IQWiG Reports – Commission No. A22-44

Nivolumab (gastric, gastro-oesophageal junction or oesophageal adenocarcinoma) –

Addendum to Commission A21-146[1]

Addendum

Commission: A22-44
Version: 1.0
Status: 6 May 2022

[1] Translation of addendum A22-44 *Nivolumab (Adenokarzinome des Magens, des gastroösophagealen Übergangs oder des Ösophagus) – Addendum zum Auftrag A21-146* (Version 1.0; Status: 6 May 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 (gastric, gastro-oesophageal junction or oesophageal adenocarcinoma) – Addendum to Commission A21-146

Commissioning agency
Federal Joint Committee

Commission awarded on
12 April 2022

Internal Commission No.
A22-44

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

- Teresa Labahn
- Charlotte Guddat
- Deborah Ingenhag-Reister
- Sabine Ostlender
- Volker Vervölgyi

Keywords: Nivolumab, Adenocarcinoma, Benefit Assessment, NCT02872116

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CPS	combined positive score
CTCAE	Common Terminology Criteria for Adverse Events
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-Ga	Functional Assessment of Cancer Therapy – Gastric
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
SAE	serious adverse event
VAS	visual analogue scale

1 Background

On 12 April 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments on Commission A21-146 (Nivolumab – benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the following assessment of the analyses presented by the pharmaceutical company (hereinafter referred to as "company") [2,3] during the commenting procedure for the CheckMate 649 study, taking into account the information provided in the dossier [4]:

- analyses of the 3rd data cut-off for the programmed cell death ligand 1 (PD-L1) positive population

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

2.1 Background of the reassessment

The randomized controlled trial (RCT) CheckMate 649 was included to assess the benefit of nivolumab in combination with fluoropyrimidine-based and platinum-based combination chemotherapy in comparison with the ACT as first-line treatment in adult patients with human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic adenocarcinoma of the stomach, the gastrooesophageal junction, or the oesophagus whose tumours express programmed death ligand 1 (PD-L1, combined positive score [CPS] ≥ 5). The CheckMate 649 study is an ongoing, open-label RCT comparing nivolumab in combination with 2 different fluoropyrimidine-based and platinum-based combination chemotherapy regimens, FOLFOX (consisting of 5-FU + folinic acid + oxaliplatin) or XELOX (consisting of capecitabine + oxaliplatin), versus FOLFOX or XELOX.

For the benefit assessment, the study results presented in the company's dossier were deemed incomplete in content because the company submitted data from the current 3rd data cut-off only for the outcome of overall survival, but not for the other patient-relevant outcomes (for details, see benefit assessment A21-146 [1]). During the commenting procedure, the company subsequently submitted analyses on the 3rd data cut-off for all patient-relevant outcomes. These analyses are assessed in this addendum.

The original benefit assessment (A21-146) was conducted in accordance with the research question specified by the G-BA, i.e. using 2 separate subpopulations of the study – for research question 1 on the basis of the patients with adenocarcinoma of the oesophagus and for research question 2 on the basis of the patients with adenocarcinoma of the stomach or the gastrooesophageal junction. During the comments and oral hearing [5], it was determined that it would be useful to conduct a joint analysis of patients with adenocarcinoma of the oesophagus, the gastrooesophageal junction, and the stomach. Unlike in dossier assessment A21-146, the entire CheckMate 649 study population with PD-L1-expressing tumours with CPS ≥ 5 (hereinafter referred to as PD-L1-positive population) is now taken into account for the benefit assessment, as commissioned.

2.2 Study characteristics

A detailed description of the CheckMate 649 study can be found in dossier assessment A21-146 [1]. The sections below present the study results for the PD-L1-positive population. This subpopulation comprises 955 patients (60.4%) from the total study population.

Patients with HER2-negative adenocarcinoma

Within the PD-L1-positive population (as described in detail in benefit assessment A21-146 for both subpopulations [1]), the total percentage of HER2-negative patients is assumed to be above 80%. In the present situation, using the results of the PD-L1-positive population for deriving added benefit is therefore deemed adequate. However, the certainty of results of the

CheckMate 649 study is reduced for the PD-L1-positive population due to uncertainty regarding the percentage of patients with HER2-negative tumours (for a detailed description, see benefit assessment A21-146 [1]).

Planned duration of follow-up observation

A description of the planned follow-up duration can be found in dossier assessment A21-146 [1]. In said description, it was noted that, due to inconsistent information being provided within the study documents and Module 4 Q, it is unclear (a) whether the Functional Assessment of Cancer Therapy – General (FACT-G) was surveyed only during treatment and (b) whether side effects were surveyed only until 100 days after treatment end or until the 2nd follow-up visit.

In its comments [2], the company clarified that the FACT-G was surveyed only during treatment. For the side effects outcomes, it remains unclear whether they were recorded up to 100 days or 114 (±14) days after the last dose of the study medication. The analyses took into account only events which occurred up to 100 days after the last dose of the study drug.

Characteristics of the study population

Table 1 shows the characteristics of the patients of the CheckMate 649 study's PD-L1-positive population.

Table 1: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Study Characteristic Category	Nivolumab + chemotherapy (FOLFOX or XELOX) N[a] = 473	Chemotherapy (FOLFOX or XELOX) N[a] = 482
CheckMate 649 (3rd data cut-off)		
Age [years], mean (SD)	61 (12)	61 (11)
Age group, n (%)		
< 65 years	266 (56)	286 (59)
≥ 65 years to < 75 years	151 (32)	147 (30)
≥ 75 years	56 (12)	49 (10)
Sex [f/m], %	30/70	28/72
Family origin n (%)		
Asian	119 (25)	117 (24)
White	328 (69)	327 (68)
Other	26 (5)	38 (8)

Table 1: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Study Characteristic Category	**Nivolumab + chemotherapy (FOLFOX or XELOX) N[a] = 473**	**Chemotherapy (FOLFOX or XELOX) N[a] = 482**
Region, n (%)		
Asia	117 (25)	111 (23)
North America	67 (14)	70 (15)
Rest of the world	289 (61)	301 (62)
ECOG-PS, n (%)		
0	194 (41)	203 (42)
1	279 (59)	278 (58)
Unknown	0 (0)	1 (< 1)
Location of primary tumour at first diagnosis, n (%)		
Stomach	333 (70)	334 (69)
Gastrooesophageal junction	84 (18)	86 (18)
Oesophagus	56 (12)	62 (13)
Disease status, n (%)		
Locally recurrent/advanced	19 (4)	21 (4)
Metastatic	454 (96)	461 (96)
Prior surgery related to current cancer, n (%)		
Yes	97 (21)	105 (22)
No	376 (79)	377 (78)
Prior radiotherapy, n (%)		
Yes	44 (9)	42 (9)
No	429 (91)	440 (91)
Laurén classification, n (%)		
Intestinal type	171 (36)	176 (37)
diffuse type	137 (29)	141 (29)
mixed type	37 (8)	30 (6)
unknown	128 (27)	135 (28)
Time between first diagnosis and randomization, n (%)		
< 6 months	399 (84)	406 (84)
6 months to < 1 year	9 (2)	21 (4)
≥ 1 year	65 (14)	55 (11)
Peritoneal metastases, n (%)		
Yes	101 (21)	96 (20)
No	358 (76)	371 (77)
Not reported	14 (3)	15 (3)

