Nivolumab (oesophageal or gastro-oesophageal junction cancer, adjuvant)

Addendum to Project A25-88 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

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

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IQWiG employees involved in the addendum

- Alina Reese
- Katrin Nink
- Katherine Rascher
- Ulrike Seay

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Abbreviation	Meaning
CRT	chemoradiotherapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
RR	relative risk
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 12 November 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-88 (Nivolumab – Benefit assessment according to §35a Social Code Book V) [1].

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

- Presentation and analysis of the subgroup analysis based on location of disease

The responsibility for this 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) CA209-577 was included for the benefit assessment of nivolumab in adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy (CRT). A detailed description of the study can be found in the dossier assessment [1].

The following potential effect modifiers were considered in dossier assessment A25-88:

- Age (< 65 years versus ≥ 65 years)
- Sex (female versus male)
- Pathologic lymph node status (ypN0 [negative] versus ≥ ypN1 [positive] versus unknown)

The presentation and assessment of the subgroup analyses on the characteristic 'location of disease' (oesophageal cancer versus gastro-oesophageal junction cancer) was commissioned for this addendum. These subgroup analyses are presented below.

2.1 Subgroup results for the characteristic 'location of disease'

As described in the dossier assessment, the following methodological specifications apply to the presentation of subgroup results.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

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

For the outcome category of side effects, the company considered the time to event, using the hazard ratio (HR) as the effect measure. The subgroup analyses conducted by the company for this outcome category were also based on the HR. In contrast to the approach of the company, the assessment A25-88 [1] used analyses of the number of patients with event with the relative risk (RR) effect measure for the side effect outcomes to derive the added benefit. Analyses based on the RR were therefore also preferable for the subgroup analyses. This benefit assessment therefore examined whether, using the HR, there was a significant effect modification at the 0.2 level. If this was the case, an interaction test was performed using the Q test, based on the RR.

The subgroup results are shown in Table 1, and the corresponding Kaplan-Meier curves for the subgroup results are shown in Appendix A.

Table 1: Subgroups (mortality, time to event) – RCT, direct comparison: nivolumab vs. placebo

Study Outcome Characteristic Subgroup	nivolumab N	nivolumab Median time to event in months [95 % CI] Patients with event n (%)	Placebo N	Placebo Median time to event in months [95 % CI] Patients with event n (%)	nivolumab vs. placebo HR [95% CI][a]	nivolumab vs. placebo p-value[a]
CA209-577						
Overall survival						
Location of disease						
Oesophageal cancer	314	49.5 [36.6; 65.4] 177 (56.4)	153	31.4 [24.4; 36.6] 105 (68.6)	0.69 [0.55; 0.88]	0.003
Gastro-oesophageal junction cancer	218	54.9 [39.2; 78.6] 122 (56.0)	109	64.2 [35.2; NC] 57 (52.3)	1.14 [0.83; 1.56]	0.418
Total					Interaction[b]:	0.015

a. HR: unstratified Cox model; p-value: log-rank test.
b. Based on Cox model adjusted for treatment, subgroup and treatment*subgroup interaction term.

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial

Mortality

There was an effect modification by the characteristic 'location of disease' for the outcome of overall survival.

For patients with tumour location in the oesophagus, there was a statistically significant difference in favour of nivolumab compared with placebo. For patients with tumour location in the gastro-oesophageal junction, there was no statistically significant difference between the treatment groups.

Neither the relevant guidelines nor the commenting procedure provide any justification for selecting this subgroup characteristic. For example, there is no indication that the location of the tumour has prognostic relevance [3-6]. Therefore, the results presented had no impact on the assessment of the added benefit of nivolumab in this therapeutic indication.

2.2 Summary

The assessment of the effect modification by the characteristic 'location of disease' does not change the conclusion on the added benefit of nivolumab from dossier assessment A25-88.

The following Table 2 shows the result of the benefit assessment of nivolumab, taking into account dossier assessment A25-88 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 adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy[b]	Watchful waiting	Added benefit not proven[c]

a. Presented is the ACT specified by the G-BA.
b. The CA209-577 study included both patients with adenocarcinoma and patients with squamous cell carcinoma in stages II and III (per AJCC 7th edition [7]) after neoadjuvant chemoradiotherapy with R0 resection and residual pathologic disease. Since only patients with complete resection were included, the G-BA assumes that patients with ≥ R1 resection are not covered by the therapeutic indication.
c. Only patients with an ECOG PS of 0 or 1 were included in the CA209-577 study. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; AJCC: American Joint Committee on Cancer; 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.

