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Nivolumab (oesophageal cancer) –

Addendum to Commission A20-121[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	preferred term
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	system organ class
VAS	visual analogue scale

1 Background

On 11 May 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-121 (Nivolumab – Benefit assessment according to § 35a Social Code Book V) [1].

For the benefit assessment of nivolumab in adult patients with unresectable, advanced, recurrent, or metastatic oesophageal squamous cell carcinoma (after prior fluoropyrimidine-based and platinum-based combination chemotherapy), the company submitted the randomized controlled trial (RCT) ATTRACTION-3. This study compares nivolumab with chemotherapy (docetaxel or paclitaxel). Since it does not fully implement the appropriate comparator therapy (ACT) of best supportive care (BSC), this study was disregarded in the benefit assessment [1].

After the oral hearing [2], the G-BA commissioned IQWiG with assessing the ATTRACTION-3 study. Furthermore, the commission comprises the assessment of subsequently submitted responder analyses of European Quality of Life Questionnaire – 5 Dimensions (EQ-5D) visual analogue scale (VAS) from ATTRACTION-3, using a response threshold of 15% [3].

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

2 Presentation of the ATTRACTION-3 study

This addendum discusses the study listed in the table below.

Table 1: Study pool of the company – RCT, direct comparison: nivolumab vs. BSC

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication and other sources[c] (yes/no [reference])
CA2009-473 (ATTRACTION-3[d])	Yes	No	Yes	No[e]	Yes [4-7]	Yes [8,9]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the tables below, the study will be referred to using this name.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the study report in Module 5 of the dossier.

BSC: best supportive care; G-BA: Federal Joint Committee; RCT: randomized controlled trial

2.1 Study characteristics

Table 2 and Table 3 present the study used in the benefit assessment.

Table 2: Characterization of the study included by the company – RCT, direct comparison: nivolumab vs. BSC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
ATTRACTION-3	RCT, open-label, parallel-group	Adult patients (≥ 20 years of age) with oesophageal squamous cell carcinoma (possibly combined with adenocarcinoma) who were refractory[b] or intolerant[b] to fluoropyrimidine-based and platinum-based combination chemotherapy	Nivolumab (N = 210) Docetaxel or paclitaxel (N = 209)[c]	Screening: 7 days Treatment: until disease progression, unacceptable toxicity or treatment discontinuation as decided by the physician or the patient Follow-up observation[d]: outcome-specific, at the longest until death, discontinuation of study participation, or study end	90 centres in Denmark, Germany, Italy, Japan, Korea, Taiwan, United Kingdom, United States 12/2015–10/2020 Data cut-off dates: Interim analysis: 199 overall survival events[e] Final analysis: 331 overall survival events	Primary: OS Secondary: Health status AEs

a. Primary outcomes include information without consideration of the relevance for this addendum. Secondary outcomes include only information on relevant available outcomes for this addendum.
b. Patients who have already received a treatment regimen of fluoropyrimidine-based and platinum-based combination chemotherapy and are ineligible for radical resection. Refractory disease was defined as follows:
- Patients with disease progression or recurrence as confirmed by imaging procedures either during initial chemotherapy (including chemoradiation) or ≤ 8 weeks after the last dose of chemotherapy
- Patients who underwent radical resection in combination with chemotherapy, including (neo)adjuvant therapy or chemoradiation, and had recurrence confirmed by imaging procedures ≤ 24 weeks after the last dose of chemotherapy
- Patients with an established complete response to the initial chemotherapy (including chemoradiation) whose recurrence was confirmed by imaging procedures either during the initial chemotherapy or ≤ 24 weeks after the last dose of chemotherapy.

c. In the comparator arm, 65 patients received docetaxel and 144 patients paclitaxel.
d. Outcome-specific information is provided in Table X.
e. The planned interim analysis was eliminated with protocol version 9.0.

AE: adverse event; BSC: best supportive care; N: number of randomized (included) patients; OS: overall survival; RCT: randomized controlled trial

Table 3: Characterization of the intervention – RCT, direct comparison: nivolumab vs. BSC

Study	Intervention	Comparison
ATTRACTION-3	Nivolumab 240 mg i. v. every 2 weeks, 1 treatment cycle for 6 weeks	Docetaxel 75 mg/m² i. v. every 3 weeks Paclitaxel 100 mg/m² i. v. every week for 6 weeks, followed by a 2-week treatment break
	No dose reduction or increase allowed	Dose modifications: ▪ docetaxel and paclitaxel: dose adjustment at a body weight change ≥ 10% compared to initial dose or most recent dose adjustment; dose reduction in case of AE according to a plan
	Non-permitted prior treatment ▪ Systemic corticosteroids ≤ 28 days before randomization (temporary treatment allowed, e.g. for treating or preventing allergic reactions or AEs) ▪ Immunosuppressants ≤ 28 days before randomization ▪ Antineoplastic medications (e.g. chemotherapeutic agents, targeted molecular therapeutic agents or immunotherapeutic agents) ≤ 28 days before randomization ▪ Taxanes for treating oesophageal carcinoma ▪ Nivolumab or other therapeutic antibodies or drugs for T-cell regulation ▪ Surgical procedures under full anaesthesia ≤ 28 days before randomization or under local or topical anaesthesia ≤ 14 days before randomization ▪ Radiotherapy ≤ 28 days before randomization or radiotherapy for treating bone metastases ≤ 14 days before randomization ▪ Radiopharmaceuticals ≤ 56 days before randomization (except radiopharmaceuticals for examination or diagnostic purposes) **Permitted concomitant treatment** ▪ Anticoagulation therapy, including low-dose acetylsalicylic acid ▪ Topical (external, intraarticular, intranasal, ophthalmological, or inhaled) application of corticosteroids ▪ Prophylactic premedication before the infusion: ▫ In the nivolumab arm: paracetamol or diphenhydramine ▫ In the paclitaxel arm: ≥ 30 minutes before administration of paclitaxel dexamethasone 8 mg i.v., ranitidine 50 mg i.v., or famotidine 20 mg i.v. with diphenhydramine 50 mg p.o. **Non-permitted concomitant treatment** ▪ Bisphosphonates and anti-RANKL antibodies ▪ Other non-approved drugs and drug combinations ▪ Disulfiram, cyanamide, carmofur, and procarbazine hydrochloride (for paclitaxel) ▪ Surgical therapy of a malignant tumour, chemotherapy/radiotherapy, radiopharmaceuticals (except radiopharmaceuticals for examination or diagnostic purposes)	

BSC: best supportive care; i.v.: intravenous; p.o.: per os (by mouth); RANKL: Receptor Activator of NF-κB Ligand; RCT: randomized controlled trial

Study characterization

ATTRACTION-3 is an open-label, multicentre RCT comparing nivolumab with docetaxel or paclitaxel monochemotherapy upon the physician's discretion. It included adults with oesophageal carcinoma who were refractory or intolerant to fluoropyrimidine-based and platinum-based combination chemotherapy, who had already received a treatment regimen, and who were ineligible for radical resection. The patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1. Prior to randomization, the investigator determined for each individual patient whether, in case of allocation to the study's control arm, the monochemotherapy was to be administered using either docetaxel or paclitaxel. The study protocol allowed no further interventions, such as surgical measures or radiotherapy/chemotherapy, to be administered alongside the drug treatment options of nivolumab or docetaxel/paclitaxel. The study protocol states that the listed additional therapy options were not allowed, because they might affect the assessment of the safety and efficacy of the study interventions (study protocol in the appendix of [8]).

A total of 419 patients were randomly allocated to the two study arms in a 1:1 ratio: 210 patients to treatment with nivolumab and 209 to treatment with docetaxel or paclitaxel. The allocation of patients to the study arms was stratified by region (Japan versus rest of the world), the number of organs with metastases (≤ 1 versus ≥ 2), and programmed death ligand 1 (PD-L1) expression (< 1% or not determined versus ≥ 1%). Switching between docetaxel and paclitaxel was not permitted. No information is available as to whether a switch between nivolumab and the comparator arm was possible.

The nivolumab treatment was administered in 6-week cycles. Docetaxel was administered in 3-week cycles, while paclitaxel cycles involved 6 weeks of treatment followed by 2 weeks without the study drug. Each treatment was continued until disease progression (after disease progression, treatment continuation was possible with patient approval; in the nivolumab arm, this option was available only upon 1st disease progression), unacceptable toxicity or treatment discontinuation as decided by the physician or the patient. Nivolumab was dosed as per Summary of Product Characteristics [10], a dose adjustment, e.g. due to adverse events (AEs), was not provided for, however. Docetaxel and paclitaxel are not approved for the treatment of oesophageal carcinoma [11,12], but the guideline [13] nevertheless lists them as potential second-line therapies in palliative situations.

The primary outcome of the study was overall survival; additional patient-relevant outcomes were health status and adverse events.

Follow-up observation

Table 4 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 4: Planned follow-up observation – RCT, direct comparison: nivolumab vs. BSC

Study **Outcome category** **Outcome**	**Planned follow-up observation**
ATTRACTION-3	
Mortality	
Overall survival	Until end of study
Morbidity	
Health status (EQ-5D-VAS)	Until end of study
AEs	
AEs	Until 28 days after treatment end or (in patients who suffer from an AE at the start of follow-up or in whom an AE has led to discontinuation) until AE resolution, improvement, or stabilization
SAEs, immune-mediated AEs	Up to 100 days after the last dose of the study drug
AE: adverse event; BSC: best supportive care; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale	

The follow-up durations for the outcome category of AEs are systematically shortened since they were surveyed only for the period of treatment with the study drug (plus 28 or 100 days). To be able to draw a reliable conclusion for the entire study period or until patient death, these outcomes, like survival, would have to be surveyed and analysed over the entire period.

Characterization of the study population

Table 5 shows the patient characteristics of the ATTRACTION-3 study.

