IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A13-44

Ipilimumab (new therapeutic indication) – 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 (neues Anwendungsgebiet) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status 13 March 2014). 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.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Ipilimumab (new therapeutic indication) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
3 December 2013

Internal Commission No.:
A13-44

Address of publisher:
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Keywords: ipilimumab, melanoma, benefit assessment

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[3] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
TI	therapeutic indication

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 3 December 2013.

Research question

The aim of this report was to assess the added benefit of ipilimumab compared with dacarbazine as appropriate comparator therapy (ACT) in adult patients with advanced (unresectable or metastatic) melanoma who have not received prior therapy to treat advanced melanoma.

The assessment was conducted based on patient-relevant outcomes.

Results

For the present benefit assessment, no data were available that were suitable to derive an added benefit of ipilimumab versus the G-BA's ACT. This result deviates from that of the company. The company also did not identify any randomized controlled trials (RCTs) that would have allowed a direct or an (adjusted) indirect comparison, but it based its conclusions on added benefit on an indirect comparison of individual patient data from different studies on ipilimumab and on one single study on dacarbazine.

On the ipilimumab side, the company included individual patient data from 6 different studies (4 RCTs and 2 one-arm retrospective observational studies), which investigated patients with an advanced stage of melanoma. The company included those patients from the RCTs who were chemotherapy-naive in an advanced stage of melanoma and who were treated with the approved dose of ipilimumab (3 mg/kg) (78 patients in total). The 2 one-arm retrospective observational studies were included completely by the company because they only included patients who were, according to the research question, treatment-naive in an advanced stage of melanoma, and who were treated with ipilimumab (3 mg/kg) (181 patients in total). Hence the company included a total of 259 patients for the ipilimumab side of the indirect comparison it presented. On the dacarbazine side, the company included all patients of the dacarbazine arm of an RCT on the comparison of an unapproved dose of ipilimumab (in combination with dacarbazine) with dacarbazine monotherapy because only non-pretreated patients with unresectable stage III or IV melanoma were investigated in this study according to the research question (N = 252).

It has to be assumed in such an indirect comparison that the study populations differ in their characteristics. In order to reduce systematic bias by differences between these factors called

confounders, the company used a methodological approach known as matching using a propensity score analysis. With the help of this statistical method, patients are allocated to individual propensity score classes according to defined parameters (e.g. age, disease severity) so that the intervention and control groups within these classes have a comparable structure with regards to these parameters. However, this matching of the patient groups with the propensity score analysis can only be conducted for known confounders in the therapeutic indication that were also recorded in the studies. In the analysis presented, the company did not consider additional known confounders in the conduct of the propensity score analysis (e.g. visceral metastases, time since diagnosis of the melanoma), although they were at least partially recorded. This further downgraded the certainty of results, which was already low.

In the analysis to determine the propensity score and in the subsequent analysis of the outcomes, the company only included those patients for whom data on all confounders considered were available. A total of 75 patients on the ipilimumab side and 2 patients on the dacarbazine side were excluded because of missing values on these confounders. In addition, on the ipilimumab side of the comparison presented, the company excluded all patients with known brain metastases from the analysis (n = 29) because, according to the exclusion criterion of the study, no patients with brain metastases were included on the dacarbazine side of the comparison so that it was not possible to match the populations on the known prognostic factor “brain metastasis” in the propensity score analysis.

An analysis in which not all patients of a study are considered produces effect estimates that are potentially biased and might therefore not be interpretable. This can be the case particularly if the missing values are not due to a random mechanism. A major difference between the groups to be compared in the proportion of patients who were not considered is an indication of this.

The company presented results on the outcomes “overall survival”, “health-related quality of life” and “adverse events” in the dossier.

Overall survival

Only 155 (approximately 60%) out of originally 259 patients were included in the analysis of overall survival in the indirect comparison presented by the company because of missing data on the confounders considered and because of the exclusion due to brain metastases on the ipilimumab side. In contrast, 250 out of originally 252 and thus almost all (> 99%) patients were analysed on the dacarbazine side.