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Appendix A Kaplan-Meier curves

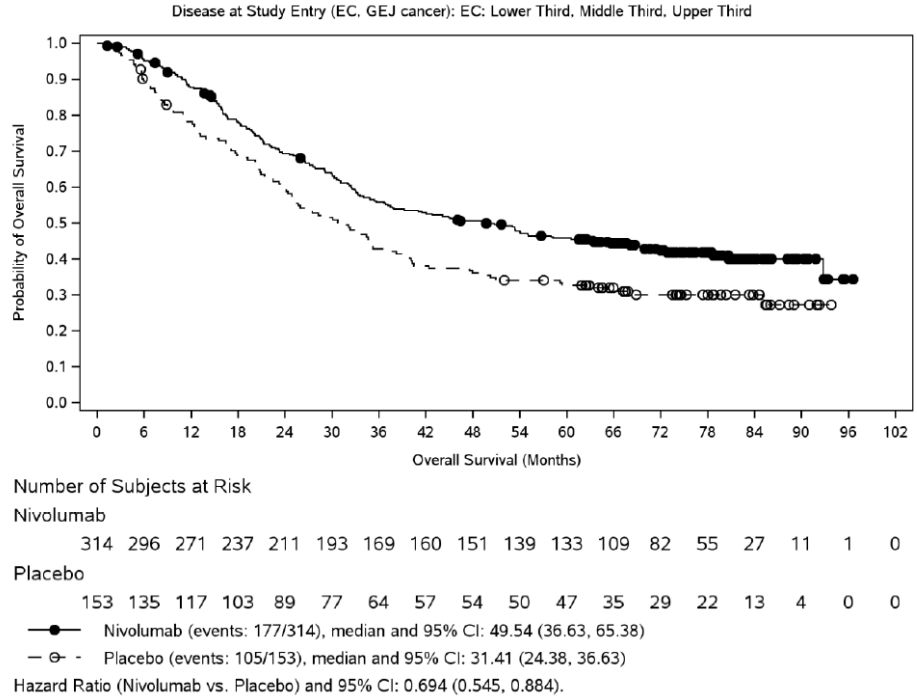

Figure 1: Kaplan-Meier curves for the outcome overall survival in patients with oesophageal cancer, CA209-577

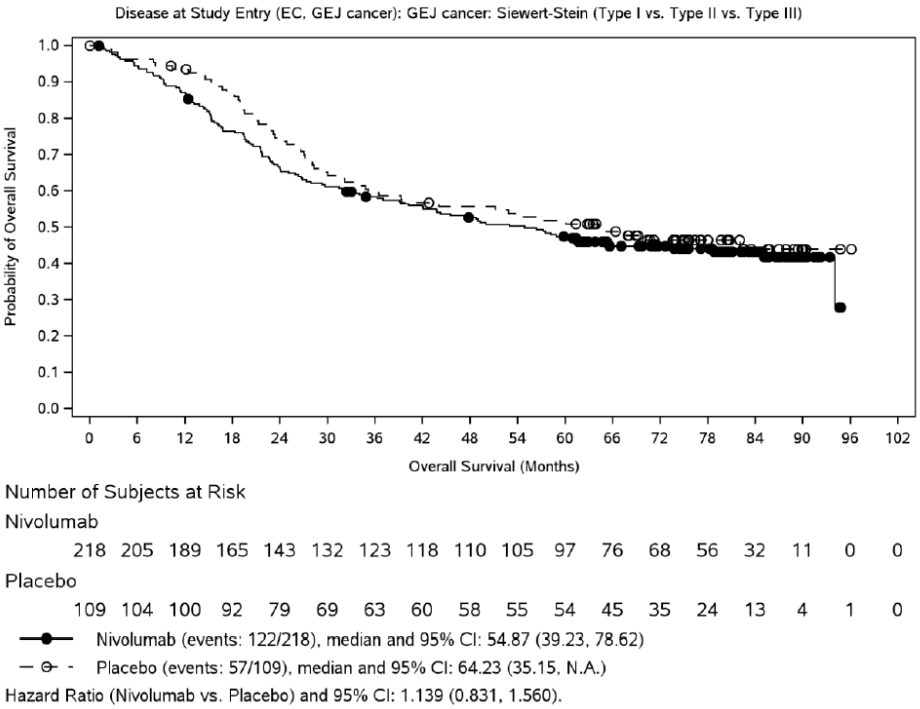

Figure 2: Kaplan-Meier curves for the outcome overall survival in patients with gastro-oesophageal junction cancer, CA209-577