Table 5: Characterization of the study population – RCT, direct comparison: nivolumab vs. docetaxel or paclitaxel

Study Characteristic Category	Nivolumab N[a] = 210	Docetaxel or paclitaxel N[a] = 209
ATTRACTION-3		
Age [years], mean (SD)	63 (9)	65 (9)
Sex [f/m], %	15/85	11/89
Family origin, n (%)		
Asian	201 (95.7)	200 (95.7)
Caucasian	9 (4.3)	9 (4.3)
ECOG-PS, n (%)		
0	101 (48.1)	107 (51.2)
1	109 (51.9)	102 (48.8)
Disease duration: Period from initial diagnosis to randomization [months], mean (SD)	8.70 (12.20)	7.28 (5.70)
Disease stage: TNM classification at randomization, n (%)		
I–III	11 (5.2)	18 (8.6)
IV	172 (81.9)	168 (80.4)
Unknown	27 (12.9)	23 (11.0)
Recurrence, n (%)		
No	107 (51.0)	120 (57.4)
Yes	103 (49.0)	89 (42.6)
Number of organs with metastases (eCRF), n (%)		
≤ 1	85 (40.5)	86 (41.1)
≥ 2	125 (59.5)	122 (58.4)
Missing	0 (0)	1 (0.5)
Prior surgery, n (%)		
Yes	111 (52.9)	94 (45.0)
Prior radiotherapy, n (%)		
Yes	153 (72.9)	142 (67.9)
PD-L1 expression status (IWRS), n (%)		
≥ 1	101 (48.1)	101 (48.3)
< 1 or cannot be determined	109 (51.9)	108 (51.7)
Treatment discontinuation, n (%)	193 (92.3)	205 (98.6)
Study discontinuation, n (%)	ND	ND

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.

ECOG-PS: Eastern Cooperative Oncology Group Performance Status; eCRF: Electronic Case Report Form; f: female; IWRS: Interactive Web Response System; m: male; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; PD-L1: programmed death ligand 1; RCT: randomized controlled trial; SD: standard deviation; TNM: tumour node metastases

The patient characteristics are, for the most part, comparable between the ATTRACTION-3 study's arms. The mean age of the included patients was 63 and 65 years, respectively; 85% and 89%, respectively, were male. Most patients included in the study (96%) were of Asian descent, and in some 80%, the disease was classified as stage IV as per tumour-node-metastasis (TNM) classification at the time of randomization. Less than half of the patients had recurrent disease. The initial diagnosis was established almost 9 months before randomization in patients of the nivolumab arm and slightly over 7 months in the docetaxel or paclitaxel arm.

Duration of treatment and follow-up observation

Table 6 shows the mean/median duration of patient treatment as well as the mean/median duration of follow-up observation for individual outcomes.

Table 6: Information on the course of the study – RCT, direct comparison: nivolumab vs. docetaxel or paclitaxel

Study **Duration of the study phase** **Outcome category**	**Nivolumab**	**Docetaxel or paclitaxel**
ATTRACTION-3		
Treatment duration [months]	N = 209	N = 208
Median [min; max]	2.56 [0.0; 29.2]	2.56 [0.0; 21.4]
Mean (SD)	4.89 (5.90)	3.33 (3.31)
Follow-up duration [months]	N = 210	N = 209
Overall survival[a]		
Median [min; max]	10.55 [0.4; 33.8]	8.02 [0.6; 34.1]
Mean (SD)	12.01 (8.36)	10.21 (7.25)
Morbidity	ND	ND
AEs	ND	ND

a. The follow-up duration was calculated as follows:
(date of death or last confirmed survival – date of randomization + 1) / 30.4375

max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The median treatment duration is equal in both treatment arms of the ATTRACTION-3 study, while the mean treatment duration in the comparator arm is slightly below 70% of the mean treatment duration of the nivolumab arm. No information is available on the follow-up durations in the outcome categories of morbidity and side effects.

Subsequent therapies

Table 7 shows which subsequent therapies patients received after discontinuing the study drug.

Table 7: Information on subsequent therapies – RCT, direct comparison: nivolumab vs. docetaxel or paclitaxel (multipage table)

Study	**Patients with subsequent therapy n (%)**	
Drug class **Drug**	**Nivolumab** **N = 210**	**Docetaxel or paclitaxel** **N = 209**
ATTRACTION-3		
Total	119 (56.7)	115 (55.0)
Subsequent radiotherapy	30 (14.3)	23 (11.0)
Subsequent surgical procedure	7 (3.3)	15 (7.2)
Subsequent systemic therapy	112 (53.3)	99 (47.4)
Sclerosing agents	1 (0.5)	0 (0)
Talcum	1 (0.5)	0 (0)
Antimetabolites	2 (1.0)	4 (1.9)
Calcium folinate	2 (1.0)	4 (1.9)
Bisphosphonates	1 (0.5)	0 (0)
Zoledronic acid	1 (0.5)	0 (0)
Fluoropyrimidine	24 (11.4)	39 (18.7)
Capecitabine	1 (0.5)	0 (0)
Fluorouracil	12 (5.7)	13 (6.2)
Gimeracil/oteracil/tegafur	13 (6.2)	28 (13.4)
Tegafur	0 (0)	1 (0.5)
Folic acid antagonists	2 (1.0)	5 (2.4)
Methotrexate	2 (1.0)	4 (1.9)
Methotrexate sodium	0 (0)	1 (0.5)
Immunotherapy	1 (0.5)	13 (6.2)
Durvalumab	0 (0)	3 (1.4)
Ipilimumab	0 (0)	1 (0.5)
Lambrolizumab	0 (0)	4 (1.9)
Nivolumab	1 (0.5)	7 (3.3)
Tremelimumab	0 (0)	3 (1.4)
Other antibodies	2 (1.0)	3 (1.4)
Bevacizumab	0 (0)	3 (1.4)
Cetuximab	2 (1.0)	0 (0)
Other systemic therapies	11 (5.2)	28 (13.4)
Buparlisib	0 (0)	1 (0.5)
Cyclophosphamide	2 (1.0)	1 (0.5)
Doxorubicin	0 (0)	1 (0.5)
Erlotinib	0 (0)	1 (0.5)
Etoposid	1 (0.5)	6 (2.9)
Gemcitabin hydrochloride	1 (0.5)	2 (1.0)
Irinotecan hydrochloride	2 (1.0)	5 (2.4)
Mitomycin	0 (0)	2 (1.0)
Vinorelbine tartrate	3 (1.4)	4 (1.9)

Table 7: Information on subsequent therapies – RCT, direct comparison: nivolumab vs. docetaxel or paclitaxel (multipage table)

Study Drug class Drug	Patients with subsequent therapy n (%)	
	Nivolumab N = 210	Docetaxel or paclitaxel N = 209
Other	3 (1.4)	10 (4.8)
Platinum-based therapy	20 (9.5)	22 (10.5)
Carboplatin	3 (1.4)	4 (1.9)
Cisplatin	14 (6.7)	12 (5.7)
Nedaplatin	4 (1.9)	8 (3.8)
Oxaliplatin	2 (1.0)	1 (0.5)
Folic acid deficiency		
Folinic acid	1 (0.5)	0 (0)
Taxanes	100 (47.6)	43 (20.6)
Docetaxel	44 (21.0)	15 (7.2)
Paclitaxel	75 (35.7)	29 (13.9)

n: number of patients receiving subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

The ATTRACTION-3 study did not restrict the potential subsequent therapies.

In both study arms, more than half of patients received at least 1 follow-up therapy, which, in most cases, also included at least 1 systemic therapy. Radiotherapy and surgical procedures as part of multimodal BSC were used after stopping the study drug in 14% and 3% of patients in the nivolumab group and in 11% and 7% of patients in the docetaxel or paclitaxel group.

Risk of bias across outcomes (study level)

Table 8 shows the risk of bias across outcomes (risk of bias at study level).

Table 8: Risk of bias across outcomes (study level) – RCT, direct comparison: nivolumab vs. docetaxel or paclitaxel

Study	Adequate random sequence generation	Allocation concealment	Blinding		Result-independent reporting	No additional aspects	Risk of bias at study level
			Patients	Treatment providers			
ATTRACTION-3	Yes	Yes	No	No	Yes	Yes	Low

RCT: randomized controlled trial

The risk of bias across outcomes was rated as low for the results of the ATTRACTION-3 study. This concurs with the company's assessment.

Restrictions resulting from the open-label study design are described in Section 2.2 under risk of bias at outcome level.

2.2 Study results

2.2.1 Outcomes included

This addendum presents the following patient-relevant outcomes for the ATTRACTION-3 study:

- Mortality
  - Overall survival
- Morbidity
  - Health status as measured by the EQ-5D VAS
- AEs
  - Serious adverse events (SAEs)
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Immune-mediated AEs
  - Further specific AEs, if any

Table 9 shows the outcomes of the ATTRACTION-3 study for which data were available.

Table 9: Matrix of outcomes – RCT, direct comparison: nivolumab vs. BSC

Study	Outcomes						
	Overall survival	Health status (EQ-5D VAS)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-mediated AEs	Other specific AEs[a,c]
ATTRACTION-3	Yes	Yes	Yes	Yes	Yes	No[b]	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. No usable analyses available; see below for the reasoning.
c. The following events were assessed (MedDRA coding): stomatitis (PT, AEs), general disorders and administration site conditions (SOC, AEs), decreased appetite (PT, AEs), alopecia (PT, AEs), musculoskeletal and connective tissue disorders (SOC, AEs), nervous system disorders (SOC, AEs), febrile neutropenia (PT, SAEs), hyponatraemia (PT, severe AEs), investigations (SOC, severe AEs), disorders of the blood and lymphatic system (SOC, severe AEs).

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class

Comment on side effects

- The ATTRACTION-3 study surveyed immune-mediated AEs on the basis of selected AEs which were treated with immunomodulatory drugs (with some exceptions). Since it does not ensure the capture of all immune-mediated events, this operationalization does not present a reliably measurable operationalization of immune-mediated AEs. For instance, AEs not severe enough to require the systemic use of corticosteroids were not completely recorded. Therefore, there is no valid operationalization of immune-mediated AEs.