The effects of excluding approximately 40% of the patients on the ipilimumab side became apparent in the comparison of the median survival time after the exclusion of patients due to missing data and due to brain metastases (grouped according to propensity score class) on both sides of the indirect comparison. Whereas on the dacarbazine side, the median survival time in the propensity score classes, with values between 7 and 12 months, spread around the median of the total study arm of 9 months, as could be expected, the picture on the

ipilimumab side was considerably different. In each single propensity score class (1 to 5), median survival on the ipilimumab side (15 to 29 months) was now higher in each single study on the basis of all patients (approximately 11 to 14 months). This shows that, on the ipilimumab side, those patients with a particularly bad prognosis were excluded from the analysis. Hence the effect resulting from this comparison was considerably biased in favour of ipilimumab.

Due to the overall uncertain data and the additional bias caused by the selective exclusion of patients from the analysis, the treatment effect was not regarded to be large enough to be able to exclude that it was based solely on systematic bias. The company's analyses on overall survival were therefore unsuitable for the derivation of an added benefit of ipilimumab versus the ACT with regards to overall survival. This deviates from the company's assessment, which claimed a "dramatic effect" based on the result after applying the propensity score analysis for the outcome "overall survival" because the company considered ipilimumab to lead to major prolongation in median overall survival compared with dacarbazine.

Health-related quality of life

The disease-specific questionnaire European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) was used in some studies to assess the outcome "health-related quality of life". Only a very small proportion of the patients were considered in the analysis so that the results on this outcome were not evaluable.

Adverse events

Several analyses on adverse events were available in the dossier, on the one hand based on raw rates, and on the other hand as time to first event. The data were not evaluable, however, because they were either based on an unadjusted comparison of raw rates or on an unadjusted comparison on the basis of a propensity score analysis, in which only a small proportion of patients were considered on the ipilimumab side as was the case for overall survival. A potentially relevant bias could therefore not be excluded so that the treatment effects presented by the company could not be interpreted.

Summary

The comparison presented by the company was unsuitable for the derivation of conclusions on the added benefit, because its uncertainty was too great due to the analysis presented (unadjusted indirect comparison). Moreover, the effect on overall survival was relevantly biased in favour of ipilimumab, because of the selective exclusion of patients from the analysis. The observed effect was therefore not sufficiently large to be able to exclude that it was only caused by systematic bias. The certainty of results was further reduced by the lack of consideration of further known confounders in the conduct of the propensity score analysis. Overall, the treatment effect on overall survival presented by the company was therefore not interpretable. This also applied to the results on further outcomes presented by the company (health-related quality of life, adverse events).

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

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

Table 2: Ipilimumab – extent and probability of added benefit

Therapeutic indication	ACT[a]	Extent and probability of added benefit
Adult patients with advanced (unresectable or metastatic) melanoma who have not received prior therapy to treat advanced melanoma	Dacarbazine	Added benefit not proven
a: Presentation of the ACT specified by the G-BA.		

The G-BA decides on the added benefit.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

2.2 Research question

The aim of this report was to assess the added benefit of ipilimumab compared with dacarbazine as ACT in adult patients with advanced (unresectable or metastatic) melanoma who have not received prior therapy to treat advanced melanoma.

The patient population relevant for the present assessment results from the new therapeutic indication of ipilimumab [3] in which, compared with the original therapeutic indication [4], the restriction to those patients who have received prior treatment, was abolished (see Sections 2.7.2.1 and 5.1 of the full dossier assessment). Moreover, the resulting population of patients who have not received prior therapy was specified by a request at the relevant regulatory authority insofar that the lack of pretreatment only referred to the stage of advanced melanoma.

The company concurred with the ACT dacarbazine specified by the G-BA. For patients with BRAF V600 mutation, the company additionally presented results for the comparison with vemurafenib because it regarded this to be a new treatment standard for the patient group. This expansion of the research question was not accepted in the benefit assessment.

The assessment was conducted based on patient-relevant outcomes.

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.

2.3 Information retrieval and study pool

2.3.1 Information retrieval

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on ipilimumab (studies completed up to 11 November 2013)
- bibliographical literature search on ipilimumab (last search on 7 November 2013)
- search in trial registries for studies on ipilimumab (last search on 13 November 2013)
- bibliographical literature search on the ACT (last search on 7 November 2013)
- search in trial registries for studies on the ACT (last search on 13 November 2013)

The Institute’s own search to check the completeness of the study pool:

- bibliographical literature search on ipilimumab (last search on 10 January 2014)
- search in trial registries for studies on ipilimumab (last search on 10 January 2014)

No additional relevant study was identified from the check.

