

Nivolumab (urothelial carcinoma, adjuvant)

Addendum to Project A25-154
(dossier assessment [expiry of the decision])¹

A decorative horizontal bar composed of 18 squares of varying shades of blue and grey. The text 'ADDENDUM (DOSSIER ASSESSMENT)' is centered in white on a dark blue background.

ADDENDUM (DOSSIER ASSESSMENT)

Project: A26-45

Version: 1.0

Status: 13 May 2026

DOI: 10.60584/A26-45_en

¹ Translation of the addendum *Nivolumab (Urothelkarzinom, adjuvant)* – Addendum zum Projekt A25-154 (*Dossierbewertung*). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Nivolumab (urothelial carcinoma, adjuvant) – Addendum to Project A25-154

Commissioning agency

Federal Joint Committee

Commission awarded on

29 April 2026

Internal Project No.

A26-45

DOI-URL

https://doi.org/10.60584/A26-45_en

Address of publisher

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Recommended citation

Institute for Quality and Efficiency in Health Care. Nivolumab (urothelial carcinoma, adjuvant); Addendum to Project A25-154 (dossier assessment [expiry of the decision]) [online]. 2026 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A26-45_en.

Keywords

Nivolumab, Carcinoma – Transitional Cell, Benefit Assessment, NCT02632409

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	Adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 29 April 2026, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-154 (nivolumab (urothelial carcinoma, adjuvant) – Benefit assessment according to §35a Social Code Book V [expiry of the resolution]) [1].

The commission comprises the assessment of the analyses submitted by the pharmaceutical company (hereinafter referred to as the “company”) [2] in the commenting procedure, taking into account the information in the dossier [3]:

- Data on immune-mediated severe adverse events (AEs) and immune-mediated serious AEs (SAEs) (effect estimates, Medical Dictionary for Regulatory Activities [MedDRA] terms, Kaplan-Meier curves, subgroup analyses)

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

In the dossier for benefit assessment A25-154, the company did not provide any analyses on immune-mediated AEs, SAEs or severe AEs. Consequently, the data on immune-mediated AEs, immune-mediated SAEs and immune-mediated severe AEs at the data cut of 17 July 2020 – which were already available for the first assessment of nivolumab in this therapeutic indication (A22-53) [4] – were used. This was possible because the follow-up for all AEs until 100 days after the last administration of the study medication had already been largely completed at the data cut of 17 July 2020, and it was not assumed that any significant number of events will have been added at the relevant data cut of 6 January 2025.

With its comments of 2 April 2026 [2], the company subsequently submitted results on the outcomes immune-mediated AEs, SAEs and severe AEs, as well as corresponding Kaplan–Meier curves, subgroup analyses and common immune-mediated AEs, SAEs and severe AEs at the data cut of 6 January 2025. These are assessed below.

2.1 Results

Table 1 summarizes the results for the outcomes immune-mediated AEs, SAEs and severe AEs at the data cut of 6 January 2025.

The Kaplan-Meier curves on the time-to-event analyses are presented in Appendix A, and the results on common immune-mediated AEs, SAEs and severe AEs are presented in I Appendix B.

Table 1: Results (side effects, time to event) – Randomized controlled trial (RCT), direct comparison: nivolumab vs. placebo

Study outcome category	Nivolumab		Placebo		Nivolumab vs. placebo
outcome	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]; p-value ^a
CA209-274 (data cut: 06 January 2025)					
Side effects					
Immune-mediated AEs (supplementary information) ^b	139	1.45 [0.95; 2.33] 111 (79.9)	139	5.42 [2.76; 8.05] 80 (57.6)	–
Immune-mediated SAEs ^b	139	NA 16 (11.5)	139	NA 6 (4.3)	2.49 [0.97; 6.37] 0.049
Immune-mediated severe AEs ^{b, c}	139	NA 27 (19.4)	139	NA 9 (6.5)	2.88 [1.35; 6.13] 0.004
a. HR and CI: Cox proportional hazards model, p-value: log-rank test; each stratified by pathological lymph node status and the use of cisplatin as neoadjuvant chemotherapy.					
b. The operationalization of a specific MedDRA PT collection (“select AEs”) presented by the company is used in each case.					
c. Operationalised as CTCAE grade ≥ 3.					
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; NA: not achieved; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event					

The assessment of the risk of bias and the certainty of conclusion from benefit assessment A25-154 applies to the results on immune-mediated AEs, severe AEs and SAEs subsequently submitted by the company. On the basis of this assessment, at most hints, e.g. of greater harm, can be determined for all outcomes presented here.