2.2.2 Risk of bias

Table 10 presents the risk of bias for the results of the relevant outcomes.

Table 10: Risk of bias at study and outcome levels – RCT, direct comparison: nivolumab vs. docetaxel or paclitaxel

Study	Study level	Outcomes						
		Overall survival	Health status (EQ-5D VAS)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-mediated AEs	Other specific AEs[a,b]
ATTRACTION-3	L	L	H[c]	H[d]	H[d]	L[e]	–[f]	H[d,g]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (MedDRA coding): stomatitis (PT, AEs), general disorders and administration site conditions (SOC, AEs), decreased appetite (PT, AEs), alopecia (PT, AEs), musculoskeletal and connective tissue disorders (SOC, AEs), nervous system disorders (SOC, AEs), febrile neutropenia (PT, SAEs), hyponatraemia (PT, severe AEs), investigations (SOC, severe AEs), disorders of the blood and lymphatic system (SOC, severe AEs).
c. High percentage of patients excluded from the analysis (> 10%), return of questionnaires decreasing over the course of the study, and lack of blinding with subjective recording of outcomes.
d. Incomplete observations for potentially informative reasons.
e. Lack of blinding with subjective recording of outcomes.
f. No usable data available; see Section 2.2.1 for the reasoning.
g. For non-serious/non-severe AEs: lack of blinding with subjective recording of outcomes.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; RCT: randomized controlled trial; SOC: system organ class; SAE: serious adverse event; VAS: visual analogue scale

In line with the company, the risk of bias is rated as low for the results on the outcome of overall survival and as high for the results on the outcomes of SAEs, severe AEs, and specific AEs. Regarding the outcomes mentioned under the side effects category, observations are incomplete for potentially informative reasons: (1) the follow-up observation depending on treatment duration and (2) a potential correlation existing between outcome and reason for treatment discontinuation. In non-serious and non-severe specific AEs, lack of blinding is an additional reason for the high risk of bias of results. If for no other reason than lack of blinding in the presence of subjective discontinuation decision, the risk of bias for the outcome of discontinuation due to AEs is rated as high.

The risk of bias for the outcome of health status (EQ-5D VAS) is rated as high, in departure from the company's rating. Firstly, a high percentage (> 10%) of patients remained excluded from analysis because either no baseline value at study start or no further value over the course

of the study was available for them. Secondly, for the patients included in the analysis, the return of questionnaires was decreasing over time. Calculated on the basis of randomized patients minus deceased patients, survey data were available for fewer than 50% of patients at Week 24, with the estimated difference between arms equalling more than 15 percentage points. Lack of blinding with subjective outcome recording is an additional reason for the high risk of bias.

2.2.3 Results

Table 11 summarizes the results on the comparison of nivolumab with docetaxel or paclitaxel in patients with oesophageal carcinoma.

Kaplan-Meier curves on the time-to-event analyses are found in Appendix A; results on common AEs are presented in Appendix B.

Table 11: Results (mortality, morbidity, side effects) – RCT, direct comparison: nivolumab vs. docetaxel or paclitaxel (multipage table)

Study Outcome category Outcome	Nivolumab		Docetaxel or paclitaxel		Nivolumab vs. docetaxel or paclitaxel
	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]
ATTRACTION-3					
Mortality					
Overall survival	210	10.91 [9.23; 13.34] 160 (76.2)	209	8.38 [7.20; 9.86] 173 (82.8)	0.77 [0.62; 0.96]; 0.019
Morbidity					
Health status (EQ-5D VAS time to 1st deterioration by ≥ 15 points)	210	NR [9.92; NC] 51 (24.3)	209	4.34 [3.02; 12.48] 78 (37.3)	0.62 [0.43; 0.88]; 0.008
Health-related quality of life					
Health-related quality of life was not investigated in the study.					
Side effects					
AEs (supplementary information)[b]	209	0.46 [0.30; 0.53] 190 (90.9)	208	0.26 [0.20; 0.26] 206 (99.0)	–
SAEs[b]	209	20.34 [8.11; NC] 79 (37.8)	208	11.10 [6.93; NC] 88 (42.3)	0.79 [0.58; 1.07]; 0.123
Severe AEs [b,c]	209	7.62 [5.39; NC] 99 (47.4)	208	0.71 [0.49; 0.99] 159 (76.4)	0.36 [0.28; 0.47]; < 0.001
Discontinuation due to AEs[b]	209	NR 30 (14.4)	208	NR 33 (15.9)	0.84 [0.51; 1.38]; 0.485
Specific AEs					
Immune-mediated AEs	No usable data				
Stomatitis (PT, AEs)	209	NR 9 (4.3)	208	NR 26 (12.5)	0.32 [0.15; 0.68]; 0.002
General disorders and administration site conditions (SOC, AEs)	209	12.06 [7.06; NC] 86 (41.1)	208	1.41 [1.02; 2.46] 138 (66.3)	0.46 [0.35; 0.60]; < 0.001
Decreased appetite (PT, AEs)	209	NR 44 (21.1)	208	NR 72 (34.6)	0.53 [0.37; 0.78]; < 0.001
Alopecia (PT, AEs)	209	NR 5 (2.4)	208	NR [0.95; NC] 100 (48.1)	0.03 [< 0.01; 0.07]; < 0.001
Musculoskeletal and connective tissue disorders (SOC, SAEs)	209	22.57 [15.31; 22.57] 38 (18.2)	208	NR 59 (28.4)	0.51 [0.33; 0.77]; 0.001

Table 11: Results (mortality, morbidity, side effects) – RCT, direct comparison: nivolumab vs. docetaxel or paclitaxel (multipage table)

Study Outcome category Outcome	Nivolumab		Docetaxel or paclitaxel		Nivolumab vs. docetaxel or paclitaxel
	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]
Nervous system disorders (SOC, AEs)	209	NR 27 (12.9)	208	3.48 [2.17; 14.29] 107 (51.4)	0.18 [0.12; 0.28]; < 0.001
Febrile neutropenia (PT, SAEs)	209	NR 2 (1.0)	208	NR 17 (8.2)	0.11 [0.03; 0.48]; < 0.001
Hyponatraemia (PT, severe AEs[c])	209	NR 3 (1.4)	208	NR 11 (5.3)	0.28 [0.08; 1.00]; 0.037
Investigations (SOC, severe AEs[c])	209	NR 25 (12.0)	208	NR [7.39; NC] 79 (38.0)	0.23 [0.15; 0.36]; < 0.001
Blood and lymphatic system disorders (SOC, severe AEs[c]):	209	NR 22 (10.5)	208	NR 70 (33.7)	0.25 [0.15; 0.40]; < 0.001

a. HR and CI: Cox proportional hazards model; p-value: log-rank test (overall survival, outcomes of the side effects category) or Cox proportional hazards model (health status); each stratified by region (Japan / rest of the world), number of organs with metastases (≤ 1 / ≥ 2) and PD-L1 expression according to IWRS (≥ 1% / < 1% or not determined); for the outcome of health status (EQ-5D VAS) additionally with the baseline value as covariate.
b. Exclusively the MedDRA PTs "lymphangiosis carcinomatosa", "progression of malignant neoplasm" and "lymph node metastases".
c. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life – 5 Dimensions; HR: hazard ratio; IWRS: Interactive Web Response System; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; PD-L1: programmed cell death ligand 1; RCT: randomized controlled study; SAE: serious adverse event; VAS: visual analogue scale

Mortality

Overall survival

For the outcome of overall survival, a statistically significant effect in favour of nivolumab was found in the ATTRACTION-3 study.

Morbidity

Health status (EQ-5D VAS)

In the ATTRACTION-3 study, the outcome of health status was surveyed using EQ-5D VAS. For this outcome, a statistically significant difference was found in favour of nivolumab.

Health-related quality of life

The ATTRACTION-3 study did not survey any outcomes on health-related quality of life.

Side effects

SAEs

For the outcome of SAEs, no statistically significant difference between treatment groups was found.

Severe AEs

For the outcome of severe AEs, a statistically significant difference was found in favour of nivolumab. There is an effect modification by the attribute of age, with a statistically significant difference in favour of nivolumab being found for both subgroups (see Section 2.2.4).

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, no statistically significant difference between treatment groups was found.

Specific AEs

For each of the specific AEs of stomatitis (AEs), general disorders and administration site conditions (AEs), decreased appetite (AEs), alopecia (AEs), musculoskeletal and connective tissue disorders (AEs), nervous system disorders (AEs), febrile neutropenia (SAEs), hyponatraemia (severe AEs), investigations (severe AEs) as well as disorders of the blood and lymphatic system (severe AEs), a statistically significant difference in favour of nivolumab is found.

2.2.4 Subgroups and other effect modifiers

For this addendum, the following potential effect modifiers are taken into account:

- sex (female/male)
- age (< 65 / ≥ 65 years)

Interaction tests were performed whenever at least 10 patients per subgroup were included in the analysis. For binary data, there must also be 10 events in at least 1 subgroup.

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

Table 12 shows the results of the subgroup analyses. Kaplan-Meier curves on the time-to-event analyses for the subgroups are presented in Figure 16 and Figure 17 of Appendix A.

Table 12: Subgroups (side effects) – RCT, direct comparison: nivolumab vs. docetaxel or paclitaxel

Study Outcome	Nivolumab		Docetaxel or paclitaxel		Nivolumab vs. docetaxel or paclitaxel	
Characteristic Subgroup	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][a]	p-value[b]
ATTRACTION-3						
Severe AEs[c,d]						
Age						
< 65 years	112	6.80 [4.24; 20.07] 56 (50.0)	85	2.17 [0.72; 4.24] 57 (67.1)	0.53 [0.37; 0.78]	< 0.001
≥ 65 years	97	9.49 [4.63; NC] 43 (44.3)	123	0.49 [0.49; 0.66] 102 (82.9)	0.27 [0.19; 0.40]	< 0.001
Total					Interaction:	0.004[e]

a. Cox proportional hazards model; unstratified.
b. Log rank test; unstratified.
c. Exclusively the MedDRA PTs "lymphangiosis carcinomatosa", progression of malignant neoplasm", and "lymph node metastases".
d. Operationalized as CTCAE grade ≥ 3.
e. Cox proportional hazards model with corresponding interaction term; unstratified.

