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Nivolumab (squamous cell carcinoma of the head and neck) –

Addendum to Commission A17-24[1]

Addendum

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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)
MTX	methotrexate
SAE	serious adverse event

1 Background

On 9 October 2017, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-24 (Nivolumab – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") had presented results of the CA209-141 study for the assessment of the added benefit of nivolumab in comparison with the appropriate comparator therapy (ACT).

With its written comment on the dossier assessment [3] and after the oral hearing [4], the company submitted further data on this study. The G-BA commissioned IQWiG with the assessment of the analyses on adverse events (AEs) and on the subgroup analyses on prior cetuximab therapy.

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

2.1 Assessment of the analyses on adverse events subsequently submitted

With its written comment, the company presented further analyses on AEs on the following 2 topics:

1) analyses on further specific AEs
2) analyses on the overall rates of severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or higher) and serious AEs (SAEs), each under consideration of progression events

These data are assessed in the following Sections.

Analyses on specific adverse events

Survival time analyses

The company had not presented survival time analyses for specific AEs in its original dossier. Dossier assessment A17-24 stated that, in view of the concrete data situation in the CA209-141 study, relative risks could be interpreted with sufficient certainty, which is why this effect measure was used.

Irrespective of this, the company subsequently submitted with its comment survival time analyses for those specific AEs that had been highlighted in dossier assessment A17-24 for the relevant methotrexate (MTX) subpopulation or for the total population [1]. The corresponding data are presented as additional information in Table 2 and Table 3 in Appendix A. The results of the survival time analyses concurred with the results based on relative risks, and the data presented did not change the certainty of conclusions on specific AEs. The conclusion of dossier assessment A17-24 was therefore not changed by the survival time analyses subsequently submitted.

Subgroup analyses

The company had not presented subgroup analyses for specific AEs in its original dossier. The company also presented corresponding data, but they were selective and hence incomplete. These analyses were therefore not considered further. Irrespective of this, the data presented showed no effect modification (see Table 4 and Table 5 in Appendix A).

Pneumonitis and immune-related events

In its original dossier, the company had presented no data for the MTX subpopulation for the specific AE “pneumonitis”. It subsequently submitted these data with the comment. According to these data, such an event occurred in 3 of 116 (2.6%) patients under nivolumab, and no such event occurred under MTX (p-value for group difference: $p = 0.368$; see also Table 2 in Appendix A). Hence these data did not change the conclusion of dossier assessment A17-24.

There was no patient-relevant operationalization on immune-related events in the CA209-141 study (see dossier assessment A17-24 for details [1]). With its comment, the company only referred to the data already presented with the dossier; it did not present new analyses with a relevant operationalization on immune-related events.

Analyses on the overall rates of severe adverse events and serious adverse events, each under consideration of progression events

In its dossier, besides AE analyses comprising all AEs, the company also presented analyses excluding events that had a high probability of being caused by progression of the underlying disease. In the CA209-141 study, AEs were recorded up to 100 days after the end of treatment. Besides an analysis comprising this total observation period, analyses with a follow-up observation period of 30 days after the end of treatment were also planned.

Analyses without progression with a follow-up observation period of 100 days were used for dossier assessment A17-24 [1]. Since survival time analyses on analyses with progression were only available for a follow-up observation period of 30 days, but not for 100 days, for severe AEs and SAEs, the influence of the concrete approach of the company (choice of events not to be considered) for this follow-up observation period could not be estimated.

The company subsequently submitted the corresponding analyses with the comment (see Table 6 for the MTX subpopulation and Table 7 for the total population, each in Appendix A). In each case, this resulted in no qualitative difference between the analysis with or without progression (MTX subpopulation: no statistically significant result for severe AEs and SAEs; total population: statistically significant result in favour of nivolumab for severe AEs, no statistically significant result for SAEs).

Summary

In summary, the further analyses on AEs presented by the company did not change the result of dossier assessment A17-24 on nivolumab.

