IQWiG Reports – Commission No. A22-97

Nivolumab (urothelial carcinoma, adjuvant) –

Addendum to Commission A22-53 (dossier assessment)[1]

Addendum

Commission: A22-97
Version: 1.0
Status: 27 September 2022

[1] Translation of addendum A22-97 *Nivolumab (Urothelkarzinom, adjuvant) – Addendum zum Auftrag A22-53 (Dossierbewertung)* (Version 1.0; Status: 27 September 2022). Please note: This document was translated by an external translator and 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 Commission A22-53

Commissioning agency
Federal Joint Committee

Commission awarded on
6 September 2022

Internal Commission No.
A22-97

Address of publisher
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

- Philip Kranz
- Teresa Labahn
- Christoph Schürmann
- Volker Vervölgyi

Keywords: Nivolumab, Carcinoma – Transitional Cell, Benefit Assessment, NCT02632409

Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life 5 Dimensions
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MIUC	muscle-invasive urothelial carcinoma
PD-L1	programmed cell death ligand 1
QLQ-C30	Quality of Life Questionnaire – Core 30
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 A22-53 (Nivolumab – benefit assessment according to §35a Social Code Book V) [1].

The commission involves both taking into account the information provided in the dossier [2] and assessing the analyses from the CA209-274 study which were subsequently submitted in the commenting procedure: time to first deterioration in the scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) and in the European Quality of Life 5 Dimensions (EQ-5D) visual analogue scale (VAS).

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

To answer research question 2 (patients who are not eligible for cisplatin-containing therapy), benefit assessment A22-53 used the CA209-274 study to assess the added benefit of nivolumab monotherapy in comparison with the appropriate comparator therapy (ACT) in the adjuvant treatment of muscle-invasive urothelial carcinoma (MIUC) with tumour cell programmed cell death ligand 1 (PD-L1) expression ≥ 1% in adult patients who are at high risk of recurrence after undergoing radical MIUC resection. The dossier of the pharmaceutical company (hereinafter referred to as the "company") provided no usable data for the CA 209-274 study's patient-reported outcomes. As part of the commenting procedure, the company submitted analyses of time to first deterioration in the CA209-274 study's EORTC QLQ-C30 scales and in the EQ-5D VAS [3].

2.1 Analyses of symptoms (EORTC QLQ-C30), health status (EQ-5D VAS), and health-related quality of life (EORTC QLQ-C30)

Data cut-offs

For the outcomes of health status (EQ-5D VAS), symptoms (EORTC QLQ-C30), and health-related quality of life (EORTC QLQ-C30), analyses are available only on the 1st data cut-off (August 2020); the company did not present any analyses from the 2nd data cut-off (February 2021).

For the symptoms and health-related quality of life outcomes, it is safe to assume that the additional amount of data to be added between the 1st and 2nd data cut-off is not relevant (for reasoning, see dossier assessment A22-53). Therefore, the analyses on the 1st data cut-off are used for the benefit assessment. Because the outcome of health status continued to be observed even after treatment end, however, the 2nd data cut-off may potentially add data on this outcome in all patients who remain in the study and have not yet had an event (for details, see dossier assessment A22-53). Therefore, it is not appropriate to submit no analyses on the 2nd data cut-off for the outcome of health status. The available analyses on the 1st data cut-off were nevertheless used for the benefit assessment because the data cut-offs are separated by an interval of only about 6 months. In the present scenario, the results are unlikely to be affected in a material way by 6 additional months of follow-up observation.

Operationalization

For the symptoms and health-related quality of life outcomes, the company's dossier contains responder analyses of time to definitive deterioration, which were deemed unsuitable (for a justification, see dossier assessment A22-53). In the context of the commenting procedure, the company presented analyses of time to first deterioration based on adequate response criteria (corresponding to 15% threshold). These analyses were used for the benefit assessment.

2.1.1 Risk of bias

The risk of bias was rated as high for the results of the outcomes of symptoms (EORTC QLQ-C30), health status (EQ-5D VAS), and health-related quality of life (EORTC QLQ-C30). For the cited outcomes of the symptoms and health-related quality of life category, observations are incomplete for potentially informative reasons due to the observation duration being linked to the treatment duration and a possible association between outcome and reason for treatment discontinuation. For the outcome of health status, the observation duration was not linked to treatment duration, but due to the missing data on overall survival, it remains unclear whether the return rates were adequately calculated (also see dossier assessment A22-53). Furthermore, the follow-up surveys were not matched to the concurrent visits, which further complicated the estimation of return rates. However, the information provided regarding return rates demonstrates that, in both arms, return rates decreased after the end of treatment with the study medication. Concerning the outcome of health status, it is therefore likewise conceivable for the percentage of incomplete observations for potentially informative reasons to be relevant.

Due to the uncertainties described in the dossier assessment regarding the patient population as well as the lack of data on overall survival, at most hints, e.g. of an added benefit, can be derived for all outcomes.

2.1.2 Results

Table 1 presents the results for the outcomes of symptoms, health status, and health-related quality of life.