Table 1: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Study Characteristic Category	**Nivolumab + chemotherapy (FOLFOX or XELOX) N[a] = 473**	**Chemotherapy (FOLFOX or XELOX) N[a] = 482**
Liver metastases, n (%)		
Yes	191 (40)	217 (45)
No	268 (57)	250 (52)
Not reported	14 (3)	15 (3)
HER2 status at study entry, n (%)		
Negative	272 (58)	271 (56)
Positive	3 (< 1)	4 (< 1)
Unknown	2 (< 1)	3 (< 1)
Not reported	196 (41)	204 (42)
HER2 status/amplification[b], n (%)		
Negative	353 (75[c])	366 (76[c])
Positive	18 (4[c])	14 (3[c])
Unknown	1 (< 1[c])	0 (0)
Not reported	101 (21[c])	102 (21[c])
Treatment discontinuation (3rd data cut-off), n (%)	ND[d]	ND[d]
Study discontinuation (3rd data cut-off), n (%)	ND[e]	ND[e]

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. According to the company, the HER2 amplification status was subsequently analysed using next generation sequencing. The company considered a number of ≥ 4 copies of the HER2 gene in the analysis to be HER2-amplified.
c. Institute's calculation.
d. The information provided by the company shows that 413 out of 468 (88%) patients with at least 1 dose of the study medication in the intervention arm and 453 out of 465 (97%) patients with at least 1 dose of the study medication in the comparator arm are "no longer on study medication" (minus those who, according to the company, have "completed treatment according to protocol"). These patients have presumably discontinued all drugs of the study medication. The following were common reasons for discontinuation (listed as intervention versus comparator arm): progression of disease (65% versus 70%), toxicity of study medication (9% versus 7%), and AEs unrelated to the medication (7% versus 5%).
e. On the basis of the information provided by the company in its comments regarding the number of patients in survival follow-up, 365 (78%) patients of the intervention arm and 412 (89%) patients of the comparator arm have already left the study (IQWiG calculation; information based on patients with at least 1 dose of the study drug); these numbers include deceased patients, however. No study discontinuation data excluding deceased patients are available.

AE: adverse event; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; f: female; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; HER2: human epidermal growth factor receptor 2; m: male; n: number of patients in the category; N: number of randomized patients; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; XELOX: capecitabine + oxaliplatin

Both study arms were very similar in the demographic and clinical characteristics of the patients of the PD-L1-positive population. The mean patient age was 61 years. In both treatment arms, about 30% were women and 70% men. About 70%; of patients had carcinoma of the stomach, 18% had carcinoma of the gastrooesophageal junction, and 12% had oesophageal carcinoma. Almost all patients (96%) had metastases. The percentage of patients with liver metastases was lower in the intervention arm at 40% than in the comparator arm at 45%. For the majority of the patients in both study arms, the time between first diagnosis and randomization was less than 6 months.

Data on the percentage of patients who discontinued 1 drug component are not available. It was inferred from the available information that about 88% of the patients in the intervention arm and 97% of the patients in the comparator arm had discontinued all treatment components by the 3rd data cut-off.

Information on the course of the study

Table 2 shows the mean/median treatment duration of the PD-L1-positive population and the mean/median follow-up observation period for individual outcomes.

Table 2: Information on the course of the study – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population

Study **Duration of the study phase** **Outcome category**	**Nivolumab + chemotherapy (FOLFOX or XELOX)** **N = 468**	**Chemotherapy (FOLFOX or XELOX)** **N = 465**
CheckMate 649 (3rd data cut-off)		
Treatment duration [months]		
Median [min; max]	7.11 [0.1; 44.3]	4.60 [0.1; 42.9]
Mean (SD)	10.06 (8.57)	6.67 (6.96)
Follow-up duration [months]		
Overall survival[a]		
Median [min; max]	14.18 [0.6; 49.5]	10.78 [0.1; 45.5]
Mean (SD)	17.17 (12.00)	13.35 (10.26)
Morbidity (health status – EQ-5D VAS)	ND	ND
Health-related quality of life (FACT-Ga)	ND	ND
Side effects	ND	ND

a. Information on how the observation period was calculated is not available.

EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACT-Ga: Functional Assessment of Cancer Therapy-Gastric; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; max: maximum; min: minimum; N: number of patients with at least 1 dose of the study medication; ND: no data; PD-L1: Programmed Cell Death Ligand 1; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; XELOX: capecitabine + oxaliplatin

Within the PD-L1-positive population, the median treatment duration was far higher in the intervention arm, at 7.1 months, than in the comparator arm, at 4.6 months. As already noted in dossier assessment A21-146, information on the observation duration is available only for the outcome of overall survival. Information on the observation duration continues to be unavailable for the outcome categories of morbidity, health-related quality of life, and side effects. Whereas the morbidity outcome was to be observed until death, the observation duration for the health-related quality of life outcome was linked to the end of treatment. The analysis of side effects outcomes took into account events occurring until 100 days after treatment end. For these outcomes, conclusions can therefore be drawn only regarding the period until treatment end or until 100 days after treatment end. Based on the information on treatment duration (7.1 versus 4.6 months) plus 100 days, the median observation duration would be 10.4 months in the intervention arm and 7.9 months in the comparator arm for the side effects outcomes. Hence, the observation durations for the health-related quality of life and side effects outcomes are shortened compared to overall survival. Data for the entire observation period are missing for these outcomes.

Information on subsequent therapies

Table 3 shows the subsequent therapies patients of the PD-L1-positive population received after discontinuing the study medication.

Table 3: Information on subsequent therapies – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**	
	Nivolumab + chemotherapy (FOLFOX or XELOX) **N = 473**	**Chemotherapy (FOLFOX or XELOX)** **N = 482**
CheckMate 649 (3rd data cut-off)		
Total	195 (41.2)	206 (42.7)
Radiotherapy	26 (5.5)	28 (5.8)
Surgical intervention	12 (2.5)	7 (1.5)
Systemic therapy	174 (36.8)	197 (40.9)
Immunotherapy	10 (2.1)	45 (9.3)
Anti-PD-1	9 (1.9)	40 (8.3)
Nivolumab	6 (1.3)	17 (3.5)
Pembrolizumab	2 (0.4)	21 (4.4)
Toripalimab	1 (0.2)	2 (0.4)
Anti-PD-L1	0 (0)	4 (0.8)
Atezolizumab	0 (0)	4 (0.8)
Other immunotherapy	1 (0.2)	2 (0.4)
Investigational immunomodulatory drug	1 (0.2)	0 (0)
Investigational immunotherapy	0 (0)	1 (0.2)
Tumour necrosis factor	0 (0)	1 (0.2)
Targeted therapy	69 (14.6)	74 (15.4)
Aflibercept	1 (0.2)	0 (0)
Apatinib	10 (2.1)	17 (3.5)
Bevacizumab	0 (0)	2 (0.4)
Cabozantinib	0 (0)	1 (0.2)
Crenolanib	1 (0.2)	0 (0)
Crizotinib	0 (0)	1 (0.2)
Endostar	0 (0)	1 (0.2)
Erdafitinib	1 (0.2)	0 (0)
Ibrutinib	1 (0.2)	1 (0.2)
Olaparib	1 (0.2)	0
Ramucirumab	53 (11.2)	50 (10.4)
Regorafenib	0 (0)	1 (0.2)
Selumetinib	0 (0)	1 (0.2)
Trastuzumab	5 (1.1)	4 (0.8)
Other systemic cancer therapy – investigational drugs	18 (3.8)	22 (4.6)
Investigational antineoplastic drug	18 (3.8)	22 (4.6)