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial

Side effects

Severe AEs

For the outcome of severe AEs, there was an effect modification by the attribute of age. For each of the subgroups, a statistically significant difference was found in favour of nivolumab.

3 References

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Appendix A – Kaplan-Meier curves on results of the ATTRACTION-3 study

A.1 Mortality

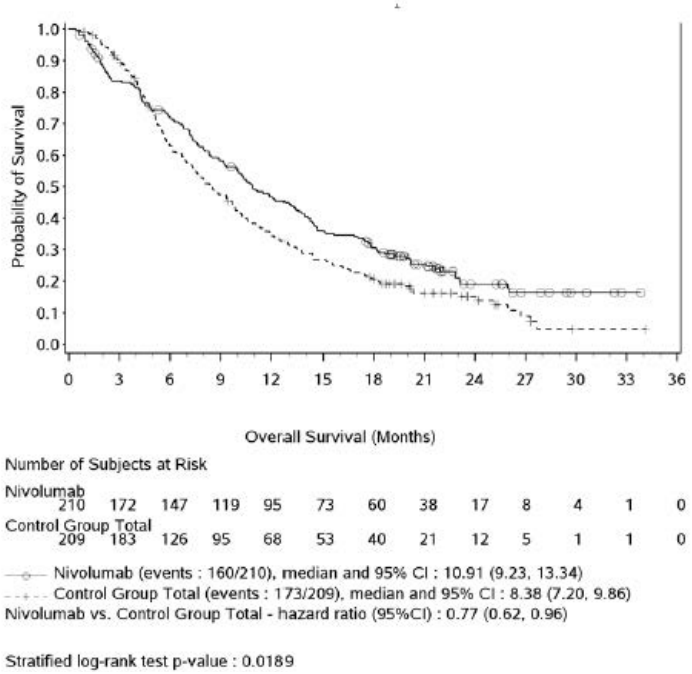
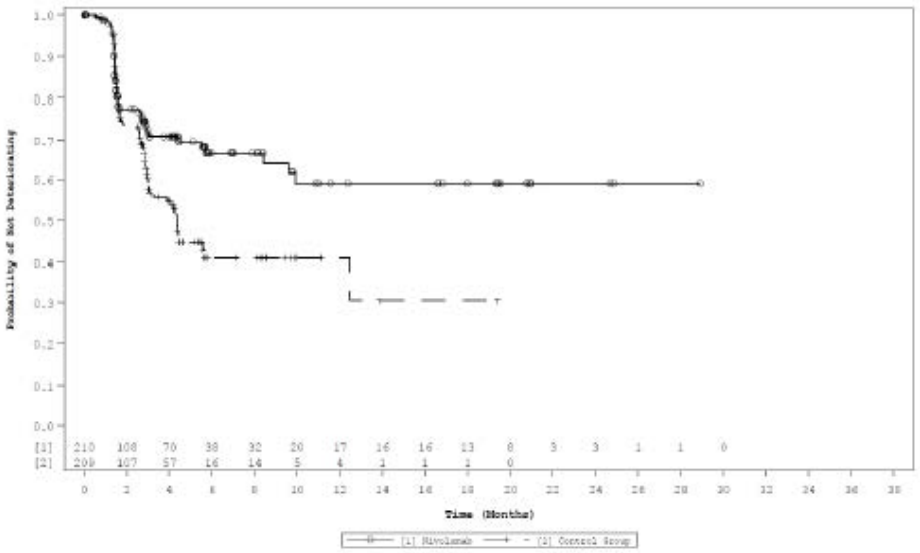


Figure 1: Kaplan-Meier curves for the outcome of overall survival

A.2 Morbidity



Kaplan-Meier curves for time to first deterioration of health status as measured with EQ-5D-VAS (MID = 15) from ATTRACTION-3

Figure 2: Kaplan-Meier curves for the outcome of health status (EQ-5D VAS time to 1st deterioration by ≥ 15 points)

A.3 Side effects

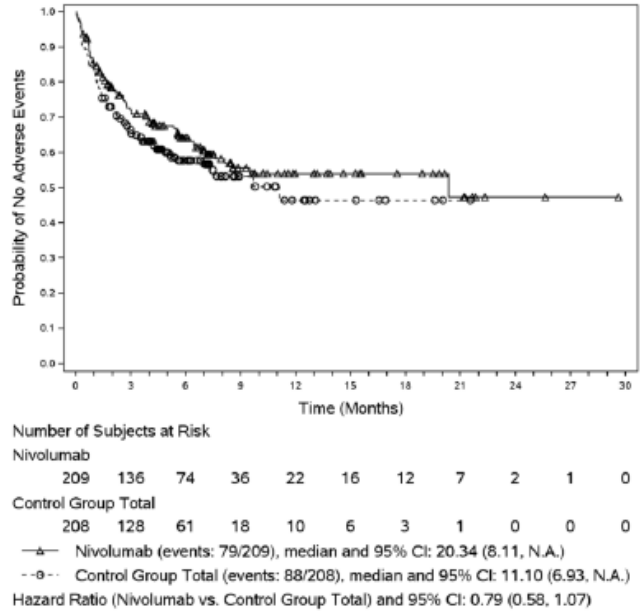


Figure 3: Kaplan-Meier curves for the outcome of SAEs

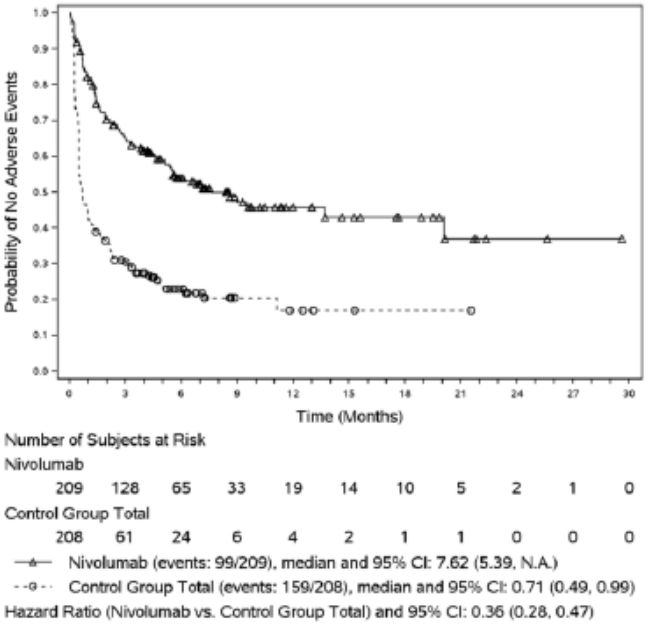


Figure 4: Kaplan-Meier curves for the outcome of severe AEs (CTCAE grade ≥ 3)

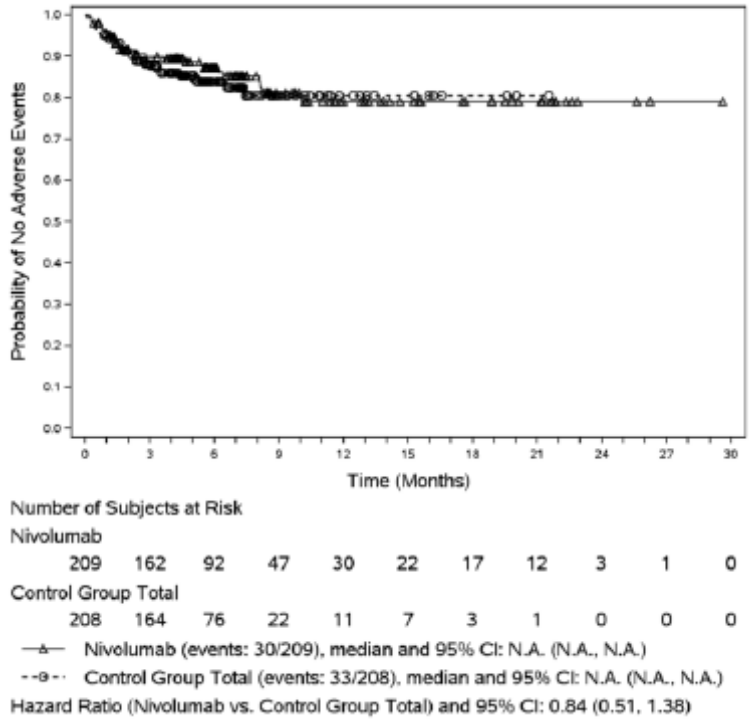


Figure 5: Kaplan-Meier curves for the outcome of discontinuation due to AEs

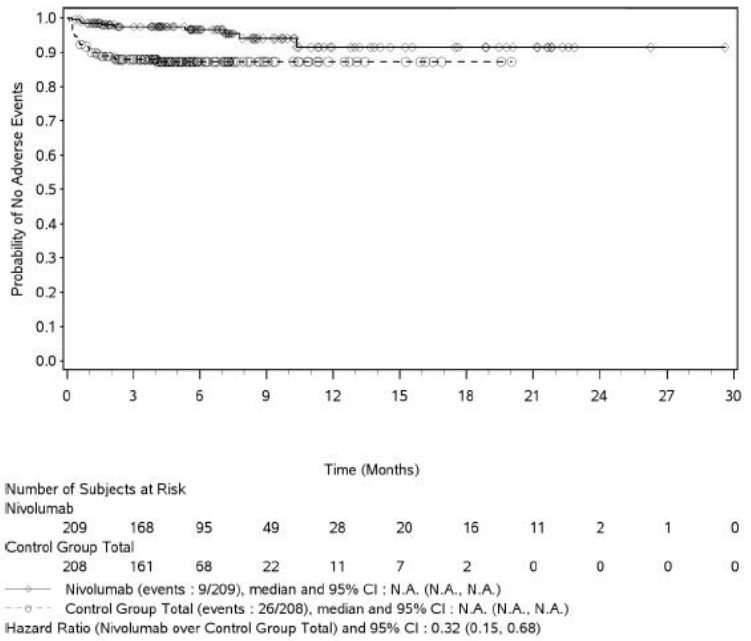


Figure 6: Kaplan-Meier curves for the outcome of stomatitis (PT, AEs)