Table 1: Results (morbidity, health-related quality of life, time to event) – RCT, direct comparison: nivolumab versus watchful waiting (multipage table)

Study Outcome category Outcome	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]; p-value[a]
CA209-274 (August 2020 data cut-off)					
Morbidity					
EORTC QLQ-C30[b]					
Fatigue	123	4.90 [2.04; 7.39] 77 (62.6)	128	3.78 [2.50; 5.19] 80 (62.5)	0.99 [0.72; 1.36]; 0.745
Nausea and vomiting	123	NR [15.41; NC] 44 (35.8)	128	NR 35 (27.3)	1.35 [0.86; 2.11]; 0.178
Pain	123	9.69 [5.16; 13.01] 67 (54.5)	128	4.76 [3.25; 7.16] 81 (63.3)	0.75 [0.54; 1.04]; 0.079
Dyspnoea	123	15.93 [8.90; NC] 51 (41.5)	127	NR [12.94; NC] 43 (33.9)	1.20 [0.80; 1.80]; 0.400
Insomnia	123	NR [8.87; NC] 48 (39.0)	128	11.04 [5.49; NC] 62 (48.4)	0.72 [0.49; 1.06]; 0.054
Appetite loss	122	15.90 [9.23; NC] 51 (41.8)	128	NR [11.73; NC] 47 (36.7)	1.21 [0.81; 1.81]; 0.614
Constipation	122	NR [NR; NC]; 37 (30.3)	127	NC 42 (33.1)	0.91 [0.58; 1.42]; 0.749
Diarrhoea	122	NR [13.83; NC] 40 (32.8)	127	NR 41 (32.3)	0.94 [0.60; 1.45]; 0.739
Health status (EQ-5D VAS)[c]	126	18.37 [11.14; NC] 59 (46.8)	129	9.00 [5.88; 17.77] 71 (55.0)	0.64 [0.45; 0.91]; 0.036
Health-related quality of life					
EORTC QLQ-C30[b]					
Global health status	123	9.95 [6.93; NC] 57 (46.3)	127	10.51 [5.59; NC] 64 (50.4)	0.95 [0.66; 1.36]; 0.529
Physical functioning	123	16.43 [8.84; NC] 48 (39.0)	128	NR [9.20; NC] 54 (42.2)	0.84 [0.57; 1.24]; 0.387
Role functioning	123	8.31 [4.63; 12.75] 68 (55.3)	128	5.55 [4.04; NC] 68 (53.1)	0.95 [0.67; 1.34]; 0.663
Emotional functioning	123	NR [15.24; NC] 45 (36.6)	127	13.14 [7.16; NC] 53 (41.7)	0.80 [0.53; 1.19]; 0.258
Cognitive functioning	123	7.66 [4.67; 15.77] 64 (52.0)	127	8.61 [4.86; NC] 64 (50.4)	1.01 [0.71; 1.43]; 0.946
Social functioning	122	14.06 [6.47; NC] 55 (45.1)	126	NR [7.56; NC] 52 (41.3)	1.06 [0.73; 1.56]; 0.621

Table 1: Results (morbidity, health-related quality of life, time to event) – RCT, direct comparison: nivolumab versus watchful waiting (multipage table)

Study	Nivolumab		Placebo		Nivolumab vs. placebo
Outcome category 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]
a. Effect and CI: Cox proportional hazards model; p-value: log-rank test, each stratified by pathological lymph node status and use of cisplatin as neoadjuvant chemotherapy. b. Time to first deterioration. A score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100). c. Time to first deterioration. A score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100). CI: confidence interval; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; RCT: randomized controlled trial					

Morbidity

Symptoms (EORTC QLQ-C30)

For the symptoms outcomes (surveyed with EORTC QLQ-C30), no statistically significant difference between treatment arms is found in any of the scales. This results in no hint of an added benefit of nivolumab in comparison with watchful waiting for any of them; added benefit is therefore not proven.

Health status (EQ-5D VAS)

For the outcome of health status (surveyed with the EQ-5D VAS), a statistically significant difference was found in favour of nivolumab in comparison with placebo. However, the effect in this outcome of the category of non-serious/non-severe symptoms / late complications was no more than marginal (see Section 2.1.4). This results in no hint of an added benefit of nivolumab in comparison with watchful waiting; added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life (surveyed with the EORTC QLQ-C30)

For the outcome of health-related quality of life (surveyed with the EORTC QLQ-C30), no statistically significant difference between treatment arms was found in any of the investigated scales. This results in no hint of an added benefit of nivolumab in comparison with watchful waiting for any of them; added benefit is therefore not proven.

2.1.3 Subgroups and other effect modifiers

According to the methods described in dossier assessment A22-53, no relevant effect modifications by the characteristics of age (< 65 versus ≥ 65), sex (female versus male), or pathological lymph node status (N+ versus N0/x with < 10 lymph nodes removed versus N0

with ≥ 10 lymph nodes removed) were found for the symptoms or health-related quality of life outcomes.

2.1.4 Determination of outcome category for the outcome of health status

In Module 4 R, the company posits that deterioration in general health is to be expected primarily in the event of recurrence or metastasis. The company argues that this is typically associated with a switch to a palliative treatment setting and is of great relevance for the patients' prognosis. Accordingly, the deterioration of general health as per EQ-5D VAS is reportedly deemed a serious symptom.

The company's assessment was not found plausible. While recurrences and metastases certainly represent serious/severe events for patients, these serious/severe events are accounted for in the benefit assessment via the outcomes of recurrences and disease-free survival and have already been factored into the overall weighing of benefit and harm (see dossier assessment A22-53). No further information is available for assessing the severity of the outcome of health status. Therefore, the outcome of health status is allocated to the outcome category of non-serious/non-severe symptoms.

2.1.5 Probability and extent of added benefit

2.1.5.1 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. There is no proof of added benefit for any of them.

2.1.5.2 Overall conclusion on added benefit

Table 2 summarizes the results which were factored into the overall conclusion on the extent of added benefit.