Immune-mediated SAEs and immune-mediated severe AEs

Benefit assessment A25-154 assumed that there were no significant differences between the results of the data cut of 17 July 2020 and the currently relevant data cut of 6 January 2025. This is confirmed by the subsequently submitted data. For the outcome severe immune-mediated AEs, the number of patients with event remains the same. For the outcome immune-mediated SAEs, the later data cut of 6 January 2025 includes one fewer patient with event than the earlier data cut of 17 July 2020. Whilst this is implausible, it has no relevant impact on the result.

For each of the outcomes immune-mediated SAEs and immune-mediated severe AEs, a statistically significant difference was found to the disadvantage of nivolumab in comparison with placebo at the data cut of 06 January 2025. In each case, this resulted in a hint of greater harm from nivolumab in comparison with the appropriate comparator therapy (ACT).

2.2 Subgroups and other effect modifiers

The following subgroup characteristics were considered in this addendum:

- Age (< 65/≥ 65)
- Sex (female versus male)
- Pathological lymph node status (N+ vs. N0/x with < 10 lymph nodes removed vs. N0 with ≥ 10 lymph nodes removed)

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.

In accordance with the methods described above, there was no further relevant effect modification for this addendum for the outcomes and the operationalizations included.

2.3 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in dossier assessment A25-154 and in Section 2.1 (see Table 2).

Table 2: Extent of added benefit at outcome level: nivolumab vs. watchful waiting

Outcome category outcome effect modifier subgroup	Nivolumab vs. placebo median time to event (months) or proportion of events (%) effect estimation [95% CI]; p-value probability ^a	Derivation of extent ^b
Side effects		
Immune-mediated SAEs	NA vs. NA months HR: 2.49 [0.97; 6.37] HR: 0.40 [0.16; 1.03] ^c ; ^d ; p = 0.049 probability: hint	Outcome category: serious/severe side effects $0.90 \leq Cl_u < 1.00$ greater harm, extent: "minor" ^e
Immune-mediated severe AEs	NA vs. NA months HR: 2.88 [1.35; 6.13] HR: 0.35 [0.16; 0.74] ^c ; p = 0.004 probability: hint	Outcome category: serious/severe side effects $Cl_u < 0.75$, risk $\geq 5\%$ greater harm, extent: major
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (Cl_u). c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit. d. The result of the statistical test is determinative for the derivation of added benefit. e. Discrepancy between CI and p-value; the extent is rated as minor. AE: adverse event; CI: confidence interval; Cl_u: upper limit of confidence interval; HR: hazard ratio; NA: not achieved; SAE: serious adverse event		

2.4 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 A25-154.

The following Table 3 shows the result of the benefit assessment of nivolumab, taking into account dossier assessment A25-154 and the present addendum.

Table 3: Nivolumab – probability and extent of added benefit

Therapeutic indication	ACT ^a	Probability and extent of added benefit
Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression $\geq 1\%$ and a high risk of recurrence after undergoing radical resection, for whom cisplatin-containing therapy is not suitable or who have already received neoadjuvant treatment with cisplatin; adjuvant treatment ^b	Watchful waiting	Adults ^c - men: hint of minor added benefit - women: added benefit not proven
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, this includes patients for whom chemotherapy with cisplatin is generally not an option (e.g. due to poor general health or impaired renal function) or who have already received neoadjuvant chemotherapy with cisplatin and for whom, for this reason, further cisplatin treatment is not an option. According to the G-BA, the patient population is therefore heterogeneous. c. Only patients with an ECOG PS of 0 or 1 were included in the CA209-274 study. 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 cell death ligand 1		