2.2 Assessment of the subgroup analyses on the characteristic "prior cetuximab therapy"

Besides the results of the relevant MTX subpopulation, the results of the total population of the CA209-141 study were also presented in dossier assessment A17-24 [1]. An interaction for the characteristic "prior cetuximab therapy" was shown in the total population, and an advantage of nivolumab for overall survival was only shown in the group of patients without prior cetuximab therapy.

Prior cetuximab therapy was the only stratification characteristic of the CA209-141 study. It can be inferred from the study protocol of the study that the rationale for this was a known or potential effect modification in overall survival by this characteristic. This assumption was confirmed by the result of the CA209-141 study.

Since no interaction for the characteristic "prior cetuximab therapy" was shown within the MTX subpopulation, possible interactions within the 2 other treatment strata (docetaxel subpopulation and cetuximab subpopulation) were discussed in the oral hearing [5]. The company subsequently submitted corresponding analyses after the oral hearing [4]. In accordance with the discussion in the oral hearing, these were limited to analyses on the outcome "overall survival".

The analyses subsequently submitted showed that the interaction apparent in the total population ($p = 0.031$) was mainly due to an interaction in the docetaxel subpopulation ($p = 0.047$). This subpopulation comprised about 39% of the total population. No interaction was shown in the cetuximab subpopulation ($p = 0.673$; about 13% of the total population), as well as in the MTX subpopulation ($p = 0.622$; about 47% of the total population).

Based on the interaction observed in the docetaxel subpopulation, the company conducted subgroup analyses on the outcome "overall survival" for the characteristic "prior cetuximab therapy" for this subpopulation. The result within the docetaxel subpopulation was not statistically significant for patients with prior cetuximab therapy or for cetuximab-naive patients ($p = 0.405$ for pretreated patients, $p = 0.095$ for treatment-naive patients). However, the company only presented the p-values mentioned. Effect estimations including confidence intervals as well as the corresponding Kaplan-Meier curves were missing. In particular, it therefore remained unclear whether there was a qualitative interaction with negative effect estimation (i.e. unfavourable for nivolumab) within the docetaxel subpopulation in the subgroup of patients with prior cetuximab therapy because no advantage for overall survival could be derived for these patients based on the results of the total population.

The results on the subgroup characteristic "prior cetuximab therapy" presented by the company did not change the conclusions of dossier assessment A17-24 because the conclusions on the added benefit of nivolumab were based on the MTX subpopulation. Instead, in view of the heterogeneous data situation between the different treatment options on

this stratification characteristic, they supported the approach not to use the results of the total population as the basis of the assessment.

2.3 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 A17-24.

The following Table 1 shows the result of the benefit assessment of nivolumab under consideration of dossier assessment A17-24 [1] and the present addendum.

Table 1: Nivolumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with squamous cell carcinoma of the head and neck who have progressed during or after platinum-based therapy	Individual treatment of physician's choice (chemotherapy, radiotherapy and/or surgery; in case of drug treatment under consideration of the respective approval)	▪ Patients with progression during or within 6 months after platinum-based therapy[b]: indication of considerable added benefit ▪ Patients with progression after more than 6 months after platinum-based therapy: added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. b: Methotrexate is usually the only remaining approved drug treatment option for this patient group. Nivolumab was investigated in comparison with methotrexate in the relevant subpopulation of the CA209-141 study. Only patients with an ECOG PS of 0 or 1 were included in the study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2. ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee		

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

3 References

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2. Bristol-Myers Squibb. Nivolumab (Opdivo): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 24.05.2017 [Accessed: 07.09.2017]. URL: https://www.g-ba.de/informationen/nutzenbewertung/294/.

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5. Gemeinsamer Bundesausschuss. Nivolumab: Mündliche Anhörung gemäß 5. Kapitel § 19 Abs. 2 Verfahrensordnung des Gemeinsamen Bundesausschusses [online]. 09.10.2017 [Accessed: 20.10.2017]. URL: https://www.g-ba.de/downloads/91-1031-294/2017_10_09_Wortprotokoll_Nivolumab_D-291.pdf.