Table 2: Favourable and unfavourable effects from the assessment of nivolumab in comparison with watchful waiting

Favourable effects	**Unfavourable effects**
Entire observation period	
Morbidity Serious/severe symptoms / late complications ▪ Recurrences: hint of an added benefit – extent: considerable	–
Shortened observation period	
Serious/severe side effects ▪ Gastrointestinal disorders (severe AEs), infections and infestations (SAEs): for each, hint of lesser harm – extent: minor[a]	Serious/severe side effects ▪ Immune-related severe AEs, lipase increased (severe AEs): each hint of greater harm – extent: major ▪ Discontinuation due to AEs, immune-related SAEs, respiratory, thoracic, and mediastinal disorders (AEs): each hint of greater harm – extent: minor
–	Non-serious/non-severe side effects ▪ Skin and subcutaneous tissue disorders (AEs), asthenia (AEs): each hint of greater harm – extent: considerable
There are no data on overall survival. For the current 2nd data cut-off dated February 2021, results are available only on the outcome of recurrence.	
a. It is questionable whether the effect is in fact attributable to the outcome category of AEs or rather reflects the symptoms of the disease. AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; VAS: visual analogue scale	

Unlike for dossier assessment A22-53, usable results on the outcomes of symptoms, health status, and health-related quality of life are available for the present addendum. Favourable or unfavourable effects of nivolumab in comparison with the ACT were not found for any of these outcomes.

Overall, this results in a hint of minor added benefit for patients who are not eligible for cisplatin-containing therapy, as was found in dossier assessment A22-53.

2.2 Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit of nivolumab drawn in dossier assessment A22-53.

The following Table 3 shows the result of the benefit assessment of nivolumab, taking into account dossier assessment A22-53 and the present addendum.

Table 3: Nivolumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult patients with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1% who are at high risk of recurrence after undergoing radical resection and who are eligible for cisplatin-containing therapy, for adjuvant treatment	▪ Cisplatin + gemcitabine or[b] ▪ Cisplatin + methotrexate	Added benefit not proven
2	Adult patients with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1% who are at high risk of recurrence after undergoing radical resection and who are not eligible for cisplatin-containing therapy, for adjuvant treatment[c]	Watchful waiting	Hint of minor added benefit[d]

a. Presented is the respective ACT specified by the G-BA.
b. Added benefit can be proven in comparison with one of the cited treatment options; this can typically be achieved in the context of a single-comparator study.
c. According to the G-BA, this includes patients who are either generally ineligible for cisplatin chemotherapy (e.g. due to poor general health or poor renal function) or have already received neoadjuvant cisplatin chemotherapy and are therefore not candidates for another round of cisplatin therapy. According to the G-BA, the patient population is therefore heterogeneous.
d. The CA209-274 study enrolled predominantly patients with an ECOG-PS of 0 or 1. Only 2.5% of patients from the study's relevant subpopulation had an ECOG-PS of 2. 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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Nivolumab (Urothelkarzinom, adjuvant) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2022 [Accessed: 01.08.2022]. URL: https://www.iqwig.de/download/a22-53_nivolumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Bristol-Myers Squibb. Nivolumab (OPDIVO); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2022 [Accessed: 30.08.2022]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/830/#dossier.

3. Bristol-Myers Squibb. Stellungnahme zum IQWiG-Bericht Nr. 1395 Nivolumab (Urothelkazinom, adjuvant). 2022: [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/830/#beschluesse in the document "Zusammenfassende Dokumentation"].

Appendix A Kaplan-Meier curves

Symptoms

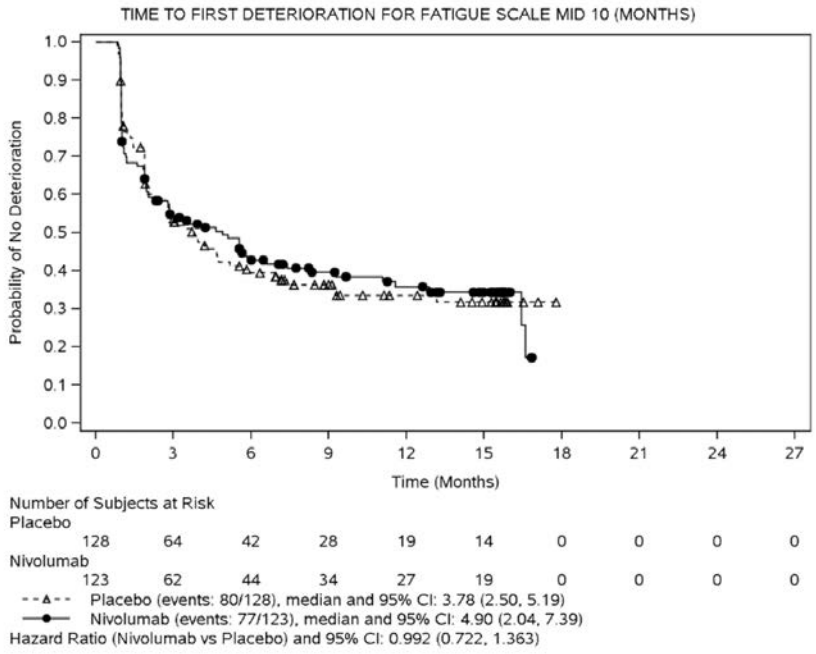

Figure 1: Kaplan-Meier curve of time to first deterioration, fatigue (EORTC QLQ-C30; August 2020 data cut-off)