Table 3: Information on subsequent therapies – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**	
	Nivolumab + chemotherapy (FOLFOX or XELOX) **N = 473**	**Chemotherapy (FOLFOX or XELOX)** **N = 482**
Other systemic cancer therapy – chemotherapy	169 (35.7)	187 (38.8)
Antineoplastic	3 (0.6)	0 (0)
Capecitabine	19 (4.0)	14 (2.9)
Carboplatin	5 (1.1)	4 (0.8)
Cisplatin	10 (2.1)	13 (2.7)
Docetaxel	12 (2.5)	18 (3.7)
Doxorubicin	0 (0)	1 (0.2)
Epirubicin	0 (0)	2 (0.4)
Etoposide	1 (0.2)	1 (0.2)
Floxuridine	0 (0)	1 (0.2)
Fluoropyrimidine	0 (0)	1 (0.2)
Fluorouracil	49 (10.4)	70 (14.5)
S-1	9 (1.9)	15 (3.1)
Herbal anti-cancer agents	0 (0)	1 (0.2)
Irinotecan	58 (12.3)	76 (15.8)
Methotrexate	1 (0.2)	0 (0)
Oxaliplatin	20 (4.2)	31 (6.4)
Paclitaxel	95 (20.1)	109 (22.6)
Raltitrexed	3 (0.6)	6 (1.2)
Tegafur	1 (0.2)	1 (0.2)
Temozolomide	0 (0)	1 (0.2)
Tipiracil/trifluridine	1 (0.2)	2 (0.4)
Tipiracil	0 (0)	1 (0.2)
Not assigned	40 (8.5)	60 (12.4)

FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; n: number of patients with subsequent therapy; N: number of analysed patients; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; XELOX: capecitabine + oxaliplatin

After discontinuation of the study medication, 42% of the patients in both treatment arms received subsequent therapy. In both treatment arms, this was mostly a systemic therapy – the majority of patients received other chemotherapeutic agents.

Limitations regarding subsequent therapies cannot be inferred from the study documents. Switching to the treatment of the other study arm was not planned.

Risk of bias across outcomes (study level)

Table 4 shows the risk of bias across outcomes (risk of bias at study level).

Table 4: Risk of bias across outcomes (study level) – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
CheckMate 649	Yes	Yes	No	No	Yes	Yes	Low

FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; PD-L1: programmed cell death-ligand 1; RCT: randomized controlled trial; XELOX: capecitabine + oxaliplatin

The risk of bias across outcomes is rated as low for the CheckMate 649 study.

Transferability of the study results to the German health care context

In the company's view, the results of the CheckMate 649 study are readily transferable to the German health care context, as the study was conducted, among other places, in Germany and in Western industrialized countries (Europe and North America) on similar population groups, with approximately 69% being of white ancestry.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.3 Results

2.3.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - overall survival
- Morbidity
  - health status, surveyed using the European Quality of Life Questionnaire – 5 Dimensions (EQ-5D) visual analogue scale (VAS)
- Health-related quality of life
  - Functional Assessment of Cancer Therapy-Gastric (FACT-Ga)

- Side effects
  - serious adverse events (SAEs)
  - severe adverse events (AEs), operationalized as Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3
  - discontinuation due to AEs
  - immune-related SAEs
  - immune-related severe AEs
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 Q).

Table 5 shows the outcomes for which data were available in the included study.

Table 5: Matrix of outcomes – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population

Study	Outcomes											
	Overall survival	**Health status (EQ-5D VAS)**	**Health-related quality of life (FACT-Ga)**	**SAEs**	**Severe AEs[a]**	**Discontinuation due to AEs**	**Immune-related SAEs[b]**	**Immune-related severe AEs[a,b]**	**Skin and subcutaneous tissue disorders (SOC, AEs)**	**Immune system disorders (SOC, AEs)**	**Amylase increased (PT, severe AEs[a])**	**Peripheral neuropathy (PT, AEs[a])**
CheckMate 649	Yes	No[c]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of select AEs is used.
c. No usable data available; see section below for the reasoning.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACT-Ga: Functional Assessment of Cancer Therapy-Gastric; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; MedDRA: Medical Dictionary for Regulatory Activities; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; XELOX: capecitabine + oxaliplatin

Notes on outcomes

Health status (EQ-5D VAS)

For the outcome of health status (EQ-5D VAS), analyses are available which are deemed by the company to show permanent deterioration. Health status was to be surveyed until death. However, the information provided on return rates shows that, in both arms, the corresponding percentages were markedly lower after the end of treatment with the study medication. Since return rate data are available only separately for the period on treatment and the period after treatment, it is impossible to determine whether the rating of "permanent deterioration" is adequate. The company still did not provide any information on the actual (e.g. median) follow-up duration. In the present scenario, the result regarding "permanent deterioration" is therefore disregarded.

As a sensitivity analysis, the company additionally submitted an analysis of change as of study start using a mixed model repeated measurement (MMRM). Since this model did not include the surveys conducted after treatment end, this result is disregarded as well.

Health-related quality of life (FACT-Ga)

In the study, health-related quality of life was surveyed with the FACT-Ga. Since the FACT-Ga has been validated for the majority of patients in the PD-L1-positive population, it is suitable for use in the benefit assessment.

In dossier assessment A21-146, it was noted that, in the present situation, the analyses of permanent deterioration submitted by the company are not interpretable without additional information and that analyses on first deterioration or confirmed first deterioration would be necessary (for details, see A21-146 [1]). Together with its written comments [3], the company has subsequently submitted analyses of first deterioration. These are used for the benefit assessment.

2.3.2 Risk of bias

Table 6 describes the risk of bias for the results of the relevant outcomes.

Table 6: Risk of bias at study and outcome levels – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population

Study		Outcomes											
	Study level	Overall survival	Health status (EQ-5D VAS)	Health-related quality of life (FACT-Ga)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-related SAEs[b]	Immune-related severe AEs[a,b]	Skin and subcutaneous tissue disorders (SOC, AEs)	Immune system disorders (SOC, AEs)	Amylase increased (PT, severe AEs[a])	Peripheral neuropathy (PT, AEs)
CheckMate 649	L	L	–[c]	H[d]	H[e]	H[e]	H[f]	H[e]	H[e]	H[e, f]	H[e, f]	H[e]	H[e]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of select AEs is used.
c. No usable data available; see Section 2.3.1 for the reasoning.
d. Large proportion of patients excluded from the analysis (> 10%), decrease in the return of questionnaires over the course of the study, and lack of blinding in subjective recording of outcomes.
e. Incomplete observations for potentially informative reasons.
f. Lack of blinding in subjective decision for discontinuation or subjective outcome recording.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACT-Ga: Functional Assessment of Cancer Therapy-Gastric; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; XELOX: capecitabine + oxaliplatin

The risk of bias for the outcome of overall survival was rated as low.

For the outcome of health-related quality of life, the risk of bias was rated as high. Firstly, a high percentage (FACT-Ga: 18% versus 27%) of patients was excluded from the analysis. Secondly, for those included in the analysis, the questionnaire return rate decreased over time and differed between treatment arms. Lack of blinding with subjective outcome recording is an additional reason for the high risk of bias.

The risk of bias was rated as high for the results of each of the outcomes of the side effects category. All outcomes of the category except discontinuation due to AEs suffer from incomplete observations for potentially informative reasons due to (a) the follow-up observation being linked to treatment duration and (b) a possible association between outcome and reason for treatment discontinuation. In non-serious and non-severe specific AEs, lack of blinding is an additional reason for high risk of bias of results. Even taken alone, lack of blinding

in subjective recording of outcomes already results in high risk of bias for the outcome of discontinuation due to AEs.

For the outcome of health status, risk of bias was not assessed because no evaluable data were available.

