 0.014 Probability:" indication"	Outcome category: non-serious/non-severe adverse events CI_o < 0.80 Greater risk of harm, extent: "considerable".

a: According to the inclusion criteria, patients with advanced, unresectable melanoma were treated in the study. According to the Summary of Product Characteristics (SPC) [1], ipilimumab is approved for patients with advanced (unresectable or metastatic) melanoma. The study population does not cover patients with metastatic resectable melanoma and thus does not include the entire therapeutic indication. It is unclear whether the observed effects also apply to these patients.

b: Probability given, if statistically significant differences are present.

c: Estimations of effect size are made depending on outcome category with different limits based on upper limit of the confidence interval (CI_o).

d: See explanation in the text.

e: The morbidity attributed to the disease (e.g. symptoms) was not used by the company for the benefit assessment; the company restricted the investigation of morbidity to treatment-related morbidity (tolerability), which includes the complex of adverse events assessed by the Institute.

f: For AEs, the groups IPI + gp100 and IPI + Plc were pooled.

g: Proportion of events placebo/BSC versus IPI/ BSC (direction of effect reversed in order to enable immediate use of the limits to derive the extent of added benefit).

AE: adverse event; BSC: best supportive care, CI: confidence interval; CTCAE: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30; HR: hazard ratio; CI_o: upper limit of confidence interval; OR: odds ratio; RR: relative risk; SAE: serious adverse event; vs.: versus

2.3.2 Overall conclusion on added benefit

Table 13 summarizes the results on which the overall conclusion about the extent of added benefit is based.

Table 13: Results accompanying the overall conclusion on added benefit

Positive effects	**Negative effects**
Indication of an added benefit – extent: "major" (overall survival)	Indication of greater harm – extent: "major" (immune-related AEs, immune-related severe AEs, immune-related SAEs, study discontinuations due to immune-related AEs)
AE: adverse event; SAE: serious adverse event	

In the global assessment (Table 13), there are both positive and negative results of the same certainty of results (indication). On the positive side, the extent "major" was attained for overall survival. On the negative side, the extent "major" was reached for immune-related adverse events. The extent for the overall rate of immune-related adverse events and study discontinuations as a result of immune-related adverse events is considerable in each case and is major for immune-related severe and serious adverse events. Due to the major risk of harm from severe and serious immune-related adverse events, the Institute decided to downgrade the added benefit of ipilimumab over the ACT *best supportive care* from "major" to "considerable". This does not affect the certainty of results.

In summary, there is a considerable added benefit of ipilimumab over the ACT *best supportive care* for patients with advanced (unresectable or metastatic) melanoma.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.8 of the full dossier assessment

2.4 List of included studies

MDX010-20

Bristol-Myers Squibb. A randomized, double-blind, multicenter study comparing MDX-010 monotherapy, MDX-010 in combination with a melanoma peptide vaccine, and melanoma vaccine monotherapy in HLA-A*0201-positive patients with previously treated unresectable stage III or IV melanoma: study MDX-010 (BMS-734016); clinical study report [unpublished]. 2010.

Bristol-Myers Squibb. MDX-010 antibody, MDX-1379 melanoma vaccine, or MDX-010/MDX-1379 combination treatment for patients with unresectable or metastatic melanoma [online]. In: International Clinical Trials Registry Platform 03.06.2010 [Accessed on: 18.04.2012]. URL: http://apps.who.int/trialsearch/Trial.aspx?TrialID=NCT00094653.

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Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363(8): 711-723.

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Please see full dossier assessment for full reference list.

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The full report (German version) is published under www.iqwig.de.