Appendix A – Data on AEs subsequently submitted by the company

Table 2: Results for outcomes "specific adverse events" from CA209-141 (MTX subpopulation; second data cut-off from 20 September 2016) – time to first AE – table from comment of the company

SOC or PT[(1)]	Nivolumab N=116 Patients with event n (%)	MTX N=46 Patients with event n (%)	Nivolumab vs. MTX HR[(2)] [95% CI]
AEs until 30 days after the end of treatment			
Respiratory, thoracic and mediastinal disorders	54 (46.6)	10 (21.7)	2.299 (1.169; 4.520)
Mucosal inflammation	5 (4.3)	8 (17.4)	0.157 (0.047; 0.527)
Skin and subcutaneous tissue disorders	34 (29.3)	6 (13.0)	2.208 (0.923; 5.281)
Headache	12 (10.3)	0	NME p = 0.0469[(3)]
Pneumonitis (AE ≥ grade 2)	3 (2.6)	0	NME p = 0.3683[(3)]

AE = adverse event; CI = confidence interval; CTC = Common Toxicity Criteria; HR = hazard ratio; MedDRA = Medical Dictionary for Regulatory Activities; MTX = methotrexate; N = number of analysed patients; NME = not meaningfully estimable; PT = Preferred Term; SOC = System Organ Class

(1) MedDRA version 19.0 and CTC version 4.0 were used.

(2) Unstratified Cox model.

(3) Unstratified log-rank test.

Table 3: Results for outcomes "specific adverse events" from CA209-141 (total population; second data cut-off from 20 September 2016) – time to first AE – table from comment of the company

SOC or PT[(1)]	**Nivolumab N=236 Patients with event n (%)**	**Treatment of physician's choice N=111 Patients with event n (%)**	**Nivolumab vs. treatment of physician's choice HR[(2)] [95% CI]**
AEs until 30 days after the end of treatment			
Alopecia	2 (0.8)	14 (12.6)	0.064 (0.015; 0.282)
Mucosal inflammation	9 (3.8)	18 (16.2)	0.171 (0.074; 0.396)
Neutropenia (AE grade 3–4)	1 (0.4)	8 (7.2)	< 0.001 (< 0.001; NA); 0.032 (0.003; 0.304) [(3)]
General disorders and administration site conditions (AE grade 3–4)	17 (7.2)	18 (16.2)	0.411 (0.211; 0.799)
Pneumonitis (AE ≥ grade 2)	4 (1.7)	2 (1.8)	0.795 (0.143; 4.418)

AE = adverse event; CI = confidence interval; CTC = Common Toxicity Criteria; HR = hazard ratio; IVRS = interactive voice response system; MedDRA = Medical Dictionary for Regulatory Activities; N = number of analysed patients; NA: not applicable or not achieved; PT = Preferred Term; SOC = System Organ Class

(1) MedDRA version 19.0 and CTC version 4.0 were used.

(2) Cox model stratified by prior cetuximab therapy according to IVRS.

(3) Unstratified Cox model.

Table 4: Results of the interaction tests for specific AEs – study CA209-141 (MTX subpopulation; second data cut-off from 20 September 2016) – table from comment of the company

Study CA209-141	**p-value of the interaction test[(1)]** **Analysis of specific AEs**		
Subgroup	**Respiratory, thoracic and mediastinal disorders**	**Mucosal inflammation**	**Skin and subcutaneous tissue disorders**
Age group I	0.9505	0.4736	0.0840*
Age group II	0.9871	0.9926	0.9997
Age group III	0.9753	0.8853	0.2567
Sex	0.9862	0.9880	0.9892
Ethnicity	0.1431*	> 0.9999	> 0.9999
Region	0.4824	> 0.9999	0.6285
ECOG Performance Status	0.5762	0.9119	0.8245
Prior cetuximab therapy according to CRF	0.7944	0.9914	0.4206
Disease stage	0.0706*	0.9936	0.5409
HPV 16 status	0.6058	0.9915	0.6304
Smoker	0.8393	0.8716	0.7083
Prior surgery	0.3642	0.5134	0.9883
Prior radiotherapy	0.8914	0.9937	0.9904
Location of primary tumour	0.3277	0.8420	0.7644
Number of prior systemic therapies	0.1928*	0.4443	0.5911
Number of prior chemotherapies in the metastatic setting	0.9910	0.4537	0.6297
Response to most recent therapy	0.3629	0.9997	0.4916
Time from diagnosis to randomization	0.8115	0.1016*	0.7798
PD-L1 status with threshold value 1%	0.7182	0.9573	0.9881