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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2. Bristol Myers Squibb. Stellungnahme zum IQWiG-Bericht Nr. A25-154: Nivolumab (Urothelkarzinom, adjuvant); Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung). 2026: [Soon available at: <https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1294/#beschluesse>) in the document "Zusammenfassende Dokumentation"].
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4. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Nivolumab (Urothelkarzinom, adjuvant) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2022 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a22-53_nivolumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

Appendix A Kaplan-Meier curves for the results of the CA209-274 study

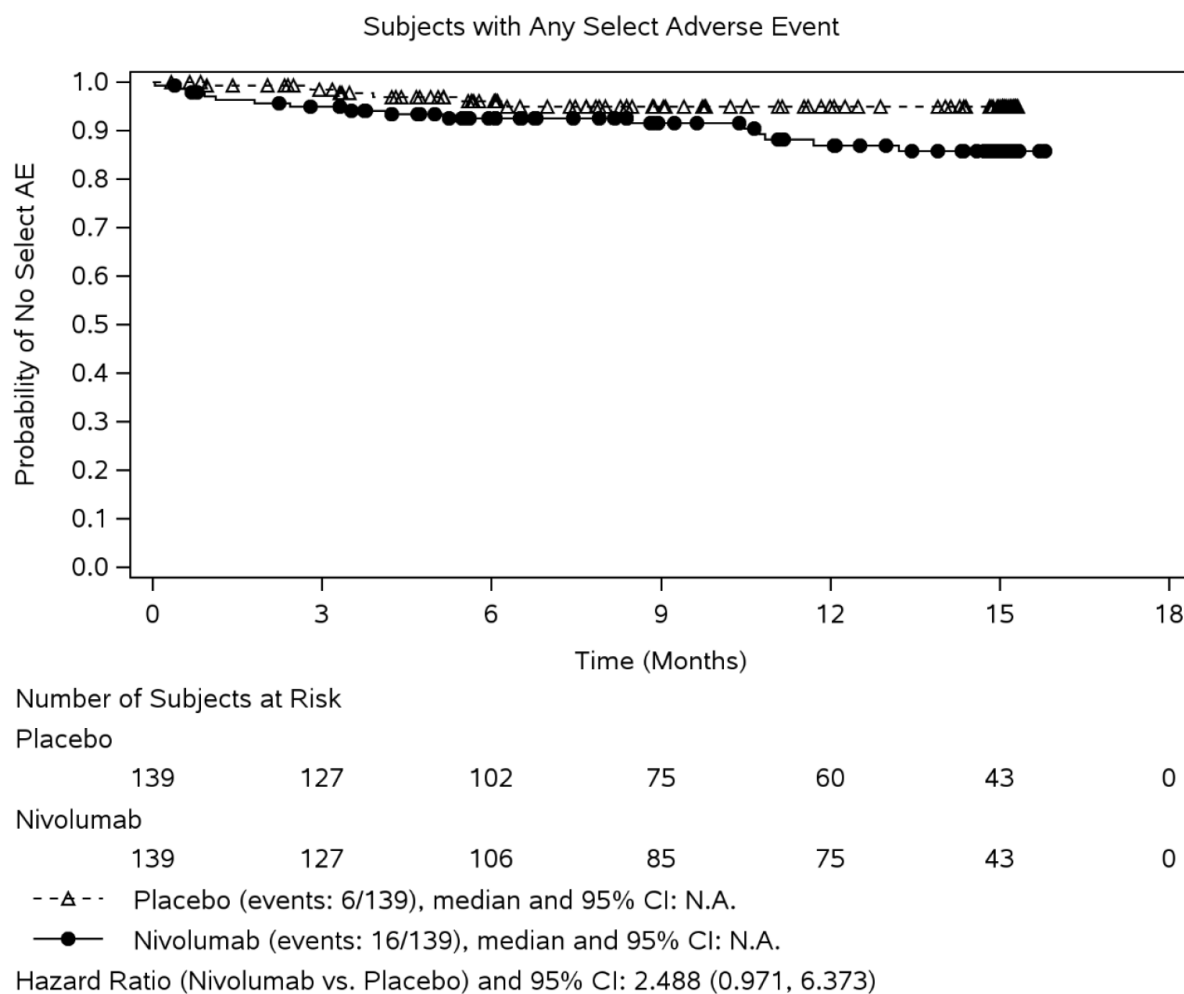


Figure 1: Kaplan-Meier curves for the outcome immune-mediated SAEs in the CA209-274 study (data cut: 06 January 2025)

