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Nivolumab (melanoma, adjuvant) –

Addendum to Commission A21-39[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	preferred term
SAE	serious adverse event
SOC	system organ class

1 Background

On 10 August 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-39 (Nivolumab – Benefit assessment according to § 35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter "company") submitted the IMMUNED study for the direct comparison of nivolumab with the appropriate comparator therapy (ACT) selected by the company, namely watchful waiting, implemented as placebo. Some of the patients included in the study fail to meet the criteria for complete resection and are therefore not covered by the present therapeutic indication of nivolumab. Therefore, the IMMUNED study was not included in the benefit assessment.

The company's dossier [2] additionally presented an indirect comparison for the assessment of nivolumab versus the ACT of watchful waiting, implemented as placebo, through the common comparator ipilimumab; this indirect comparison was used in the benefit assessment. However, the outcomes of serious adverse events (SAEs), severe adverse events (AEs) (operationalized as Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) and discontinuation due to AEs exhibit insufficient certainty of results for performing an adjusted indirect comparison and were consequently disregarded in the benefit assessment.

After the oral hearing [3], the G-BA commissioned IQWiG with the following assessment on the basis of the information provided in the dossier [2], taking into account the information provided by the company in the commenting procedure [4]:

- Assessment of the IMMUNED study
- Results from the adjusted indirect comparison regarding adverse events (SAEs, severe AEs [CTCAE grade ≥ 3], discontinuation due to AEs)

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

2 Assessment

2.1 Assessment of the IMMUNED study

The IMMUNED study [5-7] is assessed below. The IMMUNED study is a multicentre, randomized, double-blind, investigator-initiated trial (IIT) with 3 study arms, comparing nivolumab versus the combination of nivolumab and ipilimumab versus placebo. The study included adult patients with stage IV melanoma (with distant metastases) who exhibited no evidence of disease after surgery or radiation therapy A detailed description of the study is found in dossier assessment A21-39 [1].

2.1.1 Study and patient characteristics

Information on study, intervention, and patient characteristics is found in dossier assessment A21-39 [1].

For the present research question, the G-BA defined watchful waiting as the ACT. In this benefit assessment, the ACT of watchful waiting was operationalized as a follow-up strategy comprising, in particular, recurrence diagnostics in accordance with the S3 Guideline "Diagnosis, therapy and follow-up of melanoma" [8]. The IMMUNED study compares the intervention to be assessed versus placebo. It was not designed for a comparison with watchful waiting. The investigations carried out in the study do not fully reflect the guideline's recommendations (e.g., lack of lymph node sonography in the first 3 years after completion of nivolumab therapy), but they included close follow-up observation specifically to detect recurrence. This strategy is deemed a sufficient approximation of the above-described operationalization of watchful waiting.

According to the Summary of Product Characteristics (SPC), nivolumab is to be administered at a dose of either 240 mg every 2 weeks or 480 mg every 4 weeks. Study participants, in contrast, received weight-based dosing at 3 mg/kg body weight. According to the SPC, however, the above dosing regimens do not differ in a clinically meaningful way in terms of efficacy or safety. For the results of the IMMUNED study, the deviation in the nivolumab dosing regimen was deemed not to meaningfully influence observed effects.

Planned duration of follow-up observation

Table 1 shows the planned duration of follow-up observation for the individual outcomes.

Table 1: Planned follow-up observation – RCT, direct comparison: nivolumab vs. placebo

Study **Outcome category** **Outcome**	**Planned follow-up observation**
IMMUNED	
Mortality	
Overall survival	Until death, withdrawal of informed consent, loss to follow-up, or study end[a]
Morbidity	
Recurrences	Until death, withdrawal of informed consent, loss to follow-up, or study end[a]
Health-related quality of life	Not recorded
Side effects	
All outcomes of the side effects category[b]	Until 90 days after the last dose of the study medication

a. The follow-up period was 2 to 5 years.
b. AEs were recorded only until patients started a new anti-neoplastic therapy. SAEs occurring after the start of a new anti-neoplastic therapy and deemed by the investigator to be related to the study drug were recorded for a maximum of 5 years after the last dose of the study drug.

AE: adverse event; RCT: randomized controlled trial; SAE: serious adverse event

Data cut-off dates

For the IMMUNED study, data from the interim analysis on 2 July 2019 are available for the outcome of recurrences as well as on the side effects outcomes. The interim analysis of recurrence-free survival was pre-defined to be conducted after all patients had been followed up for at least 6 months and 90 events had occurred.

