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Nivolumab (oesophageal carcinoma, combination with chemotherapy) –

Addendum to Commission A22-54 (dossier assessment)[1]

Addendum

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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

- Selver Altin
- Katharina Hirsch
- Regine Potthast
- Volker Vervölgyi

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
FACT-E	Functional Assessment of Cancer Therapy – Esophagus
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PD-L1	programmed death ligand-1
RCT	randomized controlled trial
VAS	visual analogue scale

1 Background

On 6 September 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments on Commission A22-54 (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 of data on time to first deterioration, surveyed using the European Quality of Life Questionnaire – 5 Dimensions (EQ-5D) visual analogue scale (VAS)
- analyses of data on time to first deterioration, surveyed using the Functional Assessment of Cancer Therapy – Esophagus (FACT-E)

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

2 Assessment

The randomized controlled trial (RCT) CheckMate 648 was used for benefit assessment A22-54 [1], which evaluated nivolumab in combination with fluoropyrimidine-based and platinum-based combination chemotherapy (hereinafter referred to as "chemotherapy") in comparison with the appropriate comparator therapy (ACT) as first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma with tumour cell programmed death ligand-1 (PD-L1) expression ≥ 1%. The CheckMate 648 study is a 3-arm RCT comparing nivolumab either in combination with 5-fluorouracil and cisplatin (hereinafter referred to as "nivolumab + chemotherapy") or in combination with ipilimumab versus a combination chemotherapy of 5-fluorouracil and cisplatin (hereinafter referred to as "chemotherapy"). For the present benefit assessment, the only relevant comparison is that between the 2 treatment arms of nivolumab + chemotherapy (intervention arm) versus chemotherapy (comparator arm). Furthermore, only the relevant subpopulation of patients with tumour cell PD-L1 expression ≥ 1% was taken into account.

A detailed description of the CheckMate 648 study can be found in benefit assessment A22-54 [1].

From the CheckMate 648 study, the company's dossier provided no usable data on the patient-reported outcomes of health status (surveyed with the EQ-5D VAS) or health-related quality of life (surveyed with the FACT-E). In the commenting procedure, the company submitted analyses of time to first deterioration for both outcomes [2]. The company clarified that both outcomes were surveyed until the 2nd follow-up observation visit [2].

2.1 Subsequently submitted responder analyses of time to first deterioration

For the outcomes of health status (surveyed with EQ-5D) and health-related quality of life (surveyed with FACT-E), the dossier [3]contained analyses of what it referred to as time to definitive deterioration. Definitive deterioration was defined as a clinically relevant deterioration without subsequent improvement to a value which no longer represents a clinically relevant deterioration. None of these analyses were deemed usable (for reasoning, see dossier assessment A22-54 [1]).

In the commenting procedure, the company submitted responder analyses of time to first deterioration for the outcomes of health status and health-related quality of life [2]. In accordance with the Institute's General Methods[4], the subsequently submitted responder analyses include analyses with a response criterion of ≥ 15 points for the EQ-5D VAS and ≥ 27 points for the FACT-E, which corresponds to 15% of each instrument's scale range.

Given the available evidence, these analyses are deemed adequate and are used for the benefit assessment.

2.2 Risk of bias

For the outcomes of health status, surveyed with the EQ-5D VAS, and health-related quality of life, surveyed with the FACT-E, the risk of bias of results is rated as high. The reasons for this rating are (1) lack of blinding in the presence of subjective recording of outcomes and (2) incomplete observation for potentially informative reasons (predominantly due to the differences in treatment and observation durations and shortened follow-up observation [see [1]]).

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 health status and health-related quality of life.

2.3 Results

Table 1 shows the results on the outcomes of health status, surveyed with the EQ-5D VAS, and health-related quality of life, surveyed with the FACT-E. The results for the subscales of the FACT-E are presented as supplementary information (15% of the scale range of the respective subscale). No Kaplan-Meier curves are available for the responder analyses of time to first deterioration.