Summary assessment of the certainty of conclusions

Irrespective of the aspects described under risk of bias, the certainty of conclusions of study results was reduced due to the uncertainty described in Section 2.2 with regard to the percentage of patients with HER2-negative adenocarcinoma. Overall, at most hints, e.g. of an added benefit, can therefore be derived on the basis of the CheckMate 649 study.

2.3.3 Results

Table 7 summarizes the results on the comparison of nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX) in patients of the PD-L1-positive population. Where necessary, IQWiG calculations are provided in addition to the data.

Tables on common AEs, SAEs, severe AEs, and discontinuations due to AEs are presented in Appendix A. A list of the categories of immune-related AEs, severe immune-related AEs (CTCAE grade ≥ 3) and immune-related SAEs which occurred is presented as supplementary information in Appendix B. The available Kaplan-Meier curves on the presented time-to-event analyses can be found in Appendix C. The company did not submit any Kaplan-Meier curves for the outcomes of health-related quality of life (FACT-Ga), immune-related SAEs, immune-related severe AEs, or other specific AEs.

Table 7: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Study **Outcome category** **Outcome**	**Nivolumab + chemotherapy (FOLFOX or XELOX)**		**Chemotherapy (FOLFOX or XELOX)**		**Nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX)**
	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]**
CheckMate 649 (3rd data cut-off)					
Mortality					
Overall survival	473	14.39 [13.08; 16.23] 363 (76.7)	482	11.10 [10.02; 12.09] 416 (86.3)	0.70 [0.61; 0.81]; < 0.001
Morbidity					
Health status (EQ-5D VAS)	No usable data[b]				
Health-related quality of life					
FACT-Ga[c]	387	NR 56 (14.5)	354	NR [21.03; NC] 69 (19.5)	0.59 [0.41; 0.84]; 0.006
PWB[c]	393	9.79 [7.06; NC] 160 (40.7)	359	7.39 [5.55; 17.77] 144 (40.1)	0.81 [0.64; 1.02]
SWB[c]	393	15.57 [10.91; 38.47] 137 (34.9)	359	11.07 [7.23; 16.66] 116 (32.3)	0.79 [0.61; 1.03]
EWB[c]	389	NR [16.43; NC] 115 (29.6)	358	15.54 [9.72; NC] 100 (27.9)	0.77 [0.58; 1.02]
FWB[c]	389	22.24 [11.56; NC] 134 (34.4)	358	15.54 [10.28; NC] 116 (32.4)	0.89 [0.69; 1.16]
GaCS[c]	No data available[d]				
Side effects					
AEs (supplementary information)[e]	468	0.13 [0.10; 0.20] 466 (99.6)	465	0.16 [0.13; 0.20] 453 (97.4)	–
SAEs[e]	468	8.74 [7.10; 12.29] 255 (54.5)	465	11.04 [9.20; 19.09] 206 (44.3)	1.17 [0.97; 1.41]; 0.107
Severe AEs[e, f]	468	2.79 [2.43; 3.19] 373 (79.7)	465	3.25 [2.76; 3.71] 327 (70.3)	1.10 [0.95; 1.28]; 0.194
Discontinuation due to AEs[e, g]	468	7.75 [6.74; 10.51] 234 (50.0)	465	15.18 [9.49; NC] 157 (33.8)	1.39 [1.13; 1.71]; 0.002

Table 7: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Study **Outcome category** **Outcome**	**Nivolumab + chemotherapy (FOLFOX or XELOX)**		**Chemotherapy (FOLFOX or XELOX)**		**Nivolumab + chemotherapy (FOLFOX or XELOX) vs. chemotherapy (FOLFOX or XELOX)**
	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]**
Immune-related AEs[h] (supplementary information)	*468*	*1.48 [1.38; 1.74]* *376 (80.3)*	*465*	*2.89 [2.10; 4.01]* *285 (61.3)*	–
Immune-related SAEs[h]	468	NR 63 (13.5)	465	NR 24 (5.2)	2.59 [1.60; 4.18]; < 0.001
Immune-related severe AE[f, h]	468	NR [31.15; NC] 114 (24.4)	465	NR 58 (12.5)	1.81 [1.31; 2.51]; < 0.001
Skin and subcutaneous tissue disorders (SOC, AEs)	468	12.58 [9.66; NC] 202 (43.2)	465	NR 119 (25.6)	1.67 [1.33; 2.10]; < 0.001
Immune system disorders (SOC, AEs)	468	NR 53 (11.3)	465	NR 20 (4.3)	2.50 [1.49; 4.18]; < 0.001
Amylase increased (PT, severe AEs[f])	468	NR 14 (3.0)	465	NR 1 (0.2)	13.01 [1.70; 99.64]; 0.001
Peripheral neuropathy (PT, severe AEs[f])	468	NR 28 (6.0)	465	NR 10 (2.2)	2.40 [1.16; 4.94]; 0.015

a. HR and CI: Cox proportional hazards model; p-value: log-rank test; each stratified by PD-L1 expression of tumour cells (≥ 1% vs. < 1% incl. non-quantifiable), region (Asia vs. North America vs. rest of the world), ECOG Performance Status (0 vs. 1), and chemotherapy regimen (XELOX vs. FOLFOX) according to IRT.
b. See Section 2.3.1 for the rationale.
c. Time to first deterioration on treatment. A score decrease by ≥ 15% of the scale range from baseline is deemed a clinically relevant deterioration (scale range FACT-Ga: 0 to 184; PWB: 0 to 28; SWB: 0 to 28; EWB: 0 to 24; FWB: 0 to 28; GaCS: 0 to 76).
d. For this subscale, the company has not submitted any analyses across the period for which the total score was calculated.
e. Without recording of progression of the underlying disease.
f. Operationalized as CTCAE grade ≥ 3.
g. Discontinuation of at least 1 drug.
h. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of select AEs is used.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; EWB: emotional well-being; FACT-Ga: Functional Assessment of Cancer Therapy-Gastric; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; FWB: functional well-being; GaCS: Gastric Cancer Subscale; HR: hazard ratio; IRT: Interactive Response Technology; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; ND: no data; NR: not reached; PD-L1: Programmed Cell Death-Ligand 1; PT: Preferred Term; PWB: physical well-being; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; SWB: social well-being; VAS: visual analogue scale; XELOX: capecitabine + oxaliplatin

Based on the available information, at most hints, e.g. of an added benefit, can be derived for all outcomes (see also Section 2.3.2).

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of nivolumab + chemotherapy (FOLFOX or XELOX) in comparison with chemotherapy (FOLFOX or XELOX). This results in a hint of an added benefit of nivolumab in comparison with the ACT.

Morbidity

Health status recorded with the EQ-5D VAS

No usable data are available for the outcome of health status (EQ-5D VAS) (for reasons, see Section 2.3.1). This results in no hint of an added benefit of nivolumab in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life measured with the FACT-Ga

For the outcome of health-related quality of life (FACT-Ga), a statistically significant difference was found in favour of nivolumab + chemotherapy (FOLFOX or XELOX) in comparison with chemotherapy (FOLFOX or XELOX). This results in a hint of an added benefit of nivolumab in comparison with the ACT.

Side effects

SAEs and severe AEs

No statistically significant difference between treatment arms was found for either of the outcomes of SAEs and severe AEs. This results in no hint of greater or lesser harm from nivolumab in comparison with the ACT for either of them; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, a statistically significant difference was found to the disadvantage of nivolumab + chemotherapy (FOLFOX or XELOX) in comparison with chemotherapy (FOLFOX or XELOX). This results in a hint of greater harm from nivolumab in comparison with the ACT.