The studies identified from the steps of information retrieval mentioned were unsuitable for the derivation of conclusions on the added benefit of ipilimumab in comparison with the ACT. This approach deviated from that of the company. The company also did not identify any RCTs that would have allowed a direct or an (adjusted) indirect comparison, but it based its conclusions on added benefit on an indirect comparison of individual patient data from different studies on ipilimumab and on one single study on dacarbazine (hereinafter referred to as "company's comparison"). The reasons why this comparison was unsuitable for deriving an added benefit of ipilimumab versus the ACT dacarbazine are given below.

2.3.2 Description of the company's comparison

For the ipilimumab side of the indirect comparison presented by the company, it combined the individual patient data of (chemo)therapy-naive patients with advanced melanoma who were treated with ipilimumab (3 mg/kg) from different randomized and non-randomized studies to a cohort. For the dacarbazine side, the company used an RCT on the comparison of an unapproved dose of ipilimumab (in combination with dacarbazine) with dacarbazine monotherapy (study CA184024). From this study, it only used the arm in which patients were treated with dacarbazine monotherapy (+ placebo). For the present benefit assessment, the patients included by the company were considered to be an adequate approximation to the population relevant for the research question (see Section 2.7.2.3.2 of the full dossier assessment).

It has to be assumed in such an indirect comparison that the study populations differ in their characteristics. In order to reduce systematic bias by differences between these factors called confounders, the company used a methodological approach known as matching using a propensity score analysis [5,6]. With the help of this statistical method, patients are allocated to individual propensity score classes according to defined parameters (e.g. age, disease severity) so that the intervention and control groups within these classes have a comparable structure with regards to these parameters. However, this matching of the patient groups with the propensity score analysis can only be conducted for known confounders in the therapeutic indication that were also recorded in the studies. Systematic bias caused by confounders that were not measured, but are relevant, can still occur. See Section 2.3.4 for a detailed discussion of the methods used by the company.

Table 3 shows the study pool for the company's comparison and lists patients who should be used for its comparison according to the company.

Table 3: Characteristics of the studies on ipilimumab and dacarbazine included in the company's comparison

Study	Study design	Total study population	Interventions (number of randomized patients)
Studies in the ipilimumab arm			
CA184004	RCT, double-blind, multicentre, parallel, phase 2	Patients ▪ with unresectable stage III or IV melanoma ▪ with or without systemic pretreatment	1) ipilimumab 3 mg/kg (N = 40, thereof included by the company: n = 17[a]) 2) ipilimumab 10 mg/kg (N = 42)[b] in each case IV, every 3 weeks, 4 doses maximum (induction phase) and every 12 weeks for week 24 to 48 (maintenance phase[c])
CA184022	RCT, double-blind, multicentre, parallel, phase 2	Patients ▪ with stage III melanoma (unresectable) or stage IV melanoma ▪ with systemic pretreatment[d]	1) ipilimumab 0.3 mg/kg (N = 73)[b] 2) ipilimumab 3 mg/kg (N = 72, thereof included by the company: n = 8[a]) 3) ipilimumab 10 mg/kg (N = 72)[b] in each case IV, every 3 weeks, 4 doses maximum (induction phase) and every 12 weeks for week 24 to 48 (maintenance phase[c])
MDX010-08	RCT, open-label, multicentre, phase 2	Patients ▪ with unresectable metastatic melanoma ▪ without previous chemotherapy[e]	1) ipilimumab 3 mg/kg (N = 40[a]) 2) ipilimumab 3 mg/kg + dacarbazine 250 mg/m^2 (N = 36)[b] ipilimumab: in each case IV, every 28 days, 4 doses maximum (4 months) dacarbazine: IV on 5 consecutive days, every 28 days, 6 cycles maximum
MDX010-20	RCT, double-blind, multicentre, parallel, phase 3, placebo-controlled	Patients ▪ with unresectable stage III or IV melanoma ▪ pretreated[f]	1) ipilimumab 3 mg/kg + gp100[g] (N = 403) 2) ipilimumab 3 mg/kg + placebo (N = 137, thereof included by the company: n = 13[a]) 3) placebo + gp100[g] (N = 136) ipilimumab: in each case IV, every 3 weeks, 4 doses maximum (induction phase)[h] gp100: SC every 3 weeks
CA184332	Retrospective, multicentre, non-interventional observational study[i]	Patients with unresectable or metastatic stage III or IV melanoma who received ipilimumab as first-line treatment (3 mg/kg)[j]	Ipilimumab 3 mg/kg (N = 61) Treatment interval/duration: ND
CA184338	Retrospective, multicentre, non-interventional observational study[k]	Patients with unresectable or metastatic stage III or IV melanoma who received ipilimumab as first-line treatment (3 mg/kg)[j]	Ipilimumab 3 mg/kg (N = 120) Treatment interval/duration: ND