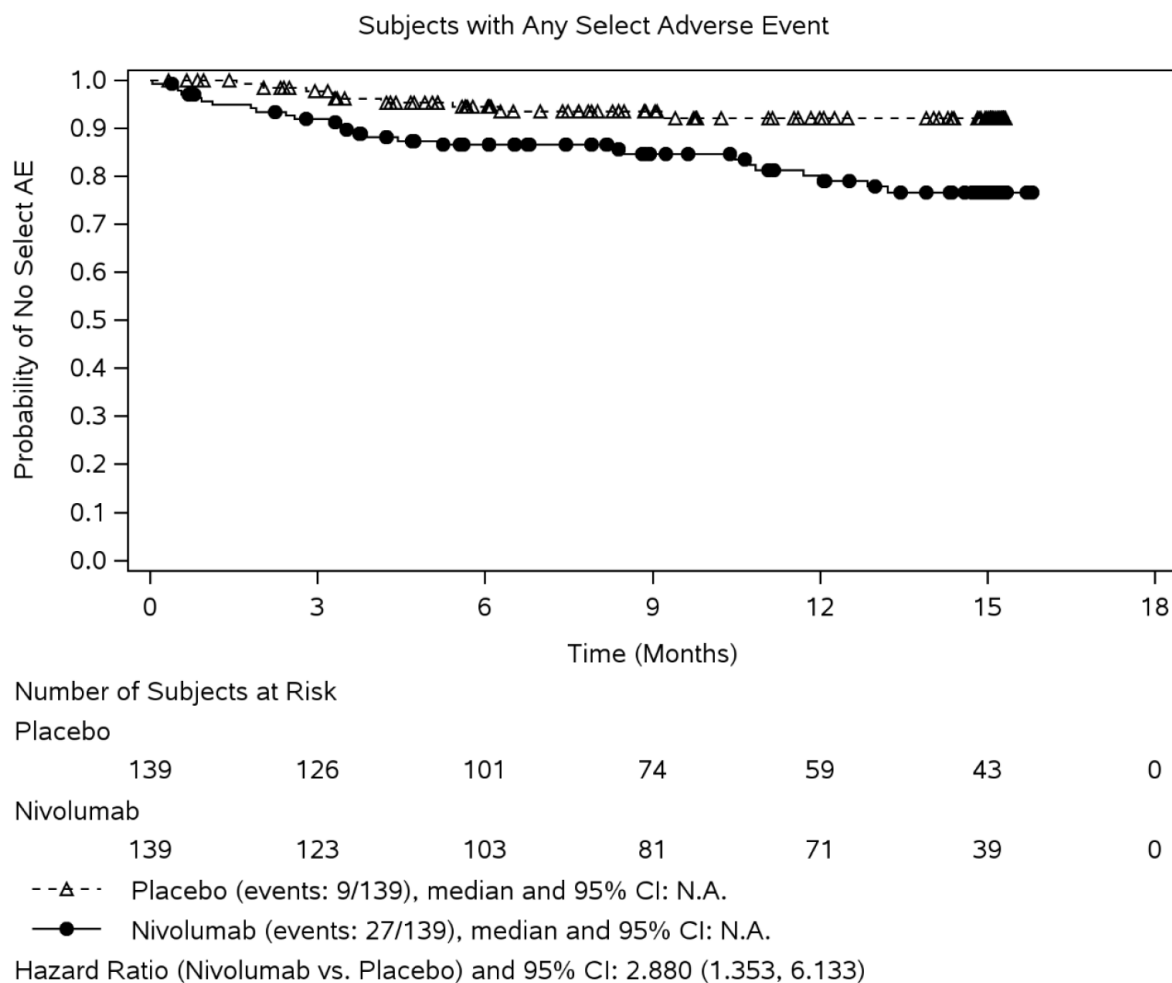


Figure 2: Kaplan-Meier curves for the outcome immune-mediated severe AEs in the CA209-274 study (data cut: 6 January 2025)

Appendix B Results on immune-mediated AEs, immune-mediated SAEs and immune-mediated severe AEs

Table 4: Categories of immune-mediated AEs – RCT, direct comparison: nivolumab vs. placebo

Study Category ^b	Patients with event n (%)	
	Nivolumab N = 139	Placebo N = 139
CA209-274 (data cut: 06 January 2025)		
Overall rate of immune-mediated AEs	111 (79.9)	80 (57.6)
ENDOCRINE AEs	30 (21.6)	11 (7.9)
GASTROINTESTINAL AEs	45 (32.4)	37 (26.6)
HEPATIC AEs	22 (15.8)	17 (12.2)
PULMONARY AEs	11 (7.9)	5 (3.6)
RENAL AEs	25 (18.0)	21 (15.1)
SKIN AEs	69 (49.6)	37 (26.6)
HYPERSENSITIVITY/INFUSION REACTIONS AEs	7 (5.0)	2 (1.4)
a. The operationalization of a specific MedDRA PT collection (“select AEs”) presented by the company is used in each case. b. Category notation taken from Module 4R of the first assessment without adjustment [4]. AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial		

Table 5: Categories of immune-mediated SAEs – RCT, direct comparison: nivolumab vs. placebo

Study Category ^b	Patients with event n (%)	
	Nivolumab N = 139	Placebo N = 139
CA209-274 (data cut: 06 January 2025)		
Overall rate of immune-mediated SAEs	16 (11.5)	6 (4.3)