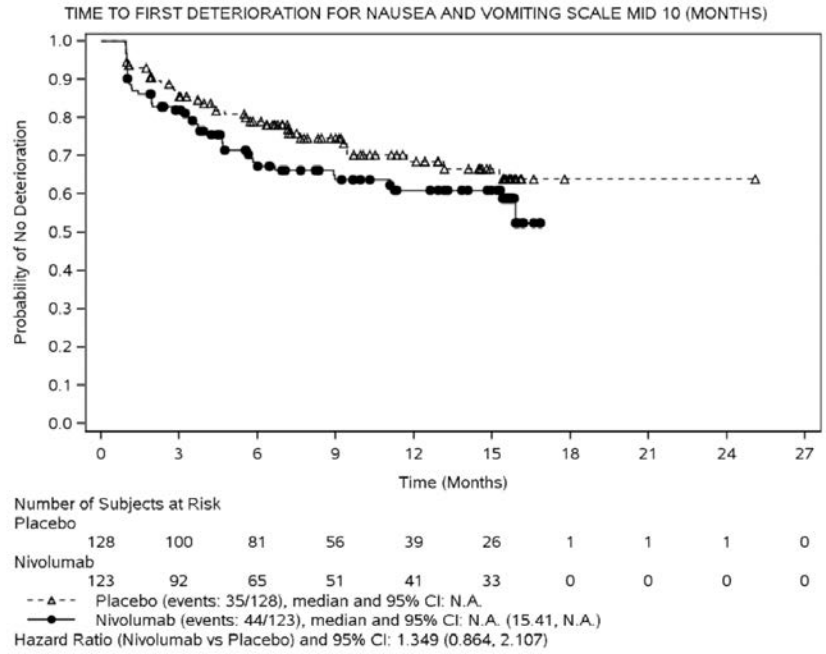

Figure 2: Kaplan-Meier curve of time to first deterioration, nausea and vomiting (EORTC QLQ-C30; August 2020 data cut-off)

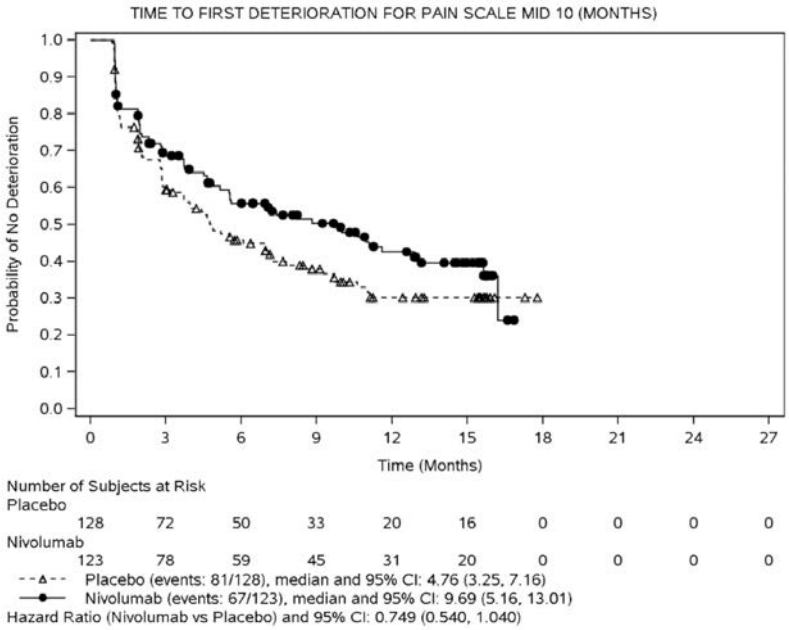

Figure 3: Kaplan-Meier curve of time to first deterioration, pain (EORTC QLQ-C30; August 2020 data cut-off)

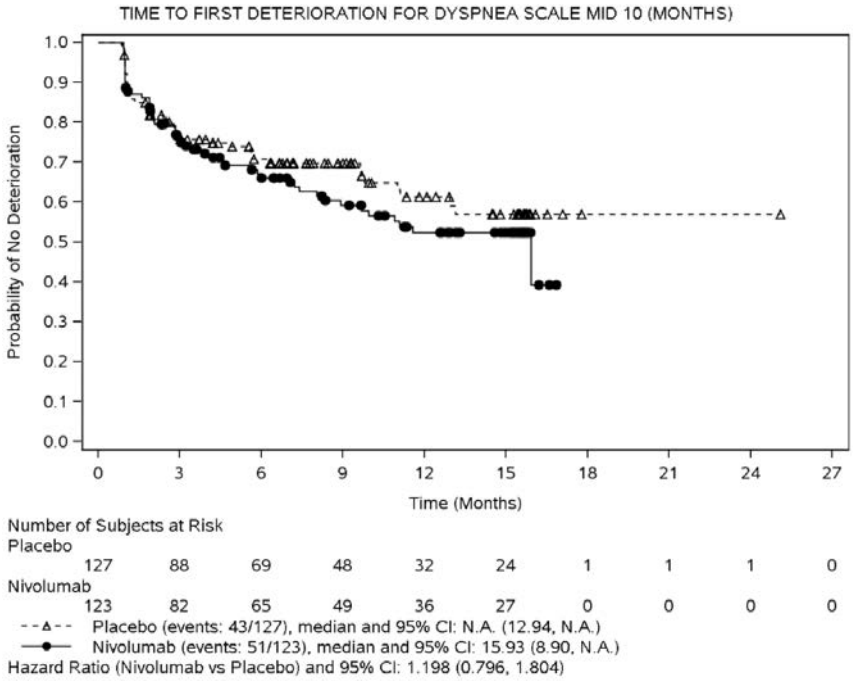

Figure 4: Kaplan-Meier curve of time to first deterioration, dyspnoea (EORTC QLQ-C30; August 2020 data cut-off)