Specific AEs

Immune-related SAEs, immune-related severe AEs, skin and subcutaneous tissue disorders (AEs), immune system disorders (AEs), amylase increased (severe AEs), peripheral neuropathy (severe AEs)

For each of the outcomes of immune-related SAEs, immune-related severe AEs, skin and subcutaneous tissue disorders (AEs), immune system disorders (AEs), amylase increased (severe AEs) as well as peripheral neuropathy (severe AEs), there is a statistically significant

difference to the disadvantage of nivolumab + chemotherapy (FOLFOX or XELOX) in comparison with chemotherapy (FOLFOX or XELOX). This results in a hint of greater harm from nivolumab in comparison with the ACT for each of them.

2.3.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- sex (male/female)
- age (< 65 years/≥ 65 years)
- disease status (local recurrence, advanced/metastatic)
- localization of primary tumour at first diagnosis (stomach / gastrooesophageal junction / oesophagus)

Each of the listed subgroup characteristics had been predefined. The company submitted the corresponding subgroup analyses for the PD-L1-positive population at the 3rd data cut-off for all relevant outcomes except those on health-related quality of life, immune-related SAEs, and immune-related severe AEs.

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup. Since no results for interaction testing were reported by the company if at least 10 patients had an event in fewer than 2 subgroups, a calculation was performed by IQWiG in these cases.

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 presented only if there is a statistically significant and relevant effect in at least 1 subgroup.

When applying the methods described above, the available subgroup analyses do not reveal any effect modifications.

2.4 Extent and probability of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [6].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.2 (Table 8).

Determination of the outcome category for outcomes

Discontinuation due to AEs

For the PD-L1-positive population, information is available on the severity degrees of the AEs due to which discontinuation took place (including progression events). This shows that the majority were severe AEs. Therefore, the outcome was assigned to the outcome category of serious/severe side effects.

Table 8: Extent of added benefit at outcome level: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Outcome category **Outcome**	**Nivolumab + FOLFOX or XELOX vs. FOLFOX or XELOX** **Median time to event (months)** **HR [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Total observation period		
Mortality		
Overall survival	14.39 vs. 11.10 months 0.70 [0.61; 0.81]; < 0.001 Probability: hint	Outcome category: mortality $CI_u < 0.85$ Added benefit; extent: major
Shortened observation period		
Morbidity		
Health status (EQ-5D VAS)	No usable data	Lesser/added benefit not proven
Health-related quality of life		
FACT-Ga	NR vs. NR 0.59 [0.41; 0.84]; 0.006 Probability: hint	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit; extent: considerable
Side effects		
SAEs	8.74 vs. 11.04 months 1.17 [0.97; 1.41]; 0.107	Greater/lesser harm not proven
Severe AEs	2.79 vs. 3.25 months 1.10 [0.95; 1.28]; 0.194	Greater/lesser harm not proven
Discontinuation due to AEs	7.75 vs. 15.18 months 1.39 [1.13; 1.71]; 0.002 0.72 [0.59; 0.89][c] Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm; extent: considerable
Immune-related SAEs	NR vs. NR 2.59 [1.60; 4.18]; < 0.001 0.39 [0.24; 0.63][c] Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% Greater harm; extent: major
Immune-related severe AEs	NR vs. NR 1.81 [1.31; 2.51]; < 0.001 0.55 [0.40; 0.76][c] Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm; extent: considerable
Skin and subcutaneous tissue disorders (SOC, AEs)	12.58 months vs. NR 1.67 [1.33; 2.10]; < 0.001 0.60 [0.48; 0.75][c] Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm; extent: considerable

Table 8: Extent of added benefit at outcome level: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Outcome category **Outcome**	**Nivolumab + FOLFOX or XELOX vs. FOLFOX or XELOX** **Median time to event (months)** **HR [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Immune system disorders (SOC, AEs)	NR vs. NR 2.50 [1.49; 4.18]; < 0.001 0.40 [0.24; 0.67][c] Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm; extent: considerable
Amylase increased (PT, severe AEs)	NR vs. NR 13.01 [1.70; 99.64]; 0.001 0.08 [0.01; 0.59][c] Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$; risk < 5% Greater harm; extent: considerable
Peripheral neuropathy (PT, severe AEs)	NR vs. NR 2.40 [1.16; 4.94]; 0.015 0.42 [0.20; 0.86][c] Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm; extent: considerable

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. IQWiG calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACT-Ga: Functional Assessment of Cancer Therapy-Gastric; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; HR: hazard ratio; NR: not reached; SAE: serious adverse event; VAS: visual analogue scale; XELOX: visual analogue scale

2.4.2 Overall conclusion on added benefit

Table 9 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 9: Favourable and unfavourable effects from the assessment of nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population

Favourable effects	Unfavourable effects
Total observation period	
Mortality ▪ Overall survival: hint of added benefit – extent: major	–
Shortened observation period	
Health-related quality of life ▪ FACT-Ga: hint of added benefit – extent: considerable	–
–	Serious/severe side effects ▪ Discontinuation due to AEs, immune-related severe AEs, amylase increased (severe AEs), peripheral neuropathy (severe AEs): each hint of greater harm – extent: considerable ▪ Immune-related SAEs: hint of greater harm – extent major
–	Non-serious/non-severe side effects ▪ Skin and subcutaneous tissue disorders (AEs), immune system disorders (AEs): each hint of greater harm – extent of considerable
AE: adverse event; FACT-Ga: Functional Assessment of Cancer Therapy-Gastric; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; PD-L1: programmed cell death ligand 1; SAE: serious adverse event; XELOX: capecitabine + oxaliplatin	

Overall, both favourable and unfavourable effects of nivolumab were found in comparison with the ACT.

Favourable effects of major and considerable extent, respectively, were found for overall survival and health-related quality of life.

Regarding side effects, only unfavourable effects were found. For serious/severe side effects, there are hints of greater harm of considerable to major extent. For non-serious/non-severe side effects, hints of considerable greater harm were found.

The observed effects for health-related quality of life and side effects are based exclusively on the shortened time period until treatment end (plus 100 days for side effects).

The unfavourable effects did not completely outweigh the advantage in overall survival and health-related quality of life but result in a downgrading of the extent of added benefit.

In summary, for adult patients with HER2-negative advanced or metastatic adenocarcinoma of the stomach, gastrooesophageal junction, or oesophagus whose tumours express PD-L1 (CPS ≥ 5), there is a hint of considerable added benefit of nivolumab in combination with

fluoropyrimidine-based and platinum-based combination chemotherapy as first-line treatment in comparison with the ACT.

2.5 Summary

The data subsequently submitted by the company in the commenting procedure have changed the conclusion on the added benefit of nivolumab in combination with fluoropyrimidine-based and platinum-based combination chemotherapy from dossier assessment A21-146 for both research questions:

Table 10 below shows the result of the benefit assessment of nivolumab in combination with fluoropyrimidine-based and platinum-based combination chemotherapy, taking into account both dossier assessment A21-146 and the present addendum.

Table 10: Nivolumab in combination with fluoropyrimidine-based and platinum-based combination chemotherapy – probability and extent of added benefit (multipage table)

Research question	**Subindication**	**ACT**[a, b]	**Probability and extent of added benefit**
1	Adults with locally advanced or metastatic HER2-negative oesophageal adenocarcinoma that cannot be treated curatively and whose tumours express PD-L1 (CPS ≥ 5); first-line treatment	Treatment of physician's choice[c]	Hint of considerable added benefit[d,e,f]
2	Adults with locally advanced or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma that cannot be treated curatively and whose tumours express PD-L1 (CPS ≥ 5); first-line treatment	▪ Cisplatin in combination with 5-fluorouracil ± folinic acid or ▪ cisplatin in combination with capecitabine or ▪ oxaliplatin in combination with 5-fluorouracil ± folinic acid[g] or ▪ oxaliplatin in combination with capecitabine or ▪ 5-fluorouracil ± folinic acid + oxaliplatin + docetaxel[h] (only for patients in good general condition and without relevant comorbidities)	

Table 10: Nivolumab in combination with fluoropyrimidine-based and platinum-based combination chemotherapy – probability and extent of added benefit (multipage table)

Research question	Subindication	ACT[a, b]	Probability and extent of added benefit
a. Presented is the respective ACT specified by the G-BA. b. It is assumed for the present therapeutic indication that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer. c. Guidelines mention several platinum- and fluoropyrimidine-based combination chemotherapies: S-1 (tegafur/gimeracil/oteracil) + cisplatin or capecitabine + cisplatin [XP], 5-fluorouracil+ cisplatin, 5-fluorouracil + oxaliplatin + folinic acid [FLO and FOLFOX], capecitabine + oxaliplatin, infusional 5-fluorouracil + folinic acid + cisplatin [PLF], epirubicin + cisplatin + capecitabine [ECX], epirubicin + oxaliplatin + capecitabine [EOX], epirubicin + cisplatin + infusional 5-fluorouracil [ECF], docetaxel + cisplatin + infusional 5-fluorouracil [DCF], 5-fluorouracil + oxaliplatin + epirubicin, infusional 5-fluorouracil + folinic acid + oxaliplatin + docetaxel [FLOT regimen]. However, only the drugs 5-fluorouracil and cisplatin are approved in the present therapeutic indication. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended in guidelines. In the context of treatment of physician's choice, the G-BA considered the treatment options cited above to be suitable comparators. d. For the present addendum, the entire CheckMate 649 study population with PD-L1-expressing tumours with CPS ≥ 5 was taken into account. This population comprises all patients included in research question 1 and research question 2 of the dossier assessment (see Section 2.1 for the discussion). e. For patients included in research question 1 for whom FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) or XELOX (capecitabine + oxaliplatin) is the suitable treatment of physician's choice. f. The CheckMate 649 study included only patients with an ECOG-PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2. g. According to the G-BA, the ACT includes the combination of infusional 5-fluorouracil + folinic acid + oxaliplatin (FLO and FOLFOX). h. According to the G-BA, the ACT includes the combination of infusional 5-fluorouracil + folinic acid + oxaliplatin + docetaxel (FLOT). ACT: appropriate comparator therapy; CPS: combined positive score; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor -2; PD-L1: programmed cell death ligand 1			

The G-BA decides on the added benefit.

3 References

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Appendix A Results on side effects

For the overall rates of AEs, SAEs, and severe AEs (CTCAE grade ≥ 3), the following tables present events for SOCs and PTs according to the Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- overall rate of AEs (irrespective of severity grade): events which occurred in at least 10% of patients of 1 study arm
- overall rates of severe AEs (e.g. CTCAE grade ≥ 3) and SAEs: events which occurred in at least 5% of patients in 1 study arm
- in addition, for all events irrespective of severity grade: 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 which occurred in at least 0.4% of patients in 1 study arm are presented.

Table 11: Common AEs[a] – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Nivolumab + chemotherapy (FOLFOX or XELOX)** **N = 468**	**Chemotherapy (FOLFOX or XELOX)** **N = 465**
CheckMate 649 (3rd data cut-off)		
Total rate of AEs[c]	466 (99.6)	456 (98.1)
GASTROINTESTINAL DISORDERS	385 (82.3)	352 (75.7)
NAUSEA	227 (48.5)	209 (44.9)
DIARRHOEA	185 (39.5)	169 (36.3)
VOMITING	152 (32.5)	139 (29.9)
CONSTIPATION	114 (24.4)	97 (20.9)
ABDOMINAL PAIN	99 (21.2)	81 (17.4)
DYSPHAGIA	41 (8.8)	36 (7.7)
STOMATITIS	39 (8.3)	35 (7.5)
ABDOMINAL PAIN UPPER	36 (7.7)	44 (9.5)
ABDOMINAL DISTENSION	26 (5.6)	24 (5.2)
DYSPEPSIA	21 (4.5)	17 (3.7)
ASCITES	20 (4.3)	22 (4.7)
GASTROOESOPHAGEAL REFLUX DISEASE	18 (3.8)	14 (3.0)
DRY MOUTH	17 (3.6)	6 (1.3)
FLATULENCE	13 (2.8)	10 (2.2)
UPPER GASTROINTESTINAL HAEMORRHAGE	13 (2.8)	11 (2.4)
COLITIS	10 (2.1)	0 (0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	319 (68.2)	283 (60.9)
FATIGUE	167 (35.7)	136 (29.2)
PYREXIA	104 (22.2)	63 (13.5)
ASTHENIA	75 (16.0)	72 (15.5)
OEDEMA PERIPHERAL	50 (10.7)	34 (7.3)
MUCOSAL INFLAMMATION	46 (9.8)	33 (7.1)
MALAISE	22 (4.7)	23 (4.9)
NON-CARDIAC CHEST PAIN	17 (3.6)	9 (1.9)
PAIN	14 (3.0)	15 (3.2)
CHILLS	10 (2.1)	6 (1.3)
INFLUENZA LIKE ILLNESS	6 (1.3)	10 (2.2)

Table 11: Common AEs[a] – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Nivolumab + chemotherapy (FOLFOX or XELOX)** **N = 468**	**Chemotherapy (FOLFOX or XELOX)** **N = 465**
NERVOUS SYSTEM DISORDERS	314 (67.1)	276 (59.4)
NEUROPATHY PERIPHERAL	149 (31.8)	125 (26.9)
PERIPHERAL SENSORY NEUROPATHY	83 (17.7)	58 (12.5)
HEADACHE	51 (10.9)	27 (5.8)
PARAESTHESIA	42 (9.0)	39 (8.4)
DIZZINESS	30 (6.4)	29 (6.2)
DYSGEUSIA	29 (6.2)	22 (4.7)
HYPOAESTHESIA	27 (5.8)	22 (4.7)
NEUROTOXICITY	14 (3.0)	20 (4.3)
SYNCOPE	10 (2.1)	7 (1.5)
DYSAESTHESIA	5 (1.1)	15 (3.2)
INVESTIGATIONS	312 (66.7)	246 (52.9)
PLATELET COUNT DECREASED	108 (23.1)	72 (15.5)
NEUTROPHIL COUNT DECREASED	107 (22.9)	84 (18.1)
ASPARTATE AMINOTRANSFERASE INCREASED	104 (22.2)	63 (13.5)
WEIGHT DECREASED	89 (19.0)	79 (17.0)
WHITE BLOOD CELL COUNT DECREASED	76 (16.2)	51 (11.0)
ALANINE AMINOTRANSFERASE INCREASED	73 (15.6)	43 (9.2)
BLOOD ALKALINE PHOSPHATASE INCREASED	61 (13.0)	37 (8.0)
LIPASE INCREASED	57 (12.2)	40 (8.6)
BLOOD BILIRUBIN INCREASED	55 (11.8)	40 (8.6)
AMYLASE INCREASED	53 (11.3)	24 (5.2)
BLOOD CREATININE INCREASED	29 (6.2)	12 (2.6)
GAMMA- GLUTAMYLTRANSFERASE INCREASED	18 (3.8)	21 (4.5)
HAEMOGLOBIN DECREASED	17 (3.6)	22 (4.7)
WEIGHT INCREASED	17 (3.6)	16 (3.4)
BLOOD LACTATE DEHYDROGENASE INCREASED	16 (3.4)	13 (2.8)
BLOOD THYROID STIMULATING HORMONE INCREASED	15 (3.2)	1 (0.2)
LYMPHOCYTE COUNT DECREASED	14 (3.0)	3 (0.6)
TRANSAMINASES INCREASED	9 (1.9)	12 (2.6)

Table 11: Common AEs[a] – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Nivolumab + chemotherapy (FOLFOX or XELOX)** **N = 468**	**Chemotherapy (FOLFOX or XELOX)** **N = 465**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	305 (65.2)	261 (56.1)
ANAEMIA	188 (40.2)	170 (36.6)
NEUTROPENIA	140 (29.9)	121 (26.0)
THROMBOCYTOPENIA	111 (23.7)	101 (21.7)
LEUKOPENIA	47 (10.0)	48 (10.3)
FEBRILE NEUTROPENIA	13 (2.8)	7 (1.5)
METABOLISM AND NUTRITION DISORDERS	262 (56.0)	222 (47.7)
DECREASED APPETITE	144 (30.8)	118 (25.4)
HYPOALBUMINAEMIA	63 (13.5)	44 (9.5)
HYPOKALAEMIA	59 (12.6)	42 (9.0)
HYPERGLYCAEMIA	51 (10.9)	34 (7.3)
HYPONATRAEMIA	49 (10.5)	36 (7.7)
HYPOCALCAEMIA	31 (6.6)	26 (5.6)
HYPOGLYCAEMIA	15 (3.2)	3 (0.6)
HYPOPROTEINAEMIA	14 (3.0)	6 (1.3)
DEHYDRATION	13 (2.8)	20 (4.3)
HYPOMAGNESAEMIA	13 (2.8)	9 (1.9)
HYPERKALAEMIA	12 (2.6)	6 (1.3)
HYPOCHLORAEMIA	10 (2.1)	5 (1.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	202 (43.2)	119 (25.6)
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	78 (16.7)	53 (11.4)
RASH	52 (11.1)	14 (3.0)
PRURITUS	49 (10.5)	6 (1.3)
DRY SKIN	22 (4.7)	15 (3.2)
ALOPECIA	18 (3.8)	21 (4.5)
RASH MACULO-PAPULAR	18 (3.8)	3 (0.6)
SKIN HYPERPIGMENTATION	13 (2.8)	6 (1.3)
ERYTHEMA	12 (2.6)	5 (1.1)

Table 11: Common AEs[a] – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Nivolumab + chemotherapy (FOLFOX or XELOX)** **N = 468**	**Chemotherapy (FOLFOX or XELOX)** **N = 465**
INFECTIONS AND INFESTATIONS	189 (40.4)	135 (29.0)
PNEUMONIA	35 (7.5)	28 (6.0)
UPPER RESPIRATORY TRACT INFECTION	26 (5.6)	15 (3.2)
NASOPHARYNGITIS	23 (4.9)	15 (3.2)
URINARY TRACT INFECTION	22 (4.7)	8 (1.7)
BRONCHITIS	13 (2.8)	6 (1.3)
RHINITIS	10 (2.1)	3 (0.6)
SEPSIS	10 (2.1)	6 (1.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	156 (33.3)	130 (28.0)
COUGH	56 (12.0)	38 (8.2)
DYSPNOEA	38 (8.1)	31 (6.7)
EPISTAXIS	24 (5.1)	30 (6.5)
PNEUMONITIS	22 (4.7)	2 (0.4)
HICCUPS	17 (3.6)	14 (3.0)
PULMONARY EMBOLISM	14 (3.0)	15 (3.2)
OROPHARYNGEAL PAIN	13 (2.8)	7 (1.5)
RHINORRHOEA	11 (2.4)	4 (0.9)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	153 (32.7)	158 (34.0)
MALIGNANT NEOPLASM PROGRESSION	137 (29.3)	150 (32.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	139 (29.7)	99 (21.3)
BACK PAIN	50 (10.7)	37 (8.0)
ARTHRALGIA	41 (8.8)	27 (5.8)
PAIN IN EXTREMITY	20 (4.3)	12 (2.6)
MYALGIA	13 (2.8)	8 (1.7)
MUSCULAR WEAKNESS	12 (2.6)	10 (2.2)
BONE PAIN	10 (2.1)	3 (0.6)
VASCULAR DISORDERS	95 (20.3)	53 (11.4)
HYPERTENSION	30 (6.4)	20 (4.3)
DEEP VEIN THROMBOSIS	17 (3.6)	8 (1.7)
HYPOTENSION	15 (3.2)	9 (1.9)
EMBOLISM	10 (2.1)	2 (0.4)

Table 11: Common AEs[a] – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Nivolumab + chemotherapy (FOLFOX or XELOX)** **N = 468**	**Chemotherapy (FOLFOX or XELOX)** **N = 465**
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	84 (17.9)	57 (12.3)
INFUSION RELATED REACTION	41 (8.8)	16 (3.4)
FALL	11 (2.4)	15 (3.2)
ENDOCRINE DISORDERS	77 (16.5)	10 (2.2)
HYPOTHYROIDISM	53 (11.3)	8 (1.7)
HYPERTHYROIDISM	22 (4.7)	2 (0.4)
PSYCHIATRIC DISORDERS	66 (14.1)	59 (12.7)
INSOMNIA	32 (6.8)	41 (8.8)
ANXIETY	18 (3.8)	9 (1.9)
RENAL AND URINARY DISORDERS	58 (12.4)	32 (6.9)
ACUTE KIDNEY INJURY	11 (2.4)	4 (0.9)
IMMUNE SYSTEM DISORDERS	53 (11.3)	20 (4.3)
HYPERSENSITIVITY	29 (6.2)	7 (1.5)
DRUG HYPERSENSITIVITY	15 (3.2)	5 (1.1)
HEPATOBILIARY DISORDERS	51 (10.9)	43 (9.2)
HYPERBILIRUBINAEMIA	10 (2.1)	10 (2.2)
HEPATIC FUNCTION ABNORMAL	5 (1.1)	13 (2.8)
CARDIAC DISORDERS	37 (7.9)	31 (6.7)
EYE DISORDERS	34 (7.3)	28 (6.0)
EAR AND LABYRINTH DISORDERS	26 (5.6)	14 (3.0)
VERTIGO	11 (2.4)	2 (0.4)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	18 (3.8)	9 (1.9)
PRODUCT ISSUES	14 (3.0)	7 (1.5)

a. Events which occurred in ≥ 10 patients in at least 1 study arm.
b. MedDRA version 23.0; SOC and PT notation taken from the documents pertaining to the comments.
c. AEs including events caused by progression of the underlying disease.