Duration of treatment and follow-up observation

Table 2 shows the mean and median treatment durations as well as the mean and median follow-up durations for individual outcomes.

Table 2: Information on the course of the study – RCT, direct comparison: nivolumab vs. placebo

Study **Duration of the study phase** **Outcome category**	**Nivolumab** **N = 59**	**Placebo** **N = 52**
IMMUNED		
Treatment duration [weeks][a]		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND
Follow-up duration [months][b, c]		
Overall survival		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND
Morbidity (recurrences)		
Median [Q1; Q3]	30.6 [17.0; 37.5]	28.6 [22.6; 36.1]
Mean (SD)	ND	ND
Side effects		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND

a. Data on treatment durations are not plausible (nivolumab: 21.9 weeks [10.1; 50.9] vs. placebo: 24.1 weeks [10.1; 46.2]). The reported results are inexplicable when taking into account the results on recurrence-free survival and patient flow (in both study arms, recurrence was the primary reason for treatment discontinuation).
b. The company did not provide any information on how the follow-up duration was determined.
c. Zimmer 2020 [5] reports a median follow-up duration of 28.4 months [Q1: 17.7; Q3: 36.8]. However, it is unclear whether this information is based on a specific outcome.

N: number of analysed patients; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation

The data provided on treatment duration are not plausible. Patients in the IMMUNED study were treated with nivolumab or placebo for a maximum of 1 year or until recurrence, whichever was first. Due to pronounced differences in median times to event in recurrence-free survival (nivolumab arm: 12.4 months; placebo arm: 6.4 months) and high percentages of patients with treatment discontinuation due to recurrence (nivolumab: 42%; placebo: 69%), treatment durations are assumed to meaningfully differ between study arms. Since the planned follow-up observation is 90 days after the last dose of the study drug, the above difference likely also translates into relevant differences between study arms in the duration of follow-up for all outcomes of the side effects category.

Subsequent therapies

Table 3 shows the subsequent therapies patients received after discontinuing the study drug.

Table 3: Information on subsequent antineoplastic therapies – RCT, direct comparison: nivolumab vs. placebo

Study Subsequent therapy	Patients with subsequent therapy n (%)	
	Nivolumab N = 59	Placebo N = 52
IMMUNED study		
Total	20 (33.9)	18 (54.5)
Surgery	5 (8.5)	2 (6.1)
Radiation	4 (6.8)	1 (3.0)
Systemic therapy	15 (25.4)	16 (48.5)
Chemotherapy	0 (0)	0 (0)
Immunotherapy	7 (11.9)	14 (42.4)
Anti-PD 1	4 (6.8)	8 (24.2)
Anti-CTLA 4	2 (3.4)	0 (0)
Anti-PD-1 + CTLA-4	1 (1.7)	5 (9.6)
IL-2	0 (0)	1 (1.9)
Targeted therapy	8 (13.6)	2 (6.1)
MEK inhibitor	1 (1.7)	0 (0)
BRAF/MEK combination	7 (11.9)	2 (6.1)

BRAF: Serine/threonine-protein kinase B-raf; CTLA-4: cytotoxic T-lymphocyte antigen 4; IL-2: interleukin-2; MEK: mitogen-activated extracellular signal-regulated kinase; n: number of patients with subsequent therapy; N: number of analysed patients; PD-1: programmed death ligand 1; RCT: randomized controlled trial

2.1.2 Results

Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - Overall survival
- Morbidity
  - Recurrences
- Health-related quality of life
- Side effects
  - SAEs
  - Severe AEs (operationalized as CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - Immune-mediated AEs
  - Further specific AEs, if any

Table 4 shows the outcomes of the IMMUNED study for which data were available.

Table 4: Matrix of outcomes – RCT, direct comparison: nivolumab vs. placebo

Study	Outcomes							
	Overall survival	Recurrences[a]	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-mediated AEs	Further specific AEs
IMMUNED	Yes[c]	Yes	No[d]	No[e]	No[e]	No[e]	No[e]	No[f]

a. Operationalized as recurrence rate and recurrence-free survival; includes the events of local recurrence, local recurrence and distant metastasis, distant metastasis, second primary melanoma, and unknown.
b. Operationalized as CTCAE grade 3–4.
c. For the data cut-off of 2 July 2019, no analysis of the outcome was planned. However, mortality data are available from study discontinuation data.
d. Outcome not recorded.
e. No usable data available; for reasoning, see body of text.
f. No usable analyses are available on AEs, rendering it impossible to select specific AEs; for reasoning, see body of text.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; RCT: randomized controlled trial; SAE: serious adverse event