Table 1: Results (morbidity, health-related quality of life) – RCT, direct comparison: nivolumab + chemotherapy[a] versus chemotherapy[a] (relevant subpopulation) (multipage table)

Study Outcome category Outcome	Nivolumab + chemotherapy[a]		Chemotherapy[a]		Nivolumab + chemotherapy[a] vs. chemotherapy[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][b]; p-value[c]
CheckMate 648					
Morbidity					
Health status (EQ-5D VAS)[d]	155	11.43 [7.6; 18.27] 65 (41.9)	143	8.25 [5.0; 12.9] 59 (41.3)	0.72 [0.50; 1.04]; 0.165
Health-related quality of life					
FACT-E[d]	152	NR 38 (25.0)	140	NR [8.5; NC] 36 (25.7)	0.72 [0.45; 1.14]; 0.202
FACT-G (supplementary information)[e]	153	NR [12.6; NC] 47 (30.7)	140	15.67 [8.5; NC] 40 (28.6)	0.78 [0.50; 1.20]; 0.227
PWB (supplementary information)[e]	155	6.97 [4.0; 7.7] 86 (55.5)	141	4.30 [2.8; 5.7] 73 (51.8)	0.85 [0.62; 1.17]; 0.252
SWB (supplementary information)[e]	155	16.89 [10.7; NC] 55 (35.5)	141	9.63 [6.7; NC] 47 (33.3)	0.67 [0.44; 1.00]; 0.190
EWB (supplementary information)[e]	154	20.76 [7.0; NC] 62 (40.3)	141	13.60 [9.0; NC] 43 (30.5)	1.16 [0.78; 1.72]; 0.628
FWB (supplementary information)[e]	153	7.72 [5.6; 12.6] 74 (48.4)	140	9.53 [4.2; 15.7] 60 (42.9)	0.82 [0.58; 1.17]; 0.548
ECS (supplementary information)[e]	154	32.26 [19.8; NC] 44 (28.6)	142	14.42 [7.1; 20.5] 51 (35.9)	0.49 [0.32; 0.75]; 0.003
FACT-G7 (supplementary information)[e]	154	9.79 [7.0; 18.3] 81 (52.6)	141	7.49 [5.3; 14.4] 66 (46.8)	0.78 [0.56; 1.10]; 0.214

a. Cisplatin in combination with 5-fluorouracil.
b. HR and CI: Cox proportional hazards model; stratified by ECOG-PS (0, 1) and number of organs with metastases (≤ 1, ≥ 2) as per IRT as well as adjusted for the respective baseline value.
c. p-value: log rank test; stratified by ECOG-PS (0, 1) and number of organs with metastases (≤ 1, ≥ 2) as per IRT.
d. Time to first deterioration. Score deceases in the EQ-5D VAS by ≥ 15 points and in the FACT-E by ≥ 27 points from baseline are deemed clinically relevant deteriorations (scale range of EQ-5D VAS: 0 to 100; scale range of FACT-E: 0 to 176).
e. Time to first deterioration. Presented are decreases in the FACT-G score by ≥ 17 points from baseline, the PWB, SWB, FWB, and FACT-G7 scores by ≥ 5 points from baseline, the EWB score by ≥ 4 points from baseline, and the ECS score by ≥ 11 points from baseline (scale ranges: FACT-G: 0 to 198; PWB, SWB, FWB, FACT-G7: 0 to 28; EWB: 0 to 24; ECS: 0 to 68).

Table 1: Results (morbidity, health-related quality of life) – RCT, direct comparison: nivolumab + chemotherapy[a] versus chemotherapy[a] (relevant subpopulation) (multipage table)

Study Outcome category Outcome	Nivolumab + chemotherapy[a]		Chemotherapy[a]		Nivolumab + chemotherapy[a] vs. chemotherapy[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][b]; p-value[c]
CI: confidence interval; ECOG-PS: Eastern Cooperative Oncology Group-Performance Status; ECS: Esophageal Cancer Subscale; EWB: emotional well-being; FACT-E: Functional Assessment of Cancer Therapy – Esophagus; FACT-G: Functional Assessment of Cancer Therapy – General; FACT-G7: Functional Assessment of Cancer Therapy – General 7-item version; FWB: functional well-being; HR: hazard ratio; IRT: Interactive Response Technology; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; PWB: physical well-being; RCT: randomized controlled trial; SWB: social well-being; VAS: visual analogue scale					

Morbidity

Health status

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

Health-related quality of life

FACT-E

For the outcome of health-related quality of life (surveyed using the FACT-E), no statistically significant difference between treatment groups was found. This results in no hint of an added benefit of nivolumab + chemotherapy in comparison with chemotherapy; an added benefit is therefore not proven.