ENDOCRINE AES	2 (1.4)	0 (0)
GASTROINTESTINAL AES	1 (0.7)	3 (2.2)
HEPATIC AES	1 (0.7)	0 (0)
PULMONARY AES	7 (5.0)	0 (0)
RENAL AES	2 (1.4)	1 (0.7)
SKIN AES	1 (0.7)	1 (0.7)
HYPERSENSITIVITY/INFUSION REACTIONS AES	2 (1.4)	1 (0.7)
a. The operationalization of a specific MedDRA PT collection (“select AEs”) presented by the company is used in each case. b. Category notation taken from Module 4R of the first assessment without adjustment [4]. AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event		

Table 6: Categories of immune-mediated severe AEs (CTCAE grade ≥ 3)^a – RCT, direct comparison: nivolumab vs. placebo

Study Category ^b	Patients with event n (%)	
	Nivolumab N = 139	Placebo N = 139
CA209-274 (data cut: 06 January 2025)		
Overall rate of immune-mediated severe AEs (CTCAE grade ≥ 3)	27 (19.4)	9 (6.5)
ENDOCRINE AES	2 (1.4)	0 (0)
GASTROINTESTINAL AES	3 (2.2)	4 (2.9)
HEPATIC AES	9 (6.5)	0 (0)
PULMONARY AES	7 (5.0)	0 (0)
RENAL AES	3 (2.2)	3 (2.2)
SKIN AES	4 (2.9)	1 (0.7)
HYPERSENSITIVITY/INFUSION REACTIONS AES	1 (0.7)	1 (0.7)
a. The operationalization of a specific MedDRA PT collection (“select AEs”) presented by the company is used in each case. b. Category notation taken from Module 4R of the first assessment without adjustment [4]. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial		