Nivolumab
(Melanoma, adjuvant, stage IIB or IIC 1)

Addendum to Project A23-94
(dossier assessment)[1]

ADDENDUM

Project: A24-23 Version: 1.0 Status: 29 Feb 2024 DOI: 10.60584/A24-23_en

[1] Translation of the addendum *Nivolumab (Melanom, adjuvant, Stadium IIB oder IIC) – Addendum zum Projekt A23-94 (Dossierbewertung)*. 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

Nivolumab (Melanoma, adjuvant, stage IIB or IIC 1) – Addendum to Project A23-94

Commissioning agency

Federal Joint Committee

Commission awarded on

6 February 2024

Internal Project No.

A24-23

DOI-URL

https://dx.doi.org/10.60584/A24-23

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Simon Bogner
- Deborah Ingenhag-Reister
- Jona Lilienthal
- Katrin Nink

Keywords

Nivolumab, Melanoma, Adolescent, Adult, Benefit Assessment, NCT04099251

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
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)
MMRM	mixed-effects model repeated measures
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
VAS	visual analogue scale

1 Background

On 6 February 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-94 (Nivolumab – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the following analyses presented by the pharmaceutical company (hereinafter referred to as "the company") in the commenting procedure [2], taking into account the information provided in the dossier [3]:

- Analyses using a mixed-effects model repeated measures (MMRM) with observation period beyond the end of treatment for the outcomes on symptoms and health-related quality of life (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C-30 [EORTC QLQ-C30]) and for the outcome of health status (EQ-5D VAS)

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The randomized controlled trial (RCT) CA209-76K was included for the benefit assessment of nivolumab compared with the appropriate comparator therapy (ACT) “watchful waiting” for the adjuvant treatment of stage IIB or IIC melanoma after complete resection in adults and adolescents aged 12 years and older. A detailed description of the study can be found in dossier assessment A23-94 [1].

In compliance with the commission, the analyses on the outcomes of the categories “morbidity” and “health-related quality of life” recorded using the EORTC QLQ-C30 and the EQ-5D VAS, subsequently submitted by the company in the commenting procedure [2] are assessed below.

2.1 Assessment of the data subsequently submitted on patient-reported outcomes of the categories of morbidity and health-related quality of life

Surveys after the end of treatment were not taken into account in the MMRM analyses presented by the company in the dossier on the patient-reported outcomes in the categories of morbidity and health-related quality of life recorded using the EORTC QLQ-C30 and the EQ-5D VAS. For the EORTC QLQ-C30 and for the EQ-5D VAS, this concerns 2 follow-up surveys on Day 30 and on Day 100 after the last dose of study medication, and, for the EQ-5D VAS, also further surveys that were to take place every 12 weeks for up to 5 years after the end of treatment (measured by the period since the start of treatment). The analyses presented were therefore not usable for the benefit assessment.

As described in the dossier assessment, it is necessary that the entire observation period, including the follow-up surveys after the end of treatment, is included in the analyses and that the values after the end of treatment are assigned to the corresponding visits in a comprehensible manner (for further explanation see [1]).

In its comments, the company presented MMRM analyses over the entire observation period (including follow-up surveys after the end of treatment [end of 12-month adjuvant treatment or premature treatment discontinuation]) for the outcomes recorded using the EORTC QLQ-C30 or the EQ-5D VAS. These are used for the benefit assessment. The company presented analyses based on response criteria neither in the dossier nor in its comments.

2.2 Risk of bias

The risk of bias of the results for the outcomes on symptoms and health-related quality of life (each recorded using the EORTC QLQ-C30) is rated as high. For these outcomes, there are incomplete observations for potentially informative reasons due to the follow-up observation linked to the treatment duration and a possible association between outcome and reason for treatment discontinuation.

The risk of bias of the results of the outcome of health status (recorded using the EQ-5D VAS) is rated as high due to decreasing response rates in the later course of the study.

2.3 Results

Table 1 shows the results for the outcomes in the categories of morbidity (health status and symptoms) and health-related quality of life.

