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Nivolumab (oesophageal carcinoma, combination with ipilimumab) –

Addendum to Commission A22-55 (dossier assessment)[1]

Addendum

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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 for Commission A22-55 (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 is 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 A22-55 [1], which evaluated nivolumab in combination with ipilimumab 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 ipilimumab (hereinafter referred to as "nivolumab + ipilimumab") or in combination with 5-fluorouracil and cisplatin versus a combination chemotherapy of 5-fluorouracil and cisplatin (hereinafter referred to as "chemotherapy"). For the present benefit assessment, the only relevant comparison is the one between the 2 treatment arms of nivolumab + ipilimumab (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 A22-55 [1].

For 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] contains analyses of what it refers 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 A22-55 [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

The risk of bias of results is rated as high for the outcomes of health status, surveyed with the EQ-5D VAS, and health-related quality of life, surveyed with the FACT-E. The reasons for these ratings are (a) lack of blinding in the presence of subjective recording of outcomes and (b) incomplete observation for potentially informative reasons (because the observation duration of these outcomes is linked to the onset of progression and the associated end of administration of the study medication [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 subscales). No Kaplan-Meier curves are available for the responder analyses of time-to-first deterioration.

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

Study Outcome category Outcome	Nivolumab + ipilimumab		Chemotherapy[a]		Nivolumab + ipilimumab 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]	154	6.24 [3.8; 25.1] 70 (45.5)	143	8.25 [5.0; 12.9] 59 (41.3)	0.93 [0.65; 1.32]; 0.768
Health-related quality of life					
FACT-E[d]	156	25.07 [12.5; NC] 51 (32.7)	140	NR [8.5; NC] 36 (25.7)	1.11 [0.72; 1.71]; 0.401
FACT-G (supplementary information)[e]	156	13.60 [8.7; NC] 60 (38.5)	140	15.67 [8.5; NC] 40 (28.6)	1.05 [0.70; 1.59]; 0.434
PWB (supplementary information)[e]	156	7.03 [5.5; 11.2] 77 (49.4)	141	4.30 [2.8; 5.7] 73 (51.8)	0.64 [0.46; 0.90]; 0.019
SWB (supplementary information)[e]	156	9.72 [5.7; NC] 58 (37.2)	141	9.63 [6.7; NC] 47 (33.3)	0.89 [0.60; 1.32]; 0.902
EWB (supplementary information)[e]	156	16.39 [8.3; NC] 54 (34.6)	141	13.60 [9.0; NC] 43 (30.5)	0.90 [0.60; 1.36]; 0.740
FWB (supplementary information)[e]	156	4.24 [2.8; 12.5] 79 (50.6)	140	9.53 [4.2; 15.7] 60 (42.9)	1.00 [0.71; 1.41]; 0.431
ECS (supplementary information)[e]	156	32.69 [11.2; NC] 55 (35.3)	142	14.42 [7.1; 20.5] 51 (35.9)	0.87 [0.59; 1.28]; 0.528
FACT-G7 (supplementary information)[e]	156	11.17 [6.2; 20.7] 77 (49.4)	141	7.49 [5.3; 14.4] 66 (46.8)	0.80 [0.57; 1.12]; 0.300

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

Study Outcome category Outcome	Nivolumab + ipilimumab		Chemotherapy[a]		Nivolumab + ipilimumab 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 + ipilimumab 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 + ipilimumab 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 A22-55 [1]):

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

Based on the methods described in dossier assessment A22-55 [1], no relevant effect modifications were found 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 the 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 A22-55 and the present addendum A22-99, 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 + ipilimumab in comparison with chemotherapy[a] (relevant subpopulation)

Favourable effects	**Unfavourable effects**
Total observation period	
Mortality ▪ Overall survival: indication of added benefit – extent: major[b]	–
Shortened observation period	
Serious/severe side effects ▪ Vomiting (SAEs), anaemia, nervous system disorders (severe AEs each): each hint of lesser harm; extent: minor ▪ Neutrophil count decreased (severe AEs): hint of lesser harm; extent: major	Serious/severe side effects ▪ SAEs: hint of greater harm; extent: minor Including: ▫ immune-mediated SAEs: hint of greater harm; extent: major ▪ Immune-mediated severe AEs: hint of greater harm – extent: "major"
Non-serious/non-severe side effects ▪ Gastrointestinal disorders, alopecia, hiccups, renal and urinary disorders (AEs each): each hint of lesser harm; extent: considerable ▪ Mucosal inflammation (AEs): hint of lesser harm; extent: nonquantifiable	–
a. Cisplatin in combination with 5-fluorouracil. b. Kaplan-Meier curves cross after about 6 months (see Figure 2 of dossier assessment A22-55 [1]); major added benefit is found only in the later course of treatment. According to the SPC, physicians should consider the delayed onset of nivolumab effect in combination with ipilimumab before initiating treatment in patients with poorer prognostic features and/or aggressive disease [5]. AE: adverse event; SAE: serious adverse event	

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of nivolumab in combination with ipilimumab from dossier assessment A22-55.

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

In terms of favourable effects, there was an indication of major added benefit for the outcome of overall survival. However, due to the Kaplan-Meier curves crossing at about 6 months, this effect in favour of nivolumab + ipilimumab becomes apparent only in the further course of treatment. On the basis of the data presented by the company, it is impossible to determine the extent to which patient characteristics or other factors explain the crossing of the Kaplan-Meier curves. Hence, it cannot be conclusively determined which patients reap major benefit from the intervention. On the basis of exploratory post hoc analyses, the European regulatory authority included a corresponding warning in the SPC, according to which physicians should consider the delayed onset of nivolumab effect in combination with ipilimumab before initiating treatment in patients with poorer prognostic features and/or aggressive disease [5,6].

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.

Furthermore, numerous specific outcomes of the side effects category show hints of lesser harm, of different extents and for both for serious/severe and nonserious/nonsevere side effects. Regarding unfavourable effects, hints of greater harm, some of them of major extent, were found for the outcomes of serious adverse events (SAEs) and immune-related serious or severe adverse events (AEs), but this did not call into question the favourable effect concerning overall survival.

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 on the added benefit of nivolumab in combination with ipilimumab from dossier assessment A22-55: 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.

The following Table 3 shows the results of the benefit assessment of nivolumab in combination with ipilimumab, taking into account both dossier assessment A22-55 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	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 assumes that, in this therapeutic indication, patients with unresectable cancer are not indicated for curative treatment with definitive chemoradiotherapy.
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. According to the SPC, physicians should consider the delayed onset of nivolumab effect in combination with ipilimumab before initiating treatment in patients with poorer prognostic features and/or aggressive disease [5].

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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