(continued)

Table 3: Characteristics of the studies on ipilimumab and dacarbazine included in the company's comparison (continued)

Study	Study design	Total study population	Interventions (number of randomized patients)
Study in the dacarbazine arm			
CA184024	RCT, double-blind (dacarbazine open-label), multicentre, parallel, phase 3	Patients ▪ with unresectable stage III or IV melanoma ▪ non-pretreated	1) ipilimumab 10 mg/kg IV + dacarbazine 850 mg/m^2 (N = 250) 2) dacarbazine 850 mg/m^2 + placebo (N = 252)[l] ipilimumab: IV every 3 weeks, 4 doses maximum (induction phase) and every 12 weeks for week 24 to 48 (maintenance phase) dacarbazine: IV, every 3 weeks until week 22

a: This was the subpopulation of chemotherapy-naive patients who received ipilimumab at a dosage of 3 mg/kg, which was included in the company's comparison.
b: This dosage and drug combination is not approved in Germany.
c: In the maintenance phase, patients could continue treatment if, until week 24, they had no tumour progression, ECOG PS 0-1, and no discontinuation of treatment due to toxicity.
d: Patients had to be pretreated with at least 1 antineoplastic regimen (experimental or non-experimental) (CD137 agonists or CTLA-4 inhibitors were excluded).
e: No prior chemotherapy for melanoma or other malignant tumours in the last 5 years. At least 4 weeks had to have passed since the last treatment for melanoma (surgery, radiotherapy, IL-2 or interferon alpha).
f: 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.
g: Unapproved drug (tumour vaccine to enhance the endogenous immune response to tumour cells).
h: Ipilimumab reinduction was allowed in stable disease of at least 3 months after week 12 or in objective response in the induction phase.
i: Recruitment of patients via the US Oncology iKnowMed database.
j: Exclusion criterion: systemic pretreatment for unresectable or metastatic melanoma.
k: Recruitment via the study centres.
l: The company used this arm as dacarbazine control for the indirect comparison.
CD: cluster of differentiation; CTLA: cytotoxic T-lymphocyte-associated antigen; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IV: intravenous; ND: no data; N: number of randomized patients; n: relevant subpopulation: RCT: randomized controlled trial; SC: subcutaneous

On the ipilimumab side, the company used individual patient data from 6 different studies. These were 4 RCTs, which investigated patients with an advanced stage of melanoma. The company included those patients from these studies who were chemotherapy-naive in an advanced stage of melanoma and who were treated with the approved dose of ipilimumab (3 mg/kg). Hence the company included a complete study arm from the MDX010-08 study, and only individual patients from the remaining RCTs. These were 78 patients in total, summarized by the company as "phase 2/3 studies". In addition, the company presented 2 one-arm retrospective observational studies with ipilimumab (3 mg/kg). Only patients were included in these studies who were, according to the research question, treatment-naive in an advanced stage of melanoma, so that the company included the complete study population in its comparison (61 patients from the CA184332 study and 120 patients from the CA184338 study). The company included a total of 259 patients for the ipilimumab side of the indirect comparison it presented.

On the dacarbazine side, the company included all patients of the dacarbazine arm of the CA184024 study because only non-pretreated patients with unresectable stage III or IV melanoma were investigated in this study according to the research question (N = 252). Dacarbazine was administered in compliance with its approval [7]. The fact that the company did not search for further evidence on the dacarbazine side presented a further limitation of the comparison presented by the company (see Section 2.7.2.3.2 of the full dossier assessment).

The patients included in the company's comparison mostly fulfilled the inclusion criteria of the present benefit assessment with regards to patient population and intervention/comparator. Individual deviating aspects are discussed in Section 2.7.2.3.2 of the full dossier assessment, but were not decisive for the suitability of the company's comparison.