Study CA209-141	**p-value of the interaction test[(1)]** **Analysis of specific AEs**		
Subgroup	**Respiratory, thoracic and mediastinal disorders**	**Mucosal inflammation**	**Skin and subcutaneous tissue disorders**
PD-L1 status with threshold value 5%	0.9635	0.9937	0.8290
PD-L1 status with threshold value 10%	0.8634	0.9941	0.8855

AE = adverse event; CRF = case report form; ECOG = Eastern Cooperative Oncology Group; HPV = human papillomavirus; NA = not applicable or not achieved; PD-L1 = programmed death ligand 1

(1) p-values between ≥ 0.05 and < 0.20 are marked with an asterisk (indication of an interaction), p-values < 0.05 are marked with 2 asterisks (proof of an interaction).

Table 5: Results of the interaction tests for specific AEs – study CA209-141 (total population; second data cut-off from 20 September 2016) – table from comment of the company

Study CA209-141	**p-value of the interaction test[(1)] Analysis of specific AEs**				
Subgroup	**Alopecia**	**Mucosal inflammation**	**Neutropenia (AE grade 3–4)**	**General disorders and administration site conditions (AE grade 3–4)**	**Pneumonitis (AE ≥ grade 2)**
Age group I	0.9929	0.4108	0.9952	0.8548	0.6295
Age group II	0.9993	0.9887	0.9996	0.9832	> 0.9999
Age group III	> 0.9999	0.8470	> 0.9999	0.7696	0.9169
Sex	0.5171	0.5652	0.9994	0.6185	0.9942
Ethnicity	> 0.9999	> 0.9999	> 0.9999	0.9999	0.7205
Region	> 0.9999	0.5344	> 0.9999	0.4306	> 0.9999
ECOG Performance Status	0.9910	0.6522	0.9943	0.6093	0.9936
Prior cetuximab therapy according to CRF	0.4939	0.3104	0.9934	0.3754	0.9942
Intended treatment of physician's choice according to IVRS	> 0.9999	0.9968	> 0.9999	0.9993	> 0.9999
Disease stage	0.9993	0.6800	0.9985	0.1094*	> 0.9999
HPV 16 status	0.9927	0.1836*	0.9941	0.0900*	0.9936
Smoker	> 0.9999	0.6912	> 0.9999	0.7027	0.8820
Prior surgery	0.9992	0.1508*	0.9937	0.2036	0.9954
Prior radiotherapy	0.9932	0.9900	0.9936	0.3321	0.9946
Location of primary tumour	0.9292	0.5655	> 0.9999	0.7213	0.9570
Number of prior systemic therapies	0.5530	0.5688	> 0.9999	0.9960	> 0.9999
Number of prior chemotherapies in the metastatic setting	0.8567	0.8113	> 0.9999	0.4243	> 0.9999

Study CA209-141	**p-value of the interaction test[(1)] Analysis of specific AEs**				
Subgroup	**Alopecia**	**Mucosal inflammation**	**Neutropenia (AE grade 3–4)**	**General disorders and administration site conditions (AE grade 3–4)**	**Pneumonitis (AE ≥ grade 2)**
Response to most recent therapy	0.9944	0.9913	0.9952	0.6496	0.9955
Time from diagnosis to randomization	0.9932	0.0855*	0.9951	0.1532*	0.6204
PD-L1 status with threshold value 1%	0.9942	0.9031	0.9996	0.6179	0.9952
PD-L1 status with threshold value 5%	0.9940	0.2959	0.9995	0.3609	0.9951
PD-L1 status with threshold value 10%	0.9939	0.9884	0.9997	0.3776	0.9955

AE = adverse event; CRF = case report form; CTC = Common Toxicity Criteria; ECOG = Eastern Cooperative Oncology Group; HPV = human papillomavirus; IVRS = interactive voice response system; NA = not applicable or not achieved; PD-L1 = programmed death ligand 1

(1) p-values between ≥ 0.05 and < 0.20 are marked with an asterisk (indication of an interaction), p-values < 0.05 are marked with 2 asterisks (proof of an interaction).