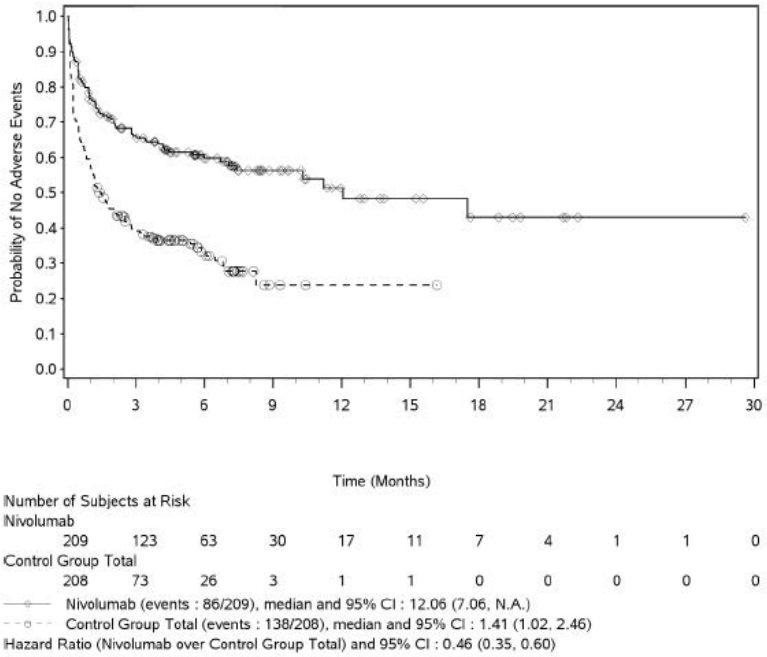


Figure 7: Kaplan-Meier curves for the outcome of general disorders and administration site conditions (SOC, AEs)

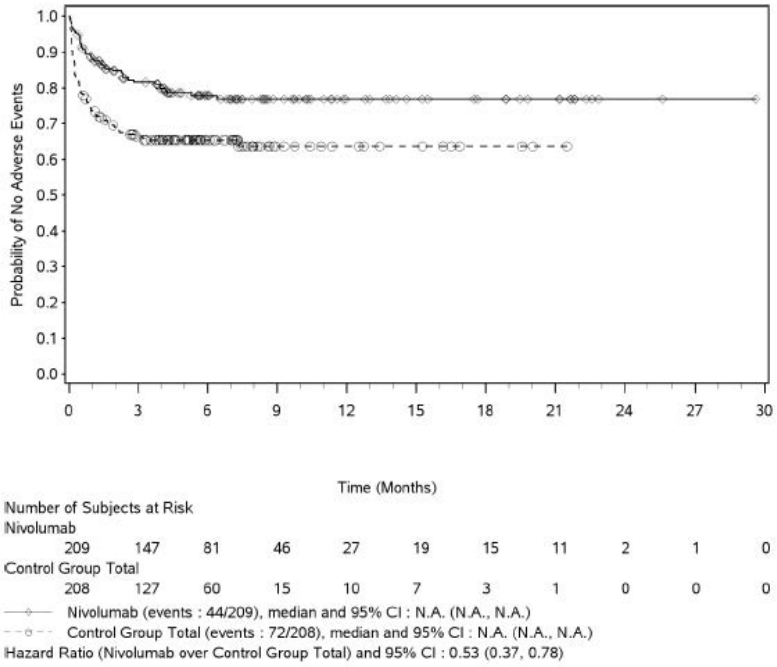


Figure 8: Kaplan-Meier curves for the outcome of decreased appetite (PT, AEs)

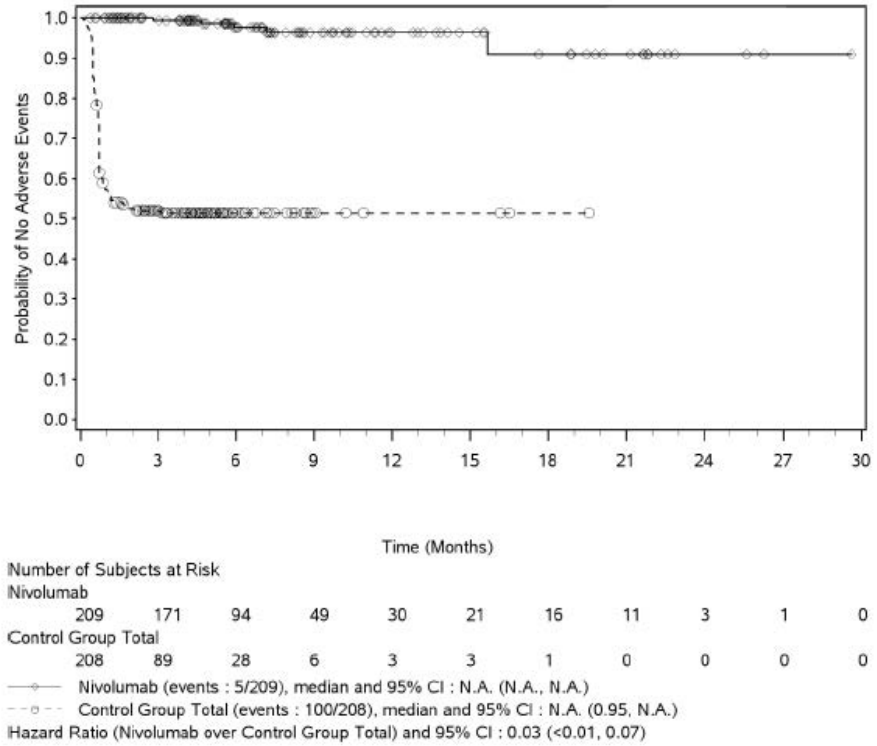


Figure 9: Kaplan-Meier curves for the outcome of alopecia (PT, AEs)

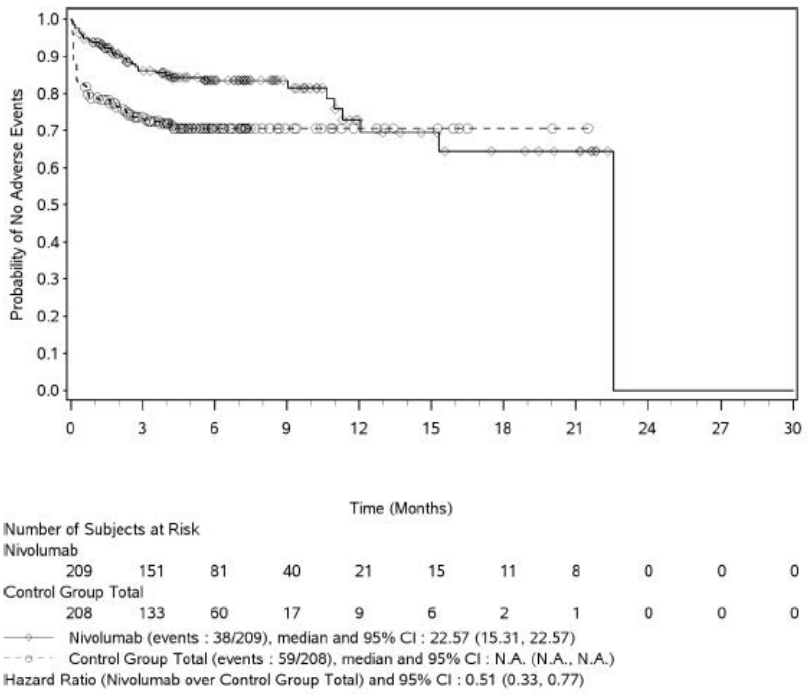


Figure 10: Kaplan-Meier curves for the outcome of musculoskeletal and connective tissue disorders (SOC, AEs)

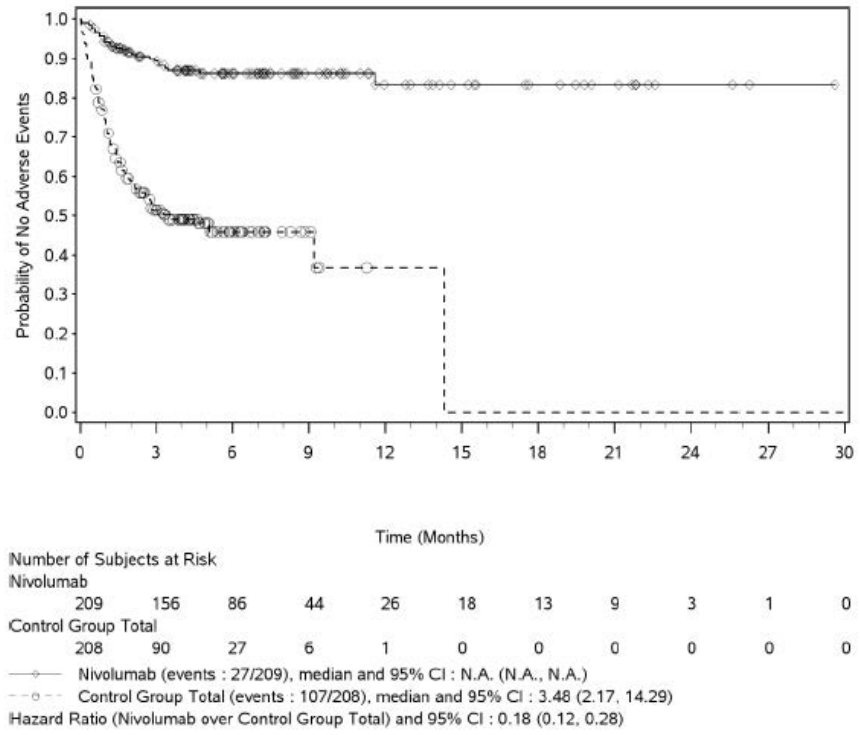


Figure 11: Kaplan-Meier curves for the outcome of nervous system disorders (SOC, AEs)