2.4 Subgroups and other effect modifiers

For the present benefit assessment, the following subgroup characteristics are relevant (see benefit assessment A22-54 [1]):

- age (< 65 years versus ≥ 65 years and < 75 years versus ≥ 75 years)
- sex (male versus female)
- disease status for current diagnosis (recurrent – locoregional versus recurrent – distant metastasis versus de novo metastatic versus unresectable advanced)

Based on the methods described in dossier assessment A22-54, there are no relevant effect modifications for the outcomes of health status and health-related quality of life.

2.5 Probability and extent of added benefit

2.5.1 Assessment of added benefit at outcome level

Because the subsequently submitted analyses result in no hint of an added or lesser benefit, the extent of added benefit at outcome level is not presented in table form. Added benefit is not proven for any of them.

2.5.2 Overall conclusion on added benefit

Table 2 presents the results of the benefit assessment for commission A22-54 and the present addendum A22-98, both of which were factored into the overall conclusion on the extent of added benefit.

Table 2: Favourable and unfavourable effects from the assessment of nivolumab + chemotherapy[a] in comparison with chemotherapy[a] (relevant subpopulation)

Favourable effects	Unfavourable effects
Entire observation period	
Mortality ▪ Overall survival: indication of added benefit – extent: major	–
Shortened observation period	
Serious/severe side effects ▪ Vomiting, pneumonia (each severe AEs): each hint of lesser harm – extent: minor	–
–	Non-serious/non-severe side effects ▪ Discontinuation due to AEs: hint of greater harm – extent: minor
a. Cisplatin in combination with 5-fluorouracil. AE: adverse event	

The data subsequently submitted by the company in the commenting procedure have changed the conclusion on the added benefit of nivolumab in combination with fluoropyrimidine-based and platinum-based combination chemotherapy from dossier assessment A22-54.

Overall, both favourable and unfavourable effects of nivolumab + chemotherapy were found in comparison with chemotherapy.

For the favourable effects, there is an indication of major added benefit for the outcome of overall survival and a hint of lesser harm of minor extent for each of the specific adverse events (AEs) of vomiting and pneumonia. For the unfavourable effects, in contrast, there is a hint of greater harm of minor extent for the outcome of discontinuation due to AEs, but this effect does not call into question the favourable effect in overall survival.

Usable data are now available for the outcome categories of morbidity and health-related quality of life, but they show no relevant favourable or unfavourable effects.

In summary, for adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%, there is an indication of major added benefit of nivolumab + chemotherapy in comparison with the ACT of chemotherapy.

2.6 Summary

The data subsequently submitted by the company in the commenting procedure change the conclusion from dossier assessment A22-54 on the added benefit of nivolumab in combination with fluoropyrimidine-based and platinum-based combination chemotherapy: There is an indication of major added benefit for first-line therapy of unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1% in adult patients.

Table 3 below shows the result of the benefit assessment of nivolumab in combination with fluoropyrimidine-based and platinum-based combination chemotherapy, taking into account both dossier assessment A22-54 and the present addendum.

Table 3: Nivolumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with unresectable[b] advanced, recurrent, or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%; first-line treatment; combination with fluoropyrimidine-based and platinum-based combination chemotherapy	Cisplatin[c] in combination with 5-fluorouracil	Indication of major added benefit[d]
a. Presented is the respective ACT specified by the G-BA. b. In accordance with the CheckMate 648 study's inclusion criteria, the G-BA presumes, in this therapeutic indication, that curative treatment with definitive chemoradiotherapy is not an option for patients with unresectable cancer. c. The G-BA presumes the patients to be candidates for cisplatin-containing chemotherapy. d. The CheckMate 648 study included only patients with an ECOG-PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2. ACT: appropriate comparator therapy; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; G-BA: Federal Joint Committee; PD-L1: programmed death ligand 1		

The G-BA decides on the added benefit.

3 References

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