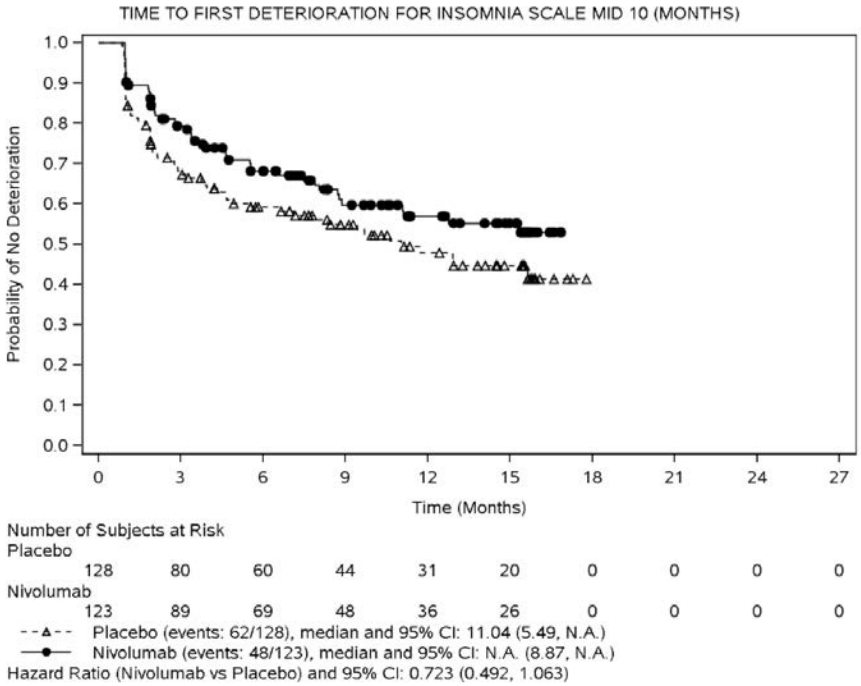

Figure 5: Kaplan-Meier curve of time to first deterioration, insomnia (EORTC QLQ-C30; August 2020 data cut-off)

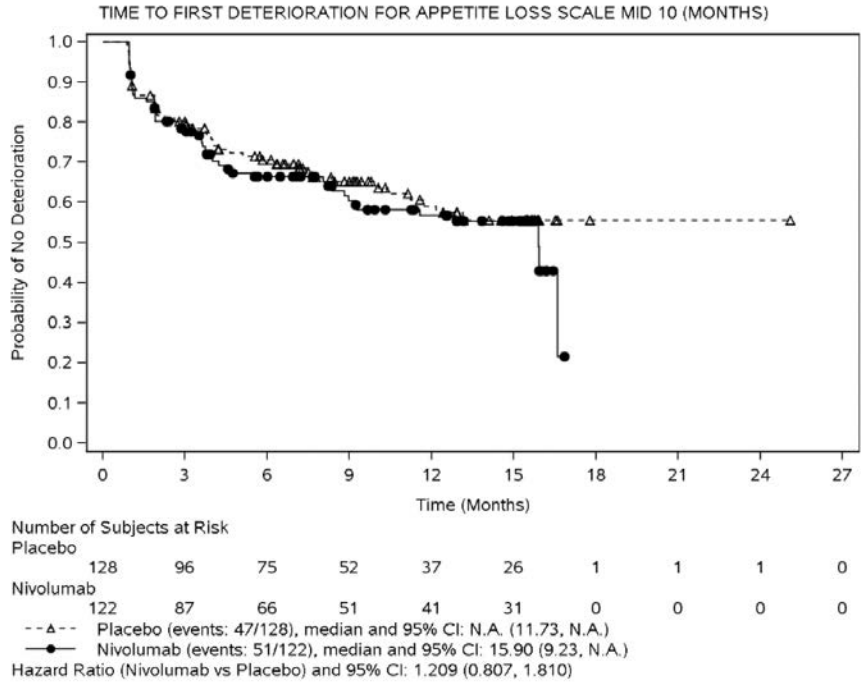

Figure 6: Kaplan-Meier curve of time to first deterioration, appetite loss (EORTC QLQ-C30; August 2020 data cut-off)

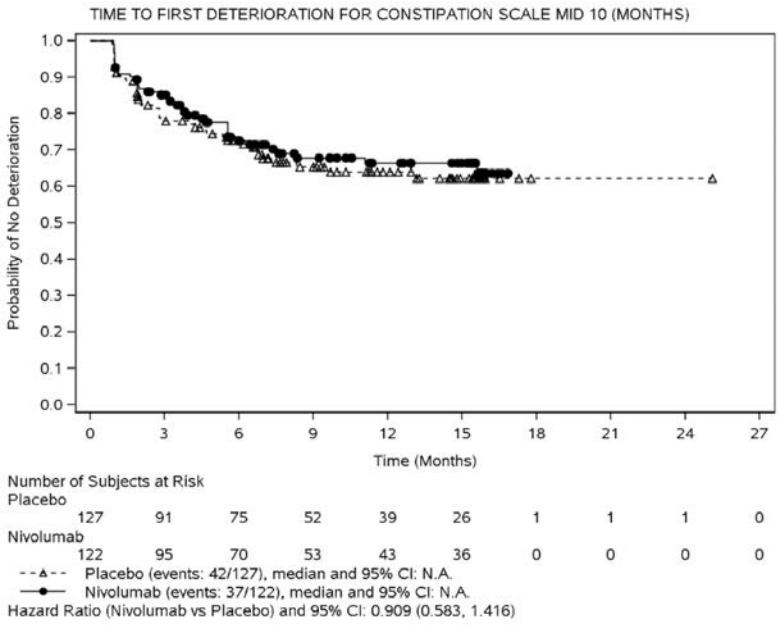

Figure 7: Kaplan-Meier curve of time to first deterioration, constipation (EORTC QLQ-C30; August 2020 data cut-off)