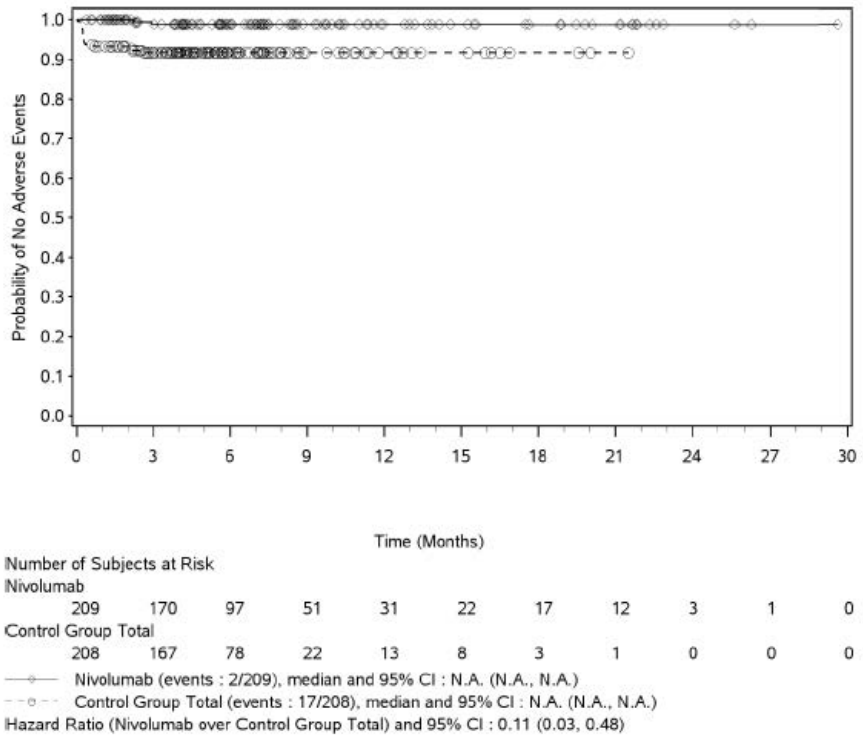


Figure 12: Kaplan-Meier curves for the outcome of febrile neutropenia (PT, SAEs)

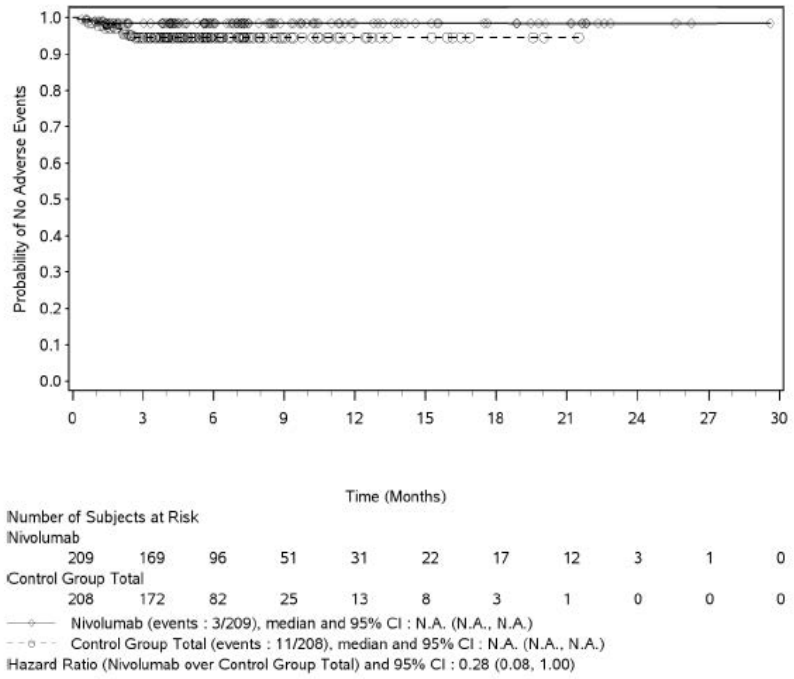


Figure 13: Kaplan-Meier curves for the outcome of hyponatraemia (PT, severe AEs)

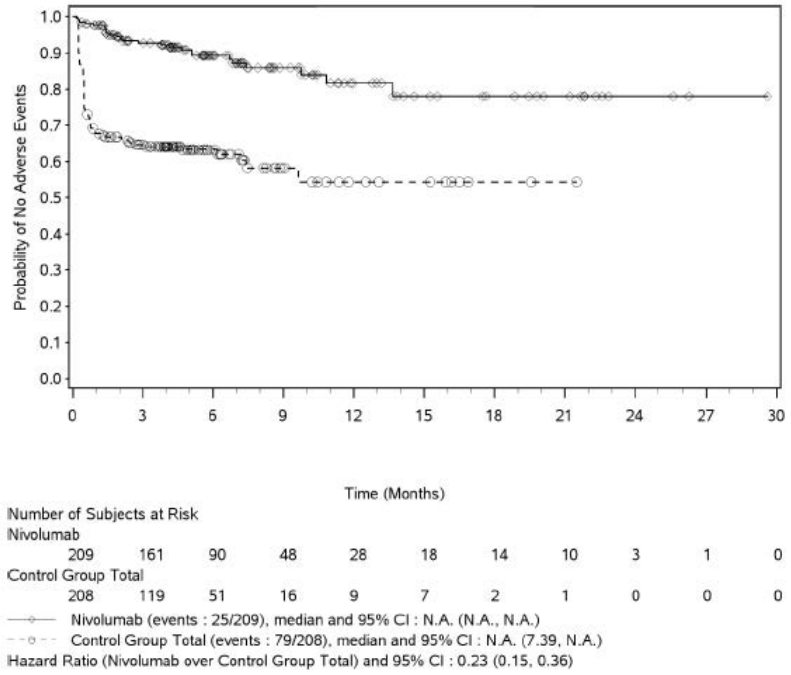


Figure 14: Kaplan-Meier curves for the outcome of investigations (SOC, severe AEs)

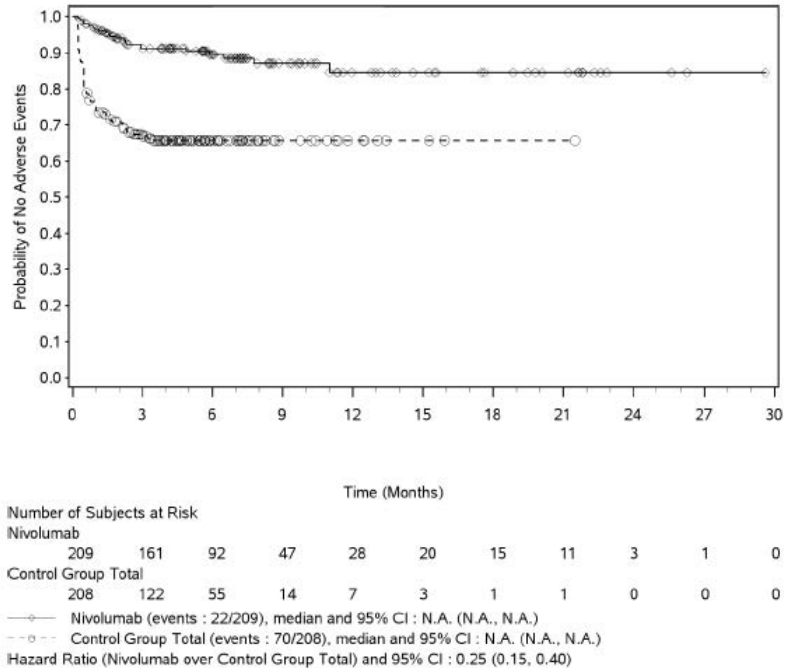


Figure 15: Kaplan-Meier curves for the outcome of disorders of the blood and lymphatic system (SOC, severe AEs)

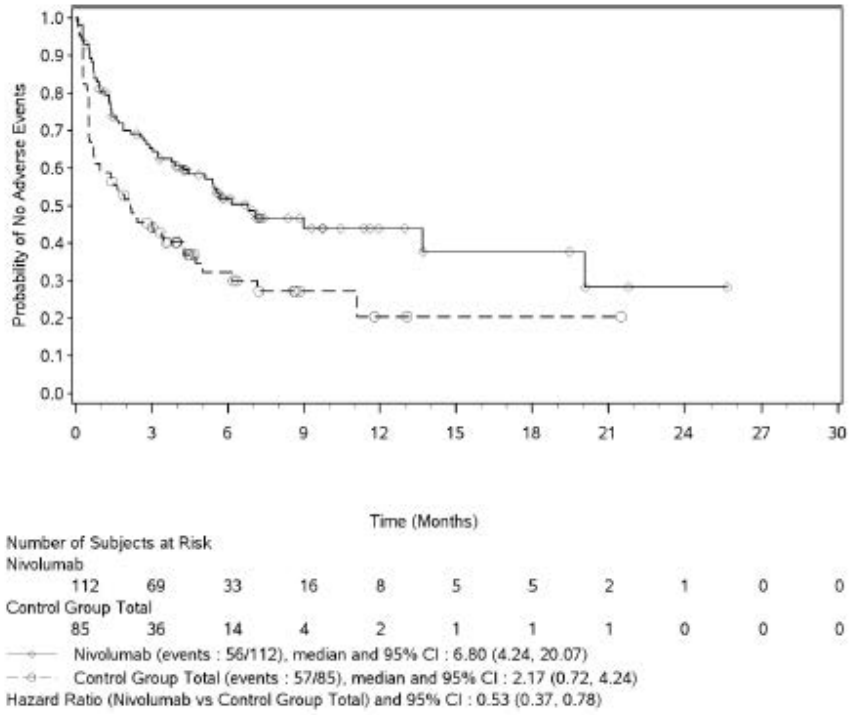


Figure 16: Kaplan-Meier curves for the outcome of severe AEs (CTCAE grade ≥ 3), subgroup < 65 years