2.3.3 Appraisal of the results from the company's comparison

The company presented results on the outcomes "overall survival", "health-related quality of life" and "adverse events" in the dossier. These outcomes were considered to be relevant for the benefit assessment (see Section 2.7.2.3.2 of the full dossier assessment).

In the analysis to determine the propensity score and in the subsequent analysis of the outcomes, the company only included those patients for whom data on all confounders considered were available (see Table 4). For example, if no baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS) value was available for a patient, this patient was not considered in the analysis. A total of 75 patients on the ipilimumab side and 2 patients on the dacarbazine side were excluded exclusively because of missing values. In addition, on the ipilimumab side of the comparison presented, the company excluded all patients with known brain metastases from the analysis because, according to the exclusion criterion of the study, no patients with brain metastases were included on the dacarbazine side of the comparison. The exclusion of these patients from the analysis is understandable because it was not possible to match the populations on the known prognostic factor "brain metastasis". On the ipilimumab side, 29 patients were excluded because of brain metastases.

An analysis in which not all patients of a study are considered produces effect estimates that are potentially biased and might therefore not be interpretable [8,1]. This can be the case particularly if the missing values are not due to a random mechanism. A major difference between the groups to be compared in the proportion of patients who were not considered is an indication of this.

Table 4 provides an overview of the number of patients included in the company's analyses for the different outcomes investigated.

Table 4: Patients in the company's analysis: ipilimumab vs. dacarbazine

	Ipilimumab side	Dacarbazine side
	N	N
Patients for the company's comparison[a]	259	252
Overall survival	155	250
Health-related quality of life[b]	14[c]	144-147[d]
AEs, SAEs and treatment discontinuations due to AEs		
▫ Rates without propensity score analysis	78	250
▫ Time to first AE (with propensity score analysis)	25	250

a: For the present research question, these patients were considered to be an adequate approximation to the population relevant for the research question.
b: Recorded using the EORTC QLQ-C30.
c: Health-related quality of life was only recorded in the studies CS184022 and MDX010-20 so that the respective data on the ipilimumab side would have been available for a maximum of 21 patients.
d: The questionnaire used comprises different components. Depending on the components, evaluable questionnaires were available for 144 to 147 patients.
AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; N: number of analysed patients; SAE: serious adverse event; vs.: versus

The results from the company's analyses are appraised separately for each outcome below.

Overall survival

Only 155 (approximately 60%) out of originally 259 patients were included in the analysis of overall survival in the indirect comparison presented by the company because of missing data on the confounders considered and because of the exclusion due to brain metastases on the ipilimumab side. In contrast, 250 out of originally 252 and thus almost all (> 99%) patients were analysed on the dacarbazine side (see Table 4).

The following tables (Table 5 and Table 6) present an overview of the effects the patients excluded from the analysis had on the result on overall survival.

Table 5 shows the median survival time before the exclusion of patients due to missing data on the confounders considered (grouped by [pool of] studies).

In contrast, Table 6 shows the median survival time after the exclusion of patients with missing data on the confounders considered (grouped by propensity score class).

Table 5: Results on median survival time **before** the exclusion of patients due to missing data (grouped by [pool of] studies): ipilimumab vs. dacarbazine

Outcome category **outcome** study	**Ipilimumab**		**Dacarbazine**	
	N	**Median survival time (months) [95% CI]**	**N**	**Median survival time (months) [95% CI]**
Mortality				
Overall survival				
Phase 2/3[a]	78	13.47 [11.2; 19.58]	-	-
CA184332	61	11.5 [6.6; ND]	-	-
CA184338	120	14.3 [12.1; ND]	-	-
CA184024	-	-	252	9.07 [7.75; 10.51]
Total	259		252	

a: Data from chemotherapy-naive patients from several phase 2 and phase 3 studies who were treated with ipilimumab in the approved dosage.
CI: confidence interval; N: number of analysed patients; ND: no data; vs.: versus

Table 6: Results on median survival time **after** the exclusion of patients due to missing data (grouped by propensity score class): ipilimumab vs. dacarbazine