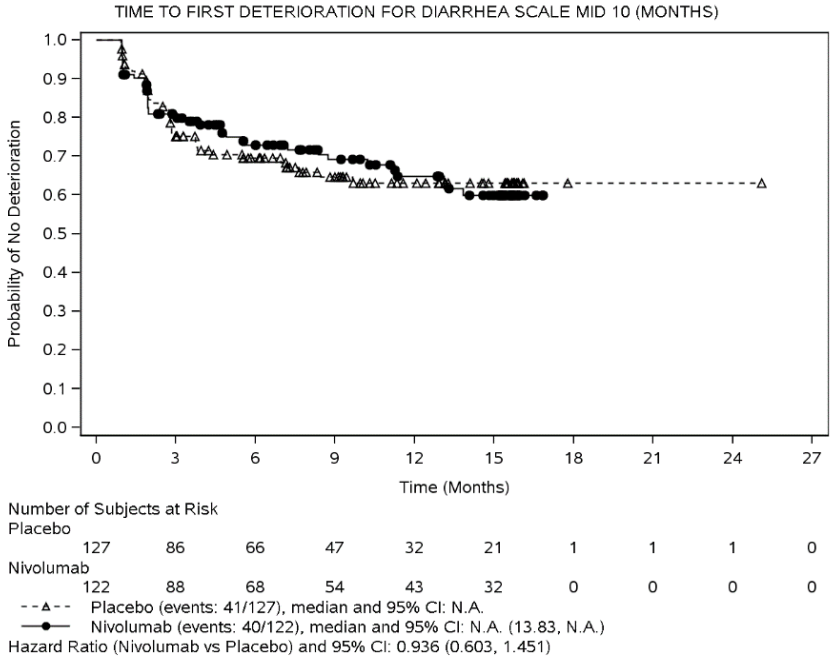

Figure 8: Kaplan-Meier curve of time to first deterioration, diarrhoea (EORTC QLQ-C30; August 2020 data cut-off)

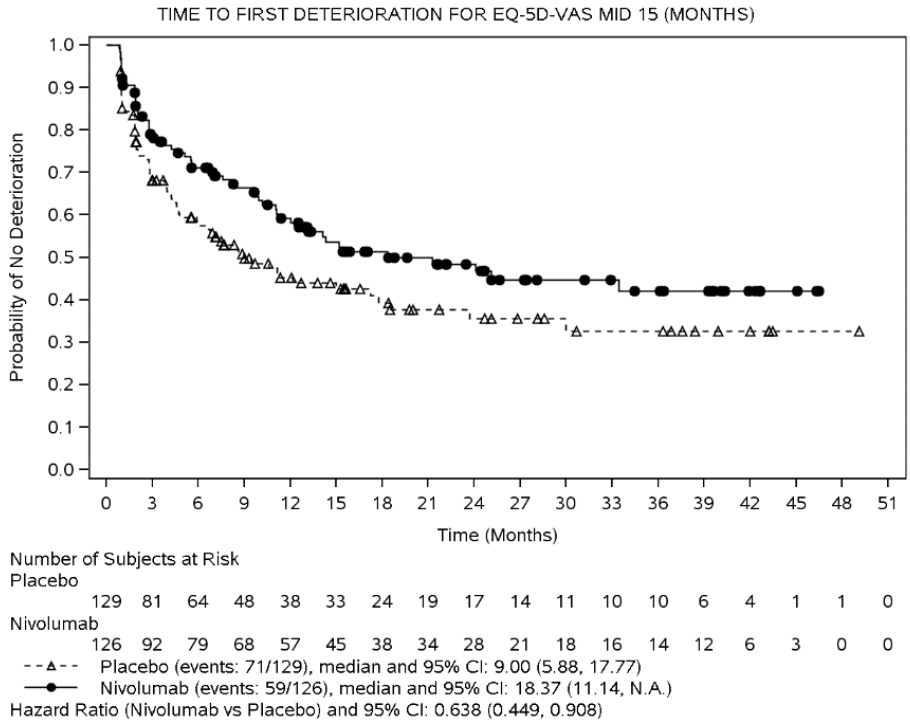

Figure 9: Kaplan-Meier curve of time to first deterioration of EQ-5D VAS (August 2020 data cut-off)

Health-related quality of life

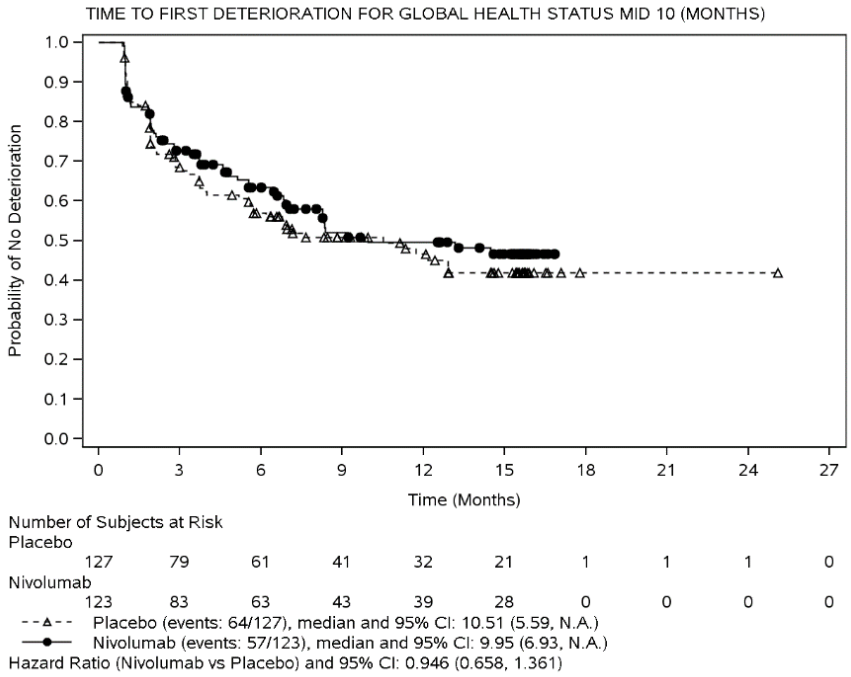

Figure 10: Kaplan-Meier curve of time to first deterioration, global health status (EORTC QLQ-C30; August 2020 data cut-off)