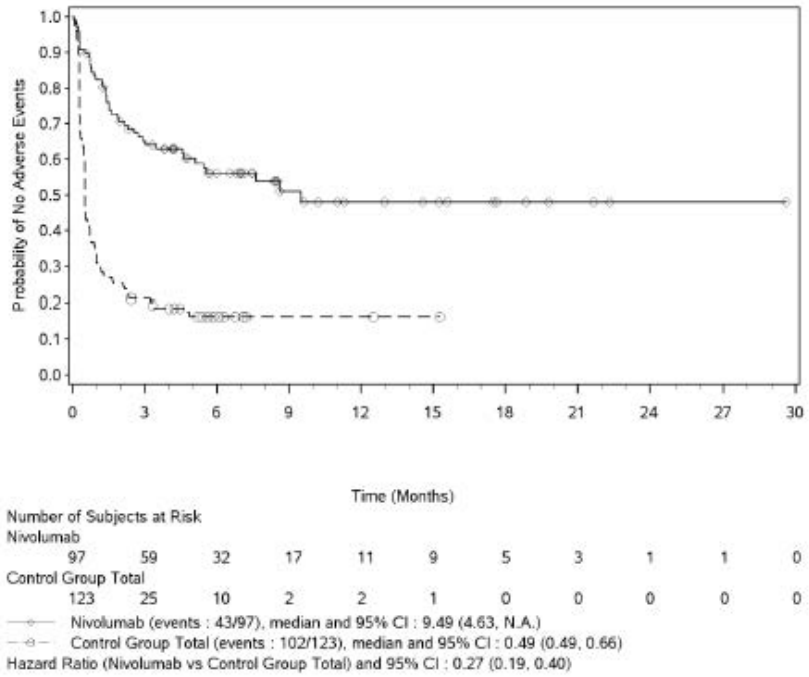


Figure 17: Kaplan-Meier curves for the outcome of severe AEs (CTCAE grade ≥ 3), subgroup ≥ 65 years

Appendix B – Results on AEs

The tables below present system organ class (SOC) and preferred term (PT) events as per Medical Dictionary for Regulatory Activities (MedDRA) for total rates of AE, SAE, and severe AE (CTCAE grade ≥ 3), each on the basis of the following criteria:

- Total rate of AEs (any severity): events which occurred in at least 10% of patients in 1 study arm
- Total rates of severe AEs (e.g. CTCAE grade ≥ 3) and SAEs: events which occurred in at least 5% of patients in 1 study arm
- Additionally, for all events of any severity: events which occurred in at least 10 patients and in at least 1% of patients in 1 study arm

For the outcome of discontinuation due to AEs, all events (SOCs/PTs) which lead to discontinuation are presented.

Table 13: Common AEs[a] – RCT, direct comparison: nivolumab vs. docetaxel or paclitaxel (multipage table)

Study	Patients with event n (%)	
SOC[b] **PT[b]**	**Nivolumab** **N = 209**	**Docetaxel or paclitaxel** **N = 208**
ATTRACTION-3		
Total rate of AEs[c]	190 (90.9)	206 (99.0)
Gastrointestinal disorders	116 (55.5)	128 (61.5)
Diarrhoea	40 (19.1)	38 (18.3)
Constipation	37 (17.7)	40 (19.2)
Nausea	23 (11.0)	42 (20.2)
Abdominal pain	14 (6.7)	11 (5.3)
Dysphagia	14 (6.7)	5 (2.4)
Vomiting	13 (6.2)	19 (9.1)
Stomatitis	9 (4.3)	26 (12.5)
General disorders and administration site conditions	86 (41.1)	138 (66.3)
Fever	35 (16.7)	42 (20.2)
Fatigue	20 (9.6)	53 (25.5)
Chest pain	14 (6.7)	5 (2.4)
Malaise	13 (6.2)	50 (24.0)
Peripheral oedema	7 (3.3)	10 (4.8)
Metabolic and nutritional disorders	84 (40.2)	100 (48.1)
Decreased appetite	44 (21.1)	72 (34.6)
Hypercalcaemia	14 (6.7)	9 (4.3)
Hypokalaemia	10 (4.8)	5 (2.4)
Hyponatraemia	5 (2.4)	12 (5.8)
Respiratory, thoracic, and mediastinal disorders	82 (39.2)	83 (39.9)
Cough	34 (16.3)	26 (12.5)
Dyspnoea	15 (7.2)	12 (5.8)
Interstitial lung disease	10 (4.8)	6 (2.9)
Productive cough	10 (4.8)	9 (4.3)
Diseases of the skin and subcutaneous tissue	80 (38.3)	135 (64.9)
Rash	27 (12.9)	38 (18.3)
Pruritus	25 (12.0)	15 (7.2)
Dry skin	12 (5.7)	7 (3.4)
Alopecia	5 (2.4)	100 (48.1)
Infections and infestations	74 (35.4)	94 (45.2)
Pneumonia	18 (8.6)	29 (13.9)
Upper respiratory tract infection	16 (7.7)	12 (5.8)
Nasopharyngitis	13 (6.2)	9 (4.3)
Pneumonia	6 (2.9)	13 (6.3)

Table 13: Common AEs[a] – RCT, direct comparison: nivolumab vs. docetaxel or paclitaxel (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	Nivolumab N = 209	Docetaxel or paclitaxel N = 208
Investigations	60 (28.7)	124 (59.6)
Aspartate aminotransferase increased	14 (6.7)	7 (3.4)
Alanine aminotransferase increased	13 (6.2)	7 (3.4)
Weight decreased	12 (5.7)	11 (5.3)
Platelet count decreased	8 (3.8)	21 (10.1)
Neutrophil count decreased	4 (1.9)	77 (37.0)
Leukocyte count decreased	4 (1.9)	72 (34.6)
Musculoskeletal and connective tissue disorders	38 (18.2)	59 (28.4)
Arthralgia	11 (5.3)	27 (13.0)
Myalgia	6 (2.9)	22 (10.6)
Disorders of the blood and lymphatic system	35 (16.7)	104 (50.0)
Anaemia	28 (13.4)	61 (29.3)
Febrile neutropenia	2 (1.0)	23 (11.1)
Neutropoenia	1 (0.5)	40 (19.2)
Leukopoenia	0 (0)	19 (9.1)
Endocrine disorders	27 (12.9)	4 (1.9)
Hypothyroidism	21 (10.0)	3 (1.4)
Nervous system disorders	27 (12.9)	107 (51.4)
Dysgeusia	5 (2.4)	14 (6.7)
Peripheral sensory neuropathy	1 (0.5)	46 (22.1)
Peripheral neuropathy	0 (0)	23 (11.1)
Injury, poisoning, and procedural complications	22 (10.5)	10 (4.8)
Psychiatric disorders	20 (9.6)	23 (11.1)
Insomnia	12 (5.7)	14 (6.7)
Renal and urinary disorders	18 (8.6)	7 (3.4)
Benign, malignant, and unspecified neoplasms (incl. cysts and polyps)	15 (7.2)	9 (4.3)
Vascular disorders	14 (6.7)	17 (8.2)
Hepatobiliary disorders	12 (5.7)	2 (1.0)
Eye disorders	8 (3.8)	12 (5.8)

a. Events which occurred in ≥ 10 patients in at least 1 study arm.
b. MedDRA version 21.1; SOC and PT terminology adopted unmodified from MedDRA.
c. Including the MedDRA PTs “lymphangiosis carcinomatosa”, “progression of malignant neoplasm”, and “lymph node metastases”.

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; SOC: system organ class

Table 14: Common AEs[a] – RCT, direct comparison: nivolumab vs. docetaxel or paclitaxel

Study	Patients with event n (%)	
SOC[b] PT[b]	Nivolumab N = 209	Docetaxel or paclitaxel N = 208
ATTRACTION-3		
Total rate of SAEs[c]	80 (38.3)	88 (42.3)
Infections and infestations	25 (12.0)	34 (16.3)
Pneumonia	11 (5.3)	20 (9.6)
Respiratory, thoracic, and mediastinal disorders	25 (12.0)	22 (10.6)
Gastrointestinal disorders	15 (7.2)	14 (6.7)
Metabolic and nutritional disorders	12 (5.7)	11 (5.3)
General disorders and administration site conditions	10 (4.8)	7 (3.4)
Disorders of the blood and lymphatic system	4 (1.9)	19 (9.1)
Febrile neutropenia	2 (1.0)	17 (8.2)

a. Events which occurred in ≥ 10 patients in at least 1 study arm.
b. MedDRA version 21.1; SOC and PT terminology adopted unmodified from MedDRA.
c. Including the MedDRA PTs “lymphangiosis carcinomatosa”, “progression of malignant neoplasm”, and “lymph node metastases”.