- Overall survival: For the outcome of overall survival, deaths reported in study discontinuation data were used. Analyses of the outcome were not planned for the interim analysis; therefore, the relative risk is presented as an approximation.
- Recurrences: For the outcome of recurrences, the percentage of patients with recurrence and additionally time to recurrence are presented.
- Side effect outcomes: Due to the major differences in median time-to-event data for recurrence-free survival and the high percentages of patients with treatment discontinuation due to recurrence, follow-up durations can be assumed to differ substantially between treatment arms (for an explanation, see Section 2.1.1). Given the available evidence, relative risk is therefore an unsuitable effect measure. However, rather than including any time-to-event analyses for these outcomes, the company's dossier presents only analyses with relative risk as effect measure. The analyses presented by the company are therefore unusable. The publication on the study likewise does not offer any time-to-event analyses of side effects outcomes [5].
    - Additional aspects on immune-mediated AEs: The company's dossier does not present any analyses for this outcome. The publication on the study [5] includes results on immune-mediated AEs. However, it remains unclear whether these data are based on

all surveyed AEs, irrespective of whether the investigator deemed them related to the study drug. Consequently, these analyses on immune-mediated AEs are unusable.

- Additional aspects on further specific AEs: The company's dossier does not include any analyses on AEs by system organ class (SOC) and preferred term (PT) as per MedDRA. The publication on the study [5] contains analyses by SOC and PT only for AEs which the investigator deemed related to the study drug. These analyses are therefore unusable for selecting specific AEs.

Risk of bias and certainty of results

The risk of bias across outcomes is rated as low for the IMMUNED study. IQWiG calculations of relative risk for the outcome of overall survival likely suffer from a high risk of bias given the high percentage of patients for whom no complete follow-up observation is available (15.3% in nivolumab arm versus 17.3% in placebo arm). For the results of the outcome of recurrences, the risk of bias is deemed low. The results on side effects outcomes are unusable because, given the available evidence, relative risk is an unsuitable effect measure. For the results on these outcomes, the risk of bias was therefore not assessed.

Results

Table 5 summarizes the results from the comparison of nivolumab versus placebo in adult patients with stage IV melanoma (with distant metastases).

Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier. Kaplan-Meier curves for the event-time analyses are found in Appendix A.

Table 5: Results (overall survival, morbidity, side effects) – RCT, direct comparison: nivolumab vs. placebo

Study Outcome category Outcome	Nivolumab N	Nivolumab Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Nivolumab vs. placebo RR [95% CI]; p-value
IMMUNED					
Mortality					
Overall survival[a]	59	8 (13.6)	52	7 (13.5)	1.01 [0.39; 2.59]; > 0.999[b]
Morbidity					
Recurrences					
Recurrence rate[c]	59	33 (55.9)	52	42 (80.8)	0.69 [0.53; 0.90]; 0.005[b]
Local recurrence	59	7 (11.9)	52	13 (25.0)	-
Local recurrence and distant metastasis	59	2 (3.4)	52	4 (7.7)	-
Distant metastasis	59	23 (39.0)	52	23 (44.2)	-
Second primary melanoma	59	1 (1.7)	52	1 (1.9)	-
Unknown	59	0	52	1 (1.9)	-
Recurrence-free survival[d]	59	Median time to event (in months): 12.4 [5.3; 33.3]	52	Median time to event (in months): 6.4 [3.3; 9.6]	HR: 0.56 [0.35; 0.89]; 0.013[e]
Side effects					
AEs (supplementary information)	56	54 (96.4)	51	49 (96.1)	-
SAEs	56	19 (33.9)	51	15 (29.4)	-[f]
Severe AEs[g]	56	23 (41.1)	51	13 (25.5)	-[f]
Discontinuation due to AEs	56	7 (12.5)	51	2 (3.9)	-[f]
Immune-mediated AEs				No usable data[h]	

a. No analyses were available on the outcome of overall survival, but study discontinuation data provided information on deaths.
b. IQWiG calculation; CI asymptotic; p-value: unconditional exact test, (CSZ method according to [9]).
c. Percentage of patients with recurrence; individual components shown in the lines below.
d. Operationalized as the time from randomization day to 1st occurrence of an event; see recurrence rate for individual components.
e. HR; CI: unstratified proportional hazards model; p-value: unstratified log rank test.
f. No usable data available because given the available evidence, RR is not a suitable effect measure. See body of text for detailed reasoning.
g. Operationalized as CTCAE grade 3–4.
h. The company's dossier does not provide any analyses for this outcome. The publication on the study includes results on immune-mediated AEs. However, it remains unclear whether these data are based on all surveyed AEs, irrespective of whether the investigator deemed them related to the study drug.

CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; CI: confidence interval; n: number of patients with (at least 1) event; CSZ: convexity, symmetry, z score; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; AE: adverse event

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. This results in no advantage or disadvantage of nivolumab versus placebo.

Morbidity

Recurrences

For the outcome of recurrences (operationalized as recurrence rate and recurrence-free survival), there is a statistically significant difference in favour of nivolumab in comparison with placebo.

Side effects

For outcomes in the side effects category, no usable data were available. This results in no advantage or disadvantage of nivolumab versus placebo.

2.1.2.1 Subgroups and other effect modifiers

For this assessment, the following potential effect modifiers were taken into account:

- Age (< 65 versus ≥ 65 years)
- Sex
- Metastasis stage (M1a versus M1b versus M1c)

Interaction tests were performed whenever at least 10 patients per subgroup were included in the analysis. For binary data, there must also be 10 events in at least 1 subgroup.

Only results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant effect in at least one subgroup.

Subgroup analyses are available only for recurrence-free survival. No effect modification was found in these subgroup analyses.

2.2 Results on adverse events from the adjusted indirect comparison

The company's dossier presents results from an adjusted indirect comparison on the basis of the CA209-238 and CA184-029 studies (hereinafter referred to as studies 238 and 029). However, the results on the outcomes of SAEs, severe AEs, and discontinuation due to AEs obtained from the adjusted indirect comparison lack the certainty of results required for performing an adjusted indirect comparison. For the outcomes of SAEs and severe AEs, this is due to a high risk of bias of results due to incomplete observation for potentially informative reasons in light of substantially different median observation durations between study arms in

both studies. Despite a low risk of bias, the outcome of discontinuation due to AEs has a reduced certainty of results due to competing events. The results are presented in Table 6.

Table 6: Results (side effects) – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Outcome category **Outcome** **Comparison** **Study**	**Nivolumab vs. placebo** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Ipilimumab** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Group difference** **HR [95% CI]; p-value[a]**
Side effects					
SAEs[b]					
Nivolumab vs. ipilimumab					
Study 238 (data cut-off 29/01/2020)	367	NR 75 (20.4)	367	NR [6.44; NR] 172 (46.9)	0.31 [0.23; 0.40]; < 0.001
Placebo vs. ipilimumab					
Study 029 (data cut-off 13/05/2016)	377[c]	NR 80 (21.2)	373	9.69 [4.21; 21.22] 200 (53.6)	0.28 [0.22; 0.36][d]; < 0.001
Indirect comparison using common comparators[e]:					
Nivolumab vs. placebo					1.10 [0.75; 1.60]; 0.633
Severe AEs[b,f]					
Nivolumab vs. ipilimumab					
Study 238 (data cut-off 29/01/2020)	367	NR 111 (30.2)	367	3.25 [2.76; 4.80] 228 (62.1)	0.30 [0.24; 0.38]; < 0.001
Placebo vs. ipilimumab					
Study 029 (data cut-off 13/05/2016)	377[c]	NR [38.60; NR] 96 (25.5)	373	8.08 [3.29; 14.52] 204 (54.7)	0.33 [0.26; 0.42][d]; < 0.001
Indirect comparison using common comparators[e]:					
Nivolumab vs. placebo					0.93 [0.66; 1.29]; 0.646

Table 6: Results (side effects) – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Outcome category Outcome Comparison Study	Nivolumab vs. placebo N	Median time to event in months [95% CI] Patients with event n (%)	Ipilimumab N	Median time to event in months [95% CI] Patients with event n (%)	Group difference HR [95% CI]; p-value[a]
Discontinuation due to AEs[b]					
Nivolumab vs. ipilimumab					
Study 238 (data cut-off 29/01/2020)	367	NR 43 (11.7)	367	NR [7.85; NR] 173 (47.1)	0.18 [0.13; 0.25]; < 0.001
Placebo vs. ipilimumab					
Study 029 (data cut-off 13/05/2016)	377[c]	NR 22 (5.8)	373	17.97 [8.31; 28.78] 184 (49.3)	0.09 [0.05; 0.13][d]; < 0.001
Indirect comparison using common comparators[e]:					
Nivolumab vs. placebo					2.07 [< 1.19; 3.62]; < 0.010