Outcome category **outcome** Propensity score class[a]	**Ipilimumab**		**Dacarbazine**	
	N	**Median survival time (months) [95% CI]**	**N**	**Median survival time (months) [95% CI]**
Mortality				
Overall survival				
Propensity score class 1	ND	20 [14; 49]	ND	8 [7; 12]
Propensity score class 2	ND	21 [14; 46]	ND	8 [6; 12]
Propensity score class 3	ND	29 [18; NC]	ND	12 [9; 18]
Propensity score class 4	ND	17 [12; 44]	ND	10 [8; 12]
Propensity score class 5	ND	15 [11; 36]	ND	7 [5; 11]
Total	155		250	

a: Patients with similar confounder characteristics are grouped in propensity score classes.
CI: confidence interval; N: number of analysed patients; NC: not calculable; ND: no data; vs.: versus

If the results on overall survival before the exclusion of patients due to missing data (grouped by [pool of] studies), the median survival time is longer in each study on the ipilimumab side than in the CA184024 study under dacarbazine (see Table 5). However, this difference based on the naive comparison of patients from different studies is not valid and does not allow to draw any reliable conclusions. This concurs with the company's assessment.

The effects of excluding approximately 40% of the patients on the ipilimumab side became apparent in the comparison of the median survival time after the exclusion of patients due to missing data and due to brain metastases (grouped according to propensity score class) on

both sides of the indirect comparison. Whereas on the dacarbazine side, the median survival time in the propensity score classes (Table 6), with values between 7 and 12 months, spread around the median of the total study arm (Table 5) of 9 months, the picture on the ipilimumab side was considerably different. In each single propensity score class (1 to 5), median survival on the ipilimumab side (15 to 29 months, see Table 6) was now higher in each single study on the basis of all patients (approximately 11 to 14 months, see Table 5). This shows that, on the ipilimumab side, those patients with a particularly bad prognosis were excluded from the analysis. Hence the effect resulting from this comparison was considerably biased in favour of ipilimumab. The observed increase in median survival time under ipilimumab can partly be explained by the exclusion of patients with brain metastases because the presence of brain metastases is a known negative prognostic factor for overall survival [9]. However, only 29 patients were excluded due to brain metastases. The majority (20 out of 29) of these patients were from the one-arm CA184332 study. The study documents of this study contain a subgroup analysis according to the presence of brain metastases. Patients with brain metastases have a bad prognosis (median survival time: 4.2 months). But the median survival time of patients without brain metastases from this study was 13.4 months and thus still below the median of each individual propensity score class. It rather was in the range of the patients of the pooled phase 2/3 studies, in which also exclusively patients without brain metastases were included. The increase in median survival time to 29 months on the ipilimumab side cannot be explained by the exclusion of patients with brain metastases. The largest part of the observed increase in median survival on the ipilimumab side of the indirect comparison presented by the company was therefore caused by bias due to the selective exclusion of patients on this side.

Due to the overall uncertain data and the additional bias caused by the selective exclusion of patients from the analysis, the treatment effect was not regarded to be large enough to be able to exclude that it was based solely on systematic bias. The company's analyses on overall survival were therefore unsuitable for the derivation of an added benefit of ipilimumab versus the ACT with regards to overall survival.

As additional information, the company presented a one-arm analysis of all study data of ipilimumab in the therapeutic indication of advanced melanoma based on individual patient data with regards to possible long-term survival (see Module 4, Section 4.3.2.3.3.2, Figure 19: Kaplan-Meier curves on long-term survival of all patients who were treated with ipilimumab 3 mg). Here all patients were considered who had received ipilimumab in the approved dosage (3 mg/kg, induction regimen), but independent from whether or not they had already had pretreatment).

The analysis in which data of 3120 patients in total were included was also unsuitable to derive an added benefit of ipilimumab versus the ACT dacarbazine. It only showed that individual patients survived for several years after ipilimumab treatment (the last patient was censored after about 118 months). It has to be considered that the number of patients who are still at risk decreases substantially over time. Already after 2 years, these are only 186 patients

(approximately 6%), after 5 years even only 29 patients (0.9%). This causes extreme uncertainty in the estimation of the survival probability on the right hand side of the Kaplan-Meier curve.

It was not clear from the analysis presented whether individual patients treated with dacarbazine had a similarly high survival because the company did not present the corresponding data on the ACT. It also did not provide reasons as to whether such a picture was not possible under dacarbazine treatment. A potential survival advantage versus dacarbazine cannot be estimated without such data. Hence it was unclear from the analysis presented whether the long-term survival of individual patients can be causally attributed to treatment with ipilimumab.

The long-term survival of ipilimumab compared with the ACT for patients with advanced (unresectable or metastatic) melanoma who have not received prior therapy for advanced melanoma cannot be assessed on the basis of this analysis.

This deviates from the company's assessment, which claimed a "dramatic effect" based on the result after applying the propensity score analysis for the outcome "overall survival" because the company considered ipilimumab to lead to major prolongation in median overall survival compared with dacarbazine.

Health-related quality of life

The disease-specific questionnaire EORTC QLQ-C30 was used in some studies (CA184022, MDX010-20 for the ipilimumab side, and CA184024 for the dacarbazine side) to assess the outcome "health-related quality of life". Results on this outcome were only available for some of the patients (ipilimumab side: 14 patients out of 21 from the studies in which health-related quality of life was recorded, dacarbazine side: 144 to 147 patients out of 252 depending on the component of the EORTC QLQ-C30, see Table 4). Because of the very small proportion of patients considered and the fact that this was an unadjusted indirect comparison of individual patients from different studies, the results on this outcome were not evaluable. This concurs with the company's assessment, which only gave a descriptive presentation of the results on health-related quality of life.

Adverse events

Several analyses on adverse events were available in the dossier, on the one hand based on raw rates, and on the other hand as time to first event. These analyses were available for the outcomes "adverse events", "serious adverse events" and "treatment discontinuation due to adverse events".

The analyses based on raw rates were based on a naive comparison of individual patients from different studies. Only the results from the RCTs were included in the analysis on the ipilimumab side. Hence the analyses were based on 78 (ipilimumab) and 250 (dacarbazine) patients. However, because this was an unadjusted analysis of individual patients from

different studies, the data presented by the company were not evaluable. There was also no effect that would have been large enough to derive conclusions on harm. This concurs with the company's assessment.

On the ipilimumab side of the indirect comparison, also only the results from the RCTs were included in the analyses of the time to first event. As for overall survival, the analyses on the basis of the propensity score analysis were available for this. Due to the missing data on the confounders considered, only 25 patients were included in the analysis on the ipilimumab side versus 250 patients on the dacarbazine side. Hence the same considerations apply to these analyses as to overall survival. A potentially relevant bias could not be excluded so that the treatment effects presented by the company could not be interpreted. This contradicts the company's assessment, which considers the data to be interpretable, but did not derive greater or lesser harm from ipilimumab because there was no statistical significance of the group difference.

2.3.4 Comments on the methods used for the company's comparison (propensity score analysis)

The certainty of results is an important criterion for the inference of conclusions on the evidence base [1]. The comparison of ipilimumab and dacarbazine using propensity scores presented by the company overall constituted a comparison that was exclusively based on individual patient data of individual treatment arms and not on the effects of randomized trials. There is general scientific consensus that the use of such unadjusted indirect comparisons is inadequate [10-12]. Conclusions on added benefit can only be derived from such analyses if the effect estimated on the basis of the available data is so large that it can be excluded that it is solely caused by systematic bias.

The company conducted the propensity score analysis to reduce possible bias caused by differences between the studies with the aim to provide "sufficient certainty of results for the assessment of the added benefit of ipilimumab" on the basis of the indirect comparison it presented. With the help of this statistical method, each patient is allocated to a certain propensity score class on the basis of the individual characteristics of the confounders (e.g. age = 60 years, ECOG PS = 1). The assumption is that the patients within one propensity score class are also comparable on average between the treatment groups with regards to the confounders. The approach of the company is comprehensible at first. However, the methodological approach is unsuitable to obtain the certainty of results of an adjusted indirect comparison, in which the randomization of the studies considered is maintained. In the propensity score analysis, only those confounders can be considered that were also recorded in the studies. It is advisable to consider as many variables as possible, particularly those known to have an influence on the treatment effect [13].

Prognostic factors under discussion that are described in the therapeutic indication (particularly for the outcome "overall survival") according to the information provided by the

company are age, sex, ethnic group, M stage of metastases, clinical patient status (ECOG PS), disease stage, presence of brain metastases, visceral disease and LDH status [9,14-18].

However, the company did not consider all of these known prognostic factors in its propensity score analysis. For example, matching for the presence of visceral metastases could not be conducted because this information was not or only partly recorded in the studies included by the company. If an important confounder is not considered in the propensity score analysis, this can lead to an increase in bias [13].