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; SAE: serious adverse event; SOC: system organ class

Table 15: Common severe AEs[a] (CTCAE grade ≥ 3) – RCT, direct comparison: nivolumab vs. docetaxel or paclitaxel

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Nivolumab** **N = 209**	**Docetaxel or paclitaxel** **N = 208**
ATTRACTION-3		
Total rate of severe AEs (CTCAE grade ≥3)[c]	101 (48.3)	159 (76.4)
Metabolic and nutritional disorders	36 (17.2)	38 (18.3)
Decreased appetite	5 (2.4)	12 (5.8)
Hyponatraemia	3 (1.4)	11 (5.3)
Investigations	25 (12.0)	79 (38.0)
Platelet count decreased	5 (2.4)	15 (7.2)
Neutrophil count decreased	1 (0.5)	59 (28.4)
Leukocyte count decreased	1 (0.5)	46 (22.1)
Infections and infestations	23 (11.0)	33 (15.9)
Pneumonia	8 (3.8)	17 (8.2)
Disorders of the blood and lymphatic system	22 (10.5)	70 (33.7)
Anaemia	19 (9.1)	24 (11.5)
Febrile neutropenia	2 (1.0)	23 (11.1)
Leukopoenia	0 (0)	15 (7.2)
Neutropoenia	0 (0)	29 (13.9)
Respiratory, thoracic, and mediastinal disorders	21 (10.0)	22 (10.6)
Gastrointestinal disorders	17 (8.1)	17 (8.2)
General disorders and administration site conditions	9 (4.3)	13 (6.3)

a. Events which occurred in ≥ 10 patients in at least 1 study arm.
b. MedDRA version 21.1; SOC and PT terminology adopted from MedDRA unmodified.
c. Including the MedDRA PTs “lymphangiosis carcinomatosa”, “progression of malignant neoplasm”, and “lymph node metastases”.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; 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; SOC: system organ class

Table 16: Discontinuation due to AEs – RCT, direct comparison: nivolumab vs. docetaxel or paclitaxel (multipage table)

Study	Patients with event n (%)	
SOC[a] PT[a]	Nivolumab N = 209	Docetaxel or paclitaxel N = 208
ATTRACTION-3		
Total rate of discontinuation due to AEs[b]	31 (14.8)	33 (15.9)
Respiratory, thoracic, and mediastinal disorders	14 (6.7)	7 (3.4)
Interstitial lung disease	6 (2.9)	3 (1.4)
Pneumonitis	5 (2.4)	2 (1.0)
Pneumothorax	1 (0.5)	0 (0)
Pulmonary embolism	1 (0.5)	0 (0)
Tracheal fistula	1 (0.5)	0 (0)
Dyspnoea	0 (0)	1 (0.5)
Pleural effusion	0 (0)	1 (0.5)
Aspiration pneumonia	0 (0)	1 (0.5)
Gastrointestinal disorders	5 (2.4)	2 (1.0)
Dysphagia	2 (1.0)	0 (0)
Diarrhoea	1 (0.5)	1 (0.5)
Gastrointestinal haemorrhage	1 (0.5)	0 (0)
Oesophageal disorder	1 (0.5)	0 (0)
Abdominal pain	0 (0)	1 (0.5)
Endocrine disorders	3 (1.4)	0 (0)
Hypothyroidism	2 (1.0)	0 (0)
Adrenocorticotropic hormone deficiency	1 (0.5)	0 (0)
General disorders and administration site conditions	2 (1.0)	3 (1.4)
Fever	1 (0.5)	0 (0)
Sudden death	1 (0.5)	1 (0.5)
Progression of a disease	0 (0)	1 (0.5)
Fatigue	0 (0)	1 (0.5)
Hepatobiliary disorders	2 (1.0)	0 (0)
Hepatic function abnormal	1 (0.5)	0 (0)
Acute hepatitis	1 (0.5)	0 (0)
Infections and infestations	2 (1.0)	8 (3.8)
Lung infection	1 (0.5)	1 (0.5)
Pneumonia	1 (0.5)	4 (1.9)
Infectious pleural effusion	0 (0)	2 (1.0)
Sepsis	0 (0)	1 (0.5)

Table 16: Discontinuation due to AEs – RCT, direct comparison: nivolumab vs. docetaxel or paclitaxel (multipage table)

Study	Patients with event n (%)	
SOC[a] PT[a]	Nivolumab N = 209	Docetaxel or paclitaxel N = 208
Metabolic and nutritional disorders	1 (0.5)	2 (1.0)
Hypercalcaemia	1 (0.5)	0 (0)
Cachexia	0 (0)	1 (0.5)
Hyponatraemia	0 (0)	1 (0.5)
Hypophagia	0 (0)	1 (0.5)
Benign, malignant, and unspecified neoplasms (incl. cysts and polyps)	1 (0.5)	2 (1.0)
Progression of a malignant neoplasm	1 (0.5)	0 (0)
Cancer pain	0 (0)	1 (0.5)
Tumour bleeding	0	1 (0.5)
Diseases of the skin and subcutaneous tissue	1 (0.5)	0
Stevens-Johnson syndrome	1 (0.5)	0
Not allocated to any PT	1 (0.5)	0
Disorders of the blood and lymphatic system	0 (0)	1 (0.5)
Neutropoenia	0 (0)	1 (0.5)
Heart disease	0 (0)	1 (0.5)
Pericarditis	0 (0)	1 (0.5)
Investigations	0 (0)	3 (1.4)
Neutrophil count decreased	0 (0)	2 (1.0)
Weight decreased	0 (0)	1 (0.5)
Musculoskeletal and connective tissue disorders	0 (0)	4 (1.9)
Arthralgia	0 (0)	1 (0.5)
Fistula	0 (0)	2 (1.0)
Muscular weakness	0 (0)	1 (0.5)
Nervous system disorders	0 (0)	5 (2.4)
Peripheral neuropathy	0 (0)	2 (1.0)
Neurotoxicity	0 (0)	1 (0.5)
Peripheral motor neuropathy	0 (0)	1 (0.5)
Peripheral sensory neuropathy	0 (0)	1 (0.5)

a.MedDRA version 21.1; SOC and PT terminology adopted from MedDRA unmodified.
b. Including the MedDRA PTs “lymphangiosis carcinomatosa”, “progression of malignant neoplasm”, and “lymph node metastases”.

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; SOC: system organ class

Appendix C – Supplementary presentation of results on morbidity

Table 17: Results (morbidity) – RCT, direct comparison: nivolumab vs. docetaxel or paclitaxel

Study Outcome category Outcome	Nivolumab N	Nivolumab Median time to event in months [95% CI] Patients with event n (%)	Docetaxel or paclitaxel N	Docetaxel or paclitaxel Median time to event in months [95% CI] Patients with event n (%)	Nivolumab vs. docetaxel or paclitaxel HR [95% CI]; p-value[a]
ATTRACTION-3					
Morbidity					
Health status (EQ-5D VAS time to 1st deterioration)					
7 points	210	4.34 [2.83; 8.21] 85 (40.5)	209	2.73 [1.68; 2.92] 117 (56.0)	0.70 [0.52; 0.93]; 0.013
10 points	210	4.44 [2.89; 8.21] 84 (40.0)	209	2.83 [1.77; 3.02] 112 (53.6)	0.71 [0.53; 0.95]; 0.022

a. HR, CI, and p-value: Cox proportional hazards model; stratified by region (Japan / rest of the world), number of organs with metastases (≤ 1 / ≥ 2) and PD-L1 expression according to IWRS (≥ 1% / < 1% or not determined) and with the baseline value as covariate.

CI: confidence interval; EQ-5D: European Quality of Life – 5 Dimensions; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; PD-L1: programmed death ligand 1; RCT: randomized controlled trial; VAS: visual analogue scale

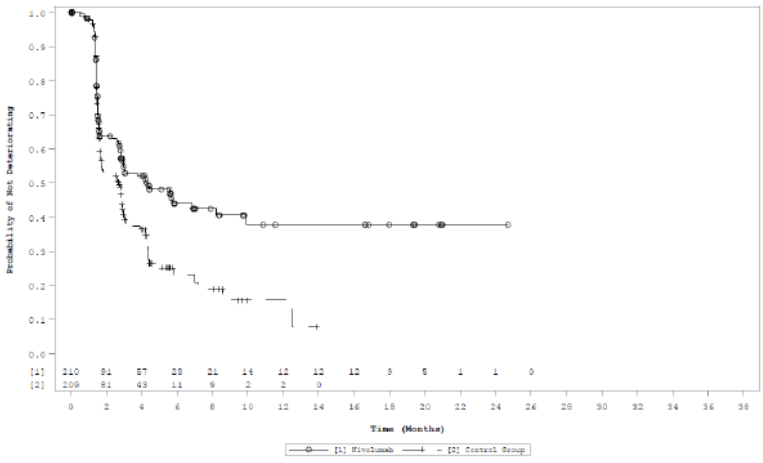


Figure 4: Kaplan-Meier curves for time to first deterioration of health status as measured with EQ-5D-VAS (MID=7) from ATTRACTION-3

Figure 18: Kaplan-Meier curves for the outcome of health status (EQ-5D VAS; time to 1st deterioration by ≥ 7 points)

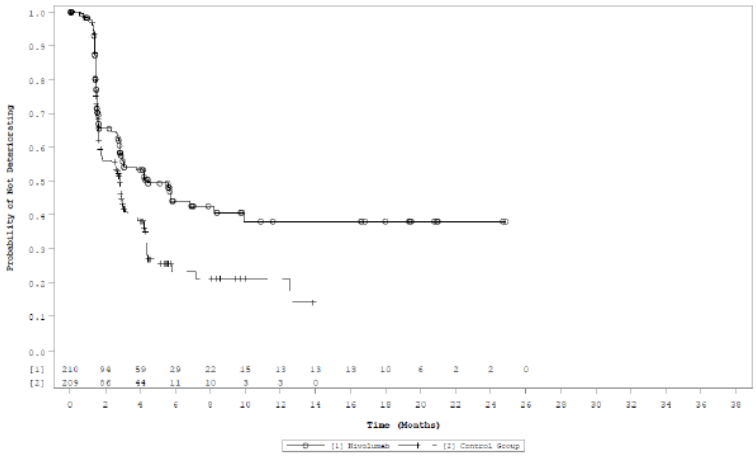


Figure 5: Kaplan-Meier curves for time to first deterioration of health status as measured with EQ-5D-VAS (sensitivity analysis 1 MID=10) from ATTRACTION-3

Figure 19: Kaplan-Meier curves for the outcome of health status (EQ-5D VAS; time to 1st deterioration by ≥ 10 points)