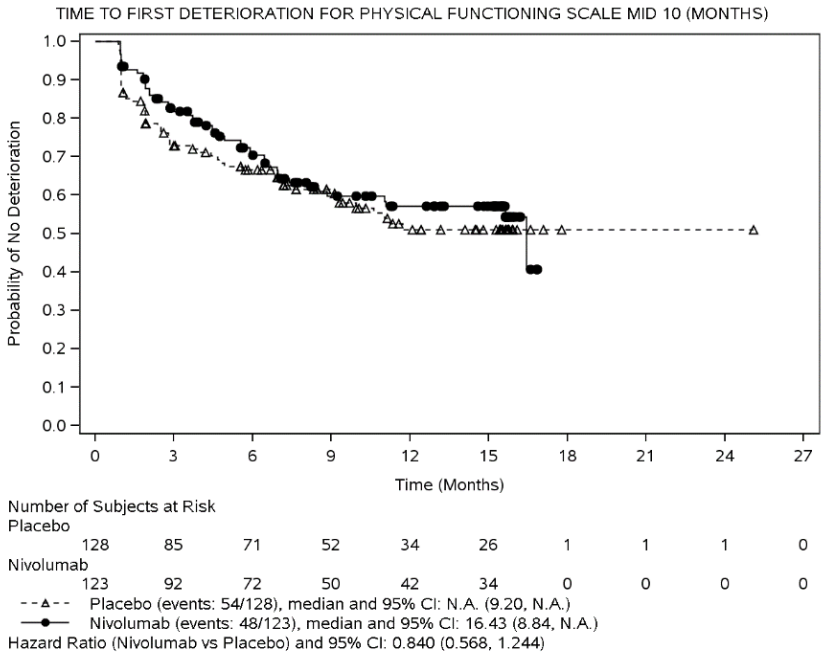

Figure 11: Kaplan-Meier curve of time to first deterioration, physical functioning (EORTC QLQ-C30; August 2020 data cut-off)

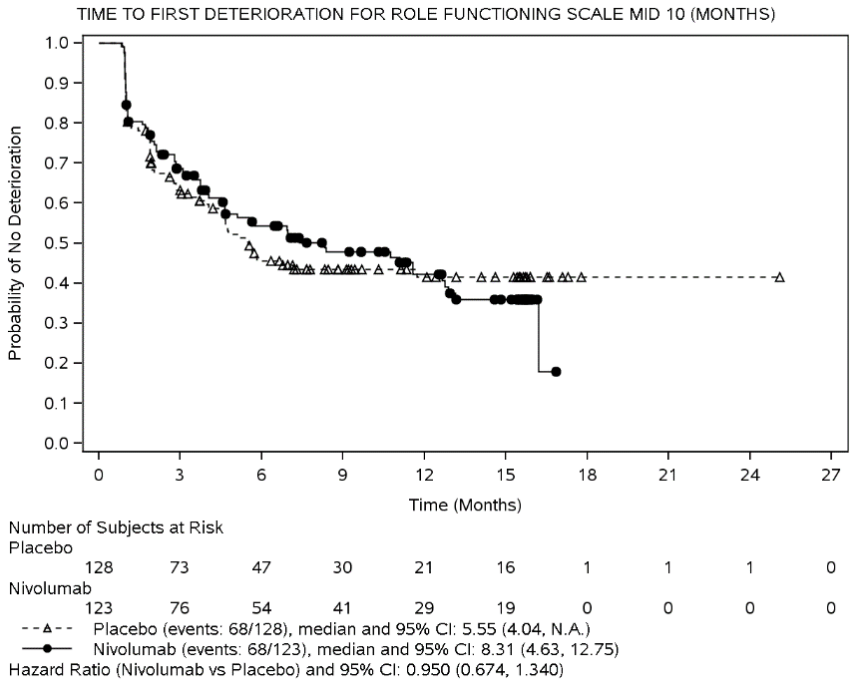

Figure 12: Kaplan-Meier curve of time to first deterioration, role functioning (EORTC QLQ-C30; August 2020 data cut-off)

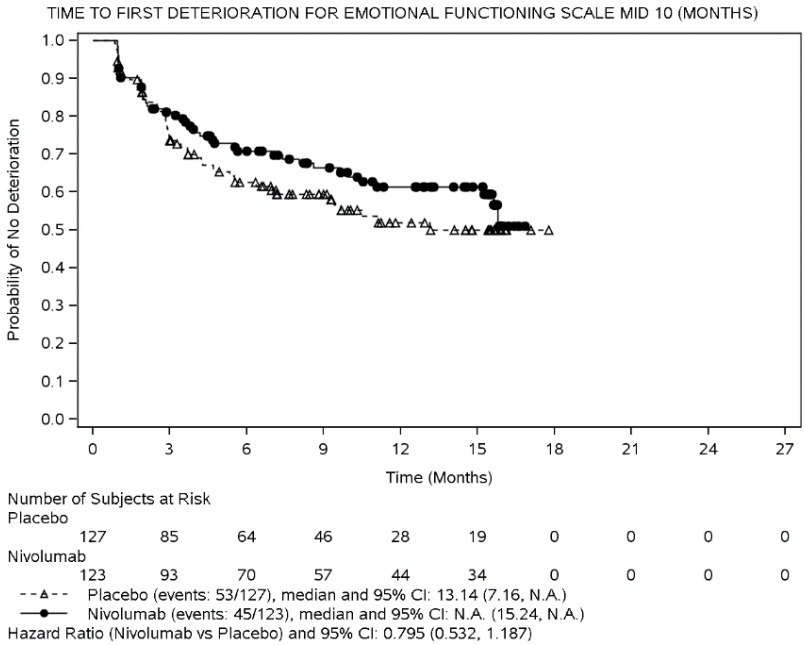

Figure 13: Kaplan-Meier curve of time to first deterioration, emotional functioning (EORTC QLQ-C30; August 2020 data cut-off)