Table 1: Results (morbidity and health-related quality of life) – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Study outcome category outcome	Nivolumab			Placebo			Nivolumab vs. placebo
	N[a]	values at baseline mean (SD)	mean change in the course of the study mean[b] [95% CI]	N[a]	values at baseline mean (SD)	mean change in the course of the study mean[b] [95% CI]	MD [95% CI]; p-value[b]
CA209-76K							
Morbidity							
Health status (EQ-5D VAS)[c]	501	84.8 (13.8)	-1.05 [-1.89; -0.21]	256	84.7 (12.1)	0.12 [-1.03; 1.27]	-1.17 [-2.57; 0.23]; 0.103
Symptoms (EORTC QLQ-C30)[d]							
Fatigue	500	12.0 (16.7)	6.10 [4.90; 7.29]	254	12.1 (17.1)	4.48 [2.86; 6.10]	1.62 [-0.36; 3.61]; 0.109
Nausea and vomiting	500	1.7 (9.0)	1.57 [1.07; 2.07]	254	0.8 (3.8)	0.81 [0.14; 1.49]	0.76 [-0.07; 1.59]; 0.074
Pain	502	9.8 (19.1)	2.79 [1.63; 3.95]	254	10.1 (18.0)	0.23 [-1.35; 1.80]	2.56 [0.64; 4.49]; 0.009 SMD: 0.20 [0.05; 0.35]
Dyspnoea	500	6.5 (16.9)	2.39 [1.30; 3.48]	254	5.6 (15.9)	3.20 [1.73; 4.67]	-0.81 [-2.61; 0.99]; 0.379
Insomnia	499	17.6 (25.1)	0.11 [-1.26; 1.48]	254	14.8 (23.8)	-0.56 [-2.41; 1.29]	0.67 [-1.60; 2.94]; 0.563
Appetite loss	500	3.7 (13.3)	3.46 [2.54; 4.38]	254	3.0 (10.5)	1.49 [0.25; 2.72]	1.97 [0.46; 3.49]; 0.011 SMD: 0.20 [0.05; 0.35]
Constipation	500	5.1 (15.0)	0.91 [0.03; 1.80]	254	5.2 (15.1)	0.77 [-0.42; 1.96]	0.15 [-1.32; 1.61]; 0.844
Diarrhoea	501	4.1 (12.5)	1.82 [1.03; 2.60]	252	4.1 (12.5)	0.36 [-0.68; 1.41]	1.45 [0.17; 2.74]; 0.027 SMD: 0.17 [0.02; 0.32]

Table 1: Results (morbidity and health-related quality of life) – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Study outcome category outcome	Nivolumab N[a]	Nivolumab values at baseline mean (SD)	Nivolumab mean change in the course of the study mean[b] [95% CI]	Placebo N[a]	Placebo values at baseline mean (SD)	Placebo mean change in the course of the study mean[b] [95% CI]	Nivolumab vs. placebo MD [95% CI]; p-value[b]
Health-related quality of life							
EORTC QLQ-C30[c]							
Global health status	500	81.6 (17.2)	-4.16 [-5.18; -3.14]	251	82.3 (15.4)	-1.98 [-3.37; -0.59]	-2.18 [-3.88; -0.48]; 0.012 SMD: -0.19 [-0.35; -0.04]
Physical functioning	499	92.5 (13.4)	-2.01 [-2.81; -1.21]	254	91.5 (14.9)	-0.65 [-1.74; 0.44]	-1.36 [-2.69; -0.03]; 0.045 SMD: -0.15 [-0.31; 0.00]
Role functioning	501	91.2 (19.2)	-2.28 [-3.48; -1.08]	254	88.8 (21.8)	0.36 [-1.27; 1.99]	-2.64 [-4.64; -0.65]; 0.009 SMD: -0.20 [-0.35; -0.05]
Emotional functioning	501	86.1 (16.8)	0.96 [-0.08; 2.00]	252	87.5 (15.8)	1.04 [-0.38; 2.45]	-0.08 [-1.81; 1.65]; 0.929
Cognitive functioning	501	93.0 (13.5)	-2.30 [-3.25; -1.35]	252	95.1 (10.3)	-2.71 [-4.00; -1.42]	0.41 [-1.18; 1.99]; 0.612
Social functioning	501	92.4 (16.7)	0.02 [-0.97; 1.00]	252	91.8 (18.3)	1.76 [0.42; 3.09]	-1.74 [-3.37; -0.10]; 0.037 SMD: -0.16 [-0.31; -0.01]

a. Number of randomized patients with 1 value at baseline and at least 1 value after the start of the study.
b. MMRM with change at baseline as dependent variable; treatment and the interaction "treatment*documentation time" as fixed effects and baseline value and stratification factor as covariates. Only time points with at least 10 patients (EORTC QLQ-C30) or 20 patients (EQ-5D VAS) were included in the analysis.
d. Higher (increasing) values indicate better health status or better quality of life; positive effects (intervention minus control) indicate an advantage for the intervention.
d. Lower (decreasing) values indicate better symptoms; negative effects (intervention minus control) indicate an advantage for the intervention.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; SMD: standardized mean difference (Hedges' g); VAS: visual analogue scale

Because of the high risk of bias, at most hints, e.g. of an added benefit, can be derived on the basis of the available information for the outcomes of the categories "morbidity" (health status and symptoms) and "health-related quality of life".

Morbidity

Health status (EQ-5D VAS)

For the outcome of health status (surveyed using the EQ-5D VAS), no statistically significant difference between treatment groups was found. There is no hint of an added benefit of nivolumab in comparison with watchful waiting; an added benefit is therefore not proven.

Symptoms (EORTC QLQ-C30)

Symptom outcomes were recorded using the EORTC QLQ-C30 symptom scales. No statistically significant difference between the treatment groups was shown for the outcomes “fatigue”, “nausea and vomiting”, “dyspnoea”, “insomnia” and “constipation”. A statistically significant difference to the disadvantage of nivolumab compared with placebo was shown for the outcomes “pain”, “appetite loss” and “diarrhoea”. However, the respective 95% CI of the standardized mean difference was not fully outside the irrelevance range of [−0.2; 0.2]. It could therefore not be inferred that the effect was relevant. There is therefore no hint of an added benefit of nivolumab compared to "watchful waiting"; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Outcomes on health-related quality of life were recorded with the EORTC QLQ-C30 functional scales. No statistically significant difference between the treatment groups was shown for the outcomes “emotional functioning” and “cognitive functioning”. A statistically significant difference to the disadvantage of nivolumab compared with placebo was shown for each of the outcomes of global health status, physical functioning, role functioning and social functioning. However, the respective 95% CI of the SMD was not fully outside the irrelevance range [−0.2; 0.2]. It could therefore not be inferred that the effect was relevant. There is therefore no hint of an added benefit of nivolumab compared to "watchful waiting"; an added benefit is therefore not proven.

2.3.1 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment (see also dossier assessment A23-94):

- age (< 65/≥ 65)
- sex (female versus male)
- AJCC tumour stage (T3b vs. T4a vs. T4b)

The company has not submitted any subgroup analyses on the subsequently submitted analyses. In the present situation, the missing subgroup analyses are not assumed to have an impact on the overall conclusion on added benefit.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit of nivolumab from dossier assessment A23-94.

The following Table 2 shows the result of the benefit assessment of nivolumab, taking into account dossier assessment A23-94 and the present addendum.

Table 2: Nivolumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adjuvant treatment of stage IIB or IIC melanoma after complete resection in adults and adolescents 12 years of age or older	Watchful waiting	▪ Adults: hint of minor added benefit[b] ▪ adolescents 12 years of age and older: added benefit not proven
a. Presented is the ACT specified by the G-BA. b. Only patients with an ECOG-PS of 0 or 1 were included in the CA209-76K study. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2. ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Nivolumab (Melanom, adjuvant, Stadium IIB oder IIC); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2023 [Accessed: 16.02.2024]. URL: https://dx.doi.org/10.60584/A23-94.

2. Bristol-Myers Squibb. Stellungnahme zum IQWiG-Bericht Nr. 1693: Nivolumab (Melanom, adjuvant, Stadium IIB oder IIC) – Nutzenbewertung gemäß § 35a SGB V. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1000/#beschluesse im Dokument "Zusammenfassende Dokumentation"].

3. Bristol-Myers Squibb. Nivolumab (OPDIVO); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2023 [Accessed: 16.01.2024]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1000/#dossier.