Another aspect which may influence the treatment effect and which was not considered in the propensity score analysis as prognostic factor is the time since the diagnosis of the melanoma: The patients included in the company's comparison differ greatly from each other in this respect (see Table 7, data are only available for the total study population). It is conceivable on the basis of these data that disease progression was different in these patients or that their disease progressed at different speed. It is completely unclear how this difference influenced the treatment effect. This aspect was also criticized in the central approval process [19].

Table 7: Characteristics of the study populations for the comparison of ipilimumab vs. dacarbazine presented by the company – time since diagnosis

	Ipilimumab side						**Dacar-bazine side**
Study	**CA184 004**	**CA184 022**	**MDX010 -08**	**MDX010 -20**	**CA184 332**	**CA184 338**	**CA184 024**
Total population[a]							
N[b]	40	72	40	137	61	120	252
Time since first diagnosis of the melanoma [months][c]							
Mean (SD)	69 (85.2)	69.3 (65.8)	5.5 (6.4)	4.3 (4.9)	25.2 (51.1)	31.2 (47.4)	40.4 (54.6)
Median	34.5	45.7	3.9	2.93	10.3	12.9	21.8
Min-max	1.1-384.0	6.2-271.1	0.1-32.5	0.0-35.9	0.2-352.5	0.3-291.4	0.4-396.0
Time since diagnosis of the advanced melanoma [months][c]							
Mean (SD)	ND	ND	ND	ND	1.2 (1.9)	1.7 (1.9)	ND
Median	ND	ND	ND	ND	0.7	1.1	ND
Min-max	ND	ND	ND	ND	0.0-10.2	0.1-12.7	ND

a: These data were not explicitly available for the "target population".
b: These data are based on the respective study arm from which patients were included in the company's comparison.
c: Time to randomization or to first treatment.
N: number of patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The methods of the analyses that the company used subsequent to the exclusion of patients and the propensity score analysis are not commented because they were not used for the assessment.

2.3.5 Summary

The comparison presented by the company was unsuitable for the derivation of conclusions on the added benefit because its uncertainty was too great due to the analysis presented (unadjusted indirect comparison). Moreover, the effect on overall survival described by the company as "dramatic", as described above, was relevantly biased in favour of ipilimumab because of the selective exclusion of patients from the analysis. The observed effect was therefore not sufficiently large to be able to exclude that it was only caused by systematic bias. The certainty of results was further reduced by the lack of consideration of further known confounders in the conduct of the propensity score analysis. Overall, the treatment effect on overall survival presented by the company was therefore not interpretable. This also applied to the results on further outcomes presented by the company (health-related quality of life, adverse events).

Hence an added benefit of ipilimumab versus the ACT is not proven for patients with advanced melanoma who have not received prior therapy to treat advanced melanoma.

Further information on the inclusion criteria for studies in this 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. Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Section 4.3.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment. Further information about the study design and the study populations can be found in Module 4, Section 4.3.1.2.1 of the dossier, and in Section 2.7.2.3.2 of the full dossier assessment.

2.4 Results on added benefit

The data included by the company in the assessment were unsuitable to derive an added benefit of ipilimumab versus the G-BA's ACT. Hence, there is no proof of an added benefit of ipilimumab over the ACT specified by the G-BA.

This result deviates from that of the company, which, on the basis of the comparison it presented, derived an added benefit of ipilimumab for treatment-naive patients with advanced melanoma.

Further information about the results on added benefit can be found in Module 4, Section 4.3.1.3 of the dossier, and in Section 2.7.2.4 of the full dossier assessment.

2.5 Extent and probability of added benefit

The result of the assessment of the added benefit of ipilimumab in comparison with the ACT is shown in Table 8.

Table 8: Ipilimumab – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Adult patients with advanced (unresectable or metastatic) melanoma who have not received prior therapy to treat advanced melanoma	Dacarbazine	Added benefit not proven
a: Presentation of the ACT specified by the G-BA.		

This assessment deviates from that of the company, which claimed an indication of major added benefit of ipilimumab in adult patients with advanced melanoma who have not received prior therapy to treat advanced melanoma.

The G-BA decides on the added benefit.

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.

2.6 List of included studies

The information usually provided here is not applicable as the company did not include any relevant studies for the assessment of the added benefit of ipilimumab versus the ACT specified by the G-BA in its assessment.

References for English extract

Please see full dossier assessment for full reference list.

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