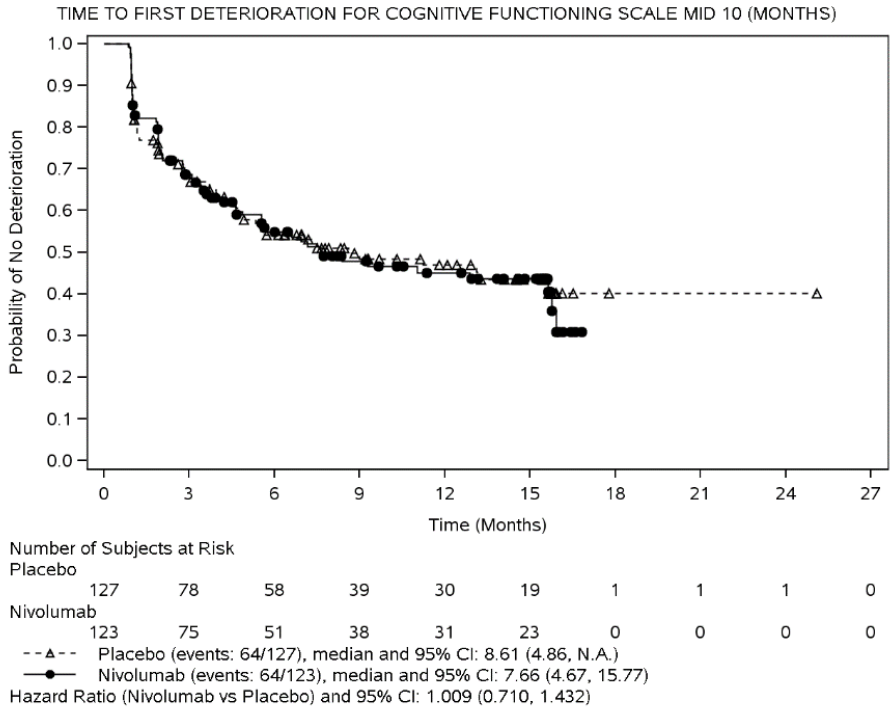

Figure 14: Kaplan-Meier curve of time to first deterioration, cognitive functioning (EORTC QLQ-C30; August 2020 data cut-off)

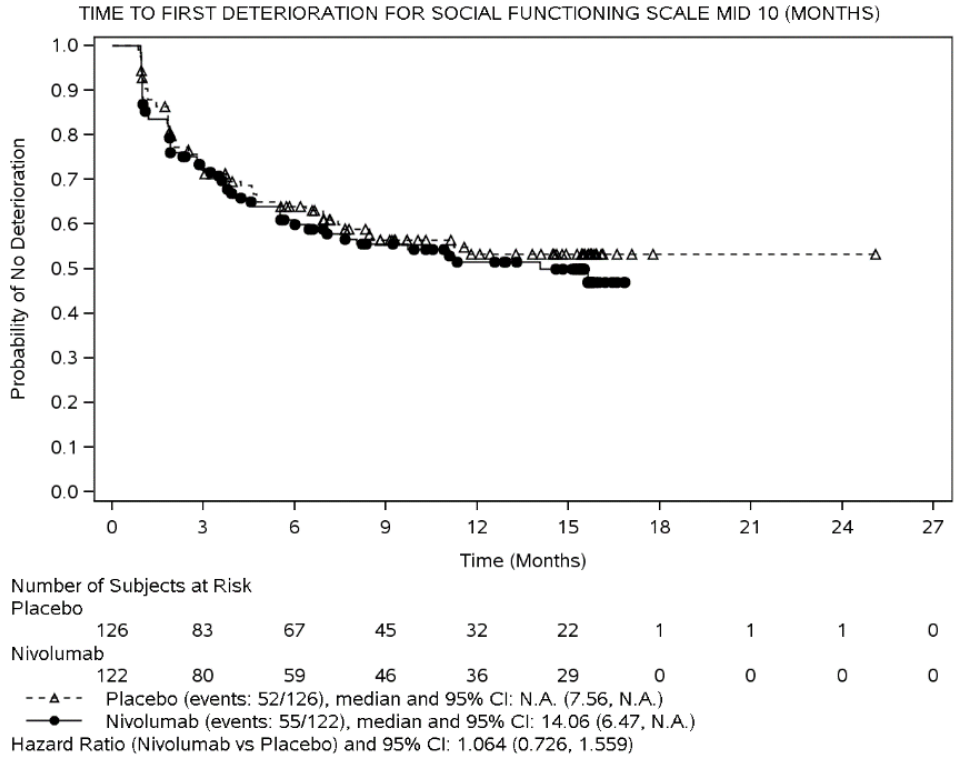

Figure 15: Kaplan-Meier curve of time to first deterioration, social functioning (EORTC QLQ-C30; August 2020 data cut-off)