a. Unstratified Cox model; unstratified log rank test.
b. For the side effects outcomes of both studies, the company presented analyses without recording progression of the underlying disease; each analysis was based on the period from treatment start until 100 days after treatment end.
c. Data on patients included in the analysis are based on selection via IRT. For the prior benefit assessment on Study 029, in contrast, the company presented analyses on the basis of selection via CRF [10]. This results in a lower percentage of randomized patients being excluded from analysis (n=11).
d. IQWiG calculations; reversed direction of effect (company submitted the comparison of ipilimumab vs. placebo).
e. Indirect comparison according to Bucher [11].
f. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CRF: case report form; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; IRT: interactive response technology; N: number of analysed patients; n: number of patients with event; NR: not reached; RCT: randomized controlled trial; SAE: serious adverse event

2.3 Summary

In summary, nivolumab offers the following advantages and disadvantages when compared to watchful waiting:

- The IMMUNED study shows an advantage in the outcome of recurrences.
- The adjusted indirect comparison reveals a disadvantage in the outcome of discontinuation due to AEs.

The G-BA decides on the added benefit.

3 References

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Appendix A – Kaplan-Meier curves

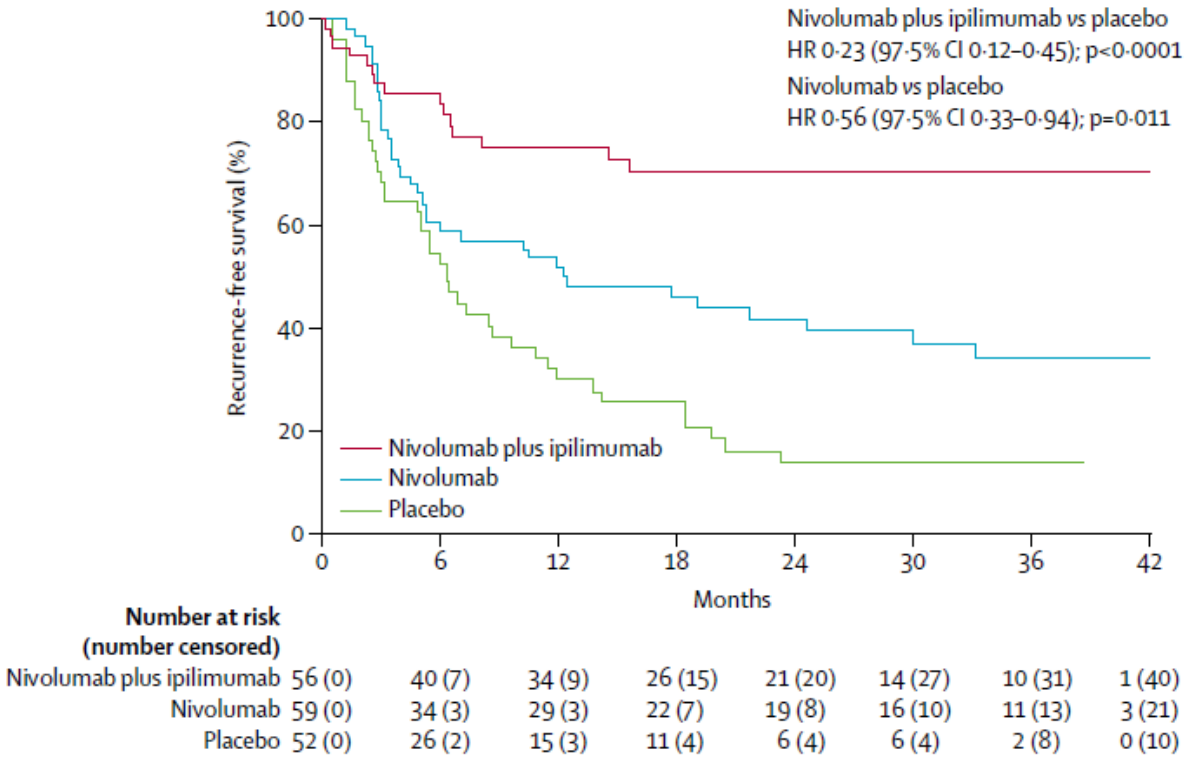

Figure 1: Kaplan-Meier curves on recurrence-free survival from the IMMUNED study (data cut-off 07/02/2019).