Table 6: Sensitivity analysis: results for outcomes “adverse events” (analysis of all recorded AEs [including progression]; 100-day follow-up) from CA209-141 (MTX subpopulation; second data cut-off from 20 September 2016) – time to first AE (long version) – table from comment of the company

	Nivolumab				Methotrexate				Nivolumab vs. methotrexate		
AEs until 100 days after the end of treatment	**N**	**Patients with event n (%)**	**Censored patients n (%)**	**Median time to first AE in months (95% CI)**	**N**	**Patients with event n (%)**	**Censored patients n (%)**	**Median time to first AE in months (95% CI)**	**HR[(1)] (95% CI)**	**p-value[(2)]**	**AD in months**
Any AE	116	115 (99.1)	1 (0.9)	0.26 (0.16; 0.39)	46	45 (97.8)	1 (2.2)	0.18 (0.07; 0.26)	0.802 (0.566; 1.135)	0.2058	0.08
AE grade 3-4	116	76 (65.5)	40 (34.5)	2.89 (1.97; 4.14)	46	33 (71.7)	13 (28.3)	1.87 (0.89; 2.79)	0.687 (0.453; 1.042)	0.0737	1.02
Serious AE	116	80 (69.0)	36 (31.0)	3.04 (1.87; 4.80)	46	37 (80.4)	9 (19.6)	2.71 (1.68; 3.98)	0.724 (0.486; 1.077)	0.1062	0.33
Treatment discontinuation due to AE	116	25 (21.6)	91 (78.4)	NA (NA; NA)	46	10 (21.7)	36 (78.3)	NA (5.32; NA)	0.887 (0.422; 1.866)	0.7516	NA

AD = absolute difference; AE = adverse event; CI: confidence interval; HR = hazard ratio; N = number of analysed patients; NA = not applicable or not achieved

(1) Unstratified Cox model.
(2) Unstratified log-rank test.

Table 7: Sensitivity analysis: results for outcomes "adverse events" (analysis of all recorded AEs [including progression]; 100-day follow-up) from CA209-141 (total population; second data cut-off from 20 September 2016) – time to first AE (long version) – table from comment of the company

	Nivolumab				Treatment of physician's choice				Nivolumab vs. treatment of physician's choice		
AEs until 100 days after the end of treatment	**N**	**Patients with event n (%)**	**Censored patients n (%)**	**Median time to first AE in months (95% CI)**	**N**	**Patients with event n (%)**	**Censored patients n (%)**	**Median time to first AE in months (95% CI)**	**HR[(1)] (95% CI)**	**p-value[(2)]**	**AD in months**
Any AE	236	233 (98.7)	3 (1.3)	0.26 (0.16; 0.36)	111	110 (99.1)	1 (0.9)	0.16 (0.10; 0.26)	0.721 (0.572; 0.908)	0.0037	0.10
AE grade 3-4	236	150 (63.6)	86 (36.4)	2.79 (1.97; 4.14)	111	89 (80.2)	22 (19.8)	1.74 (1.28; 2.10)	0.606 (0.464; 0.792)	0.0002	1.05
Serious AE	236	160 (67.8)	76 (32.2)	3.06 (2.10; 4.50)	111	85 (76.6)	26 (23.4)	2.96 (1.97; 3.65)	0.774 (0.592; 1.011)	0.0593	0.10
Treatment discontinuation due to AE	236	61 (25.8)	175 (74.2)	20.50 (18.20; NA)	111	25 (22.5)	86 (77.5)	NA (9.17; NA)	1.017 (0.633; 1.633)	0.9430	NA

AD = absolute difference; AE = adverse event; CI: confidence interval; HR = hazard ratio; IVRS = interactive voice response system; N = number of analysed patients; NA = not applicable or not achieved

(1) Cox model stratified by prior cetuximab therapy according to IVRS.

(2) Log-rank test stratified by prior cetuximab therapy according to IVRS.