AE: adverse event; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; XELOX: capecitabine + oxaliplatin

Table 12: Common SAEs[a] – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population

Study	Patients with event n (%)	
SOC[b] PT[b]	Nivolumab + chemotherapy (FOLFOX or XELOX) N = 468	Chemotherapy (FOLFOX or XELOX) N = 465
CheckMate 649 (3rd data cut-off)		
Total rate of SAEs[c]	313 (66.9)	281 (60.4)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	146 (31.2)	156 (33.5)
MALIGNANT NEOPLASM PROGRESSION	137 (29.3)	150 (32.3)
GASTROINTESTINAL DISORDERS	91 (19.4)	88 (18.9)
VOMITING	19 (4.1)	13 (2.8)
DIARRHOEA	12 (2.6)	8 (1.7)
DYSPHAGIA	5 (1.1)	14 (3.0)
INFECTIONS AND INFESTATIONS	60 (12.8)	36 (7.7)
PNEUMONIA	20 (4.3)	12 (2.6)
SEPSIS	10 (2.1)	6 (1.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	34 (7.3)	24 (5.2)
ANAEMIA	17 (3.6)	13 (2.8)
FEBRILE NEUTROPENIA	11 (2.4)	6 (1.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	32 (6.8)	32 (6.9)
PYREXIA	12 (2.6)	7 (1.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	29 (6.2)	25 (5.4)
PNEUMONITIS	12 (2.6)	1 (0.2)
PULMONARY EMBOLISM	7 (1.5)	12 (2.6)
METABOLISM AND NUTRITION DISORDERS	23 (4.9)	19 (4.1)
HEPATOBILIARY DISORDERS	22 (4.7)	9 (1.9)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	18 (3.8)	14 (3.0)
NERVOUS SYSTEM DISORDERS	16 (3.4)	12 (2.6)
CARDIAC DISORDERS	15 (3.2)	11 (2.4)
VASCULAR DISORDERS	14 (3.0)	8 (1.7)
INVESTIGATIONS	10 (2.1)	8 (1.7)

a. Events which occurred in ≥ 10 patients in at least 1 study arm.
b. MedDRA version 23.0; SOC and PT notation taken from the documents pertaining to the comments.
c. AEs including events caused by progression of the underlying disease.

FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; XELOX: capecitabine + oxaliplatin

Table 13: Common severe AEs (CTCAE grade ≥ 3)[a] – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Nivolumab + chemotherapy (FOLFOX or XELOX)** **N = 468**	**Chemotherapy (FOLFOX or XELOX)** **N = 465**
CheckMate 649 (3rd data cut-off)		
Total rate of severe AEs[c] (CTCAE grade ≥ 3)	398 (85.0)	367 (78.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	149 (31.8)	117 (25.2)
NEUTROPENIA	81 (17.3)	63 (13.5)
ANAEMIA	57 (12.2)	50 (10.8)
THROMBOCYTOPENIA	14 (3.0)	10 (2.2)
FEBRILE NEUTROPENIA	12 (2.6)	6 (1.3)
LEUKOPENIA	5 (1.1)	11 (2.4)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	144 (30.8)	153 (32.9)
MALIGNANT NEOPLASM PROGRESSION	136 (29.1)	147 (31.6)
INVESTIGATIONS	134 (28.6)	109 (23.4)
NEUTROPHIL COUNT DECREASED	59 (12.6)	49 (10.5)
LIPASE INCREASED	25 (5.3)	17 (3.7)
WHITE BLOOD CELL COUNT DECREASED	19 (4.1)	11 (2.4)
PLATELET COUNT DECREASED	17 (3.6)	17 (3.7)
ASPARTATE AMINOTRANSFERASE INCREASED	16 (3.4)	6 (1.3)
AMYLASE INCREASED	14 (3.0)	1 (0.2)
BLOOD BILIRUBIN INCREASED	11 (2.4)	10 (2.2)
GASTROINTESTINAL DISORDERS	102 (21.8)	114 (24.5)
DIARRHOEA	20 (4.3)	15 (3.2)
VOMITING	19 (4.1)	17 (3.7)
ASCITES	10 (2.1)	9 (1.9)
ABDOMINAL PAIN	9 (1.9)	12 (2.6)
NAUSEA	9 (1.9)	13 (2.8)
DYSPHAGIA	8 (1.7)	17 (3.7)
METABOLISM AND NUTRITION DISORDERS	72 (15.4)	54 (11.6)
DECREASED APPETITE	21 (4.5)	16 (3.4)
HYPONATRAEMIA	15 (3.2)	12 (2.6)
HYPOKALAEMIA	13 (2.8)	13 (2.8)
HYPERGLYCAEMIA	11 (2.4)	7 (1.5)

Table 13: Common severe AEs (CTCAE grade ≥ 3)[a] – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Nivolumab + chemotherapy (FOLFOX or XELOX)** **N = 468**	**Chemotherapy (FOLFOX or XELOX)** **N = 465**
NERVOUS SYSTEM DISORDERS	58 (12.4)	39 (8.4)
NEUROPATHY PERIPHERAL	28 (6.0)	10 (2.2)
PERIPHERAL SENSORY NEUROPATHY	10 (2.1)	10 (2.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	57 (12.2)	54 (11.6)
FATIGUE	27 (5.8)	16 (3.4)
ASTHENIA	11 (2.4)	11 (2.4)
INFECTIONS AND INFESTATIONS	55 (11.8)	37 (8.0)
PNEUMONIA	16 (3.4)	10 (2.2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	32 (6.8)	25 (5.4)
PULMONARY EMBOLISM	7 (1.5)	13 (2.8)
VASCULAR DISORDERS	27 (5.8)	16 (3.4)
HYPERTENSION	10 (2.1)	6 (1.3)
HEPATOBILIARY DISORDERS	25 (5.3)	11 (2.4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	24 (5.1)	7 (1.5)
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	10 (2.1)	5 (1.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	15 (3.2)	13 (2.8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	14 (3.0)	11 (2.4)
CARDIAC DISORDERS	13 (2.8)	11 (2.4)

a. Events which occurred in ≥ 10 patients in at least 1 study arm.
b. MedDRA version 23.0; SOC and PT notation taken from the documents pertaining to the comments.
c. AEs including events caused by progression of the underlying disease.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; XELOX: capecitabine + oxaliplatin

Table 14: Common discontinuation due to AEs[a] – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Nivolumab + chemotherapy (FOLFOX or XELOX)** **N = 468**	**Chemotherapy (FOLFOX or XELOX)** **N = 465**
CheckMate 649 (3rd data cut-off)		
Total rate of discontinuations due to AEs[c]	252 (53.8)	170 (36.6)
Nervous system disorders	87 (18.6)	67 (14.4)
Neuropathy peripheral	43 (9.2)	25 (5.4)
Peripheral sensory neuropathy	20 (4.3)	21 (4.5)
Paraesthesia	6 (1.3)	4 (0.9)
Hypoaesthesia	5 (1.1)	5 (1.1)
Neurotoxicity	3 (0.6)	2 (0.4)
Cerebrovascular accident	2 (0.4)	1 (0.2)
Headache	2 (0.4)	1 (0.2)
Polyneuropathy	1 (0.2)	2 (0.4)
Dysaesthesia	0 (0)	3 (0.6)
Investigations	37 (7.9)	25 (5.4)
Platelet count decreased	10 (2.1)	5 (1.1)
Neutrophil count decreased	9 (1.9)	10 (2.2)
Blood creatinine increased	5 (1.1)	1 (0.2)
Aspartate aminotransferase increased	4 (0.9)	2 (0.4)
Weight decreased	4 (0.9)	0 (0)
White blood cell count decreased	3 (0.6)	3 (0.6)
Alanine aminotransferase increased	2 (0.4)	3 (0.6)
Blood alkaline phosphatase increased	2 (0.4)	0 (0)
Blood bilirubin increased	2 (0.4)	5 (1.1)
Gastrointestinal disorders	36 (7.7)	18 (3.9)
Diarrhoea	12 (2.6)	4 (0.9)
Abdominal pain	3 (0.6)	1 (0.2)
Ascites	3 (0.6)	0 (0)
Colitis	3 (0.6)	0 (0)
Vomiting	3 (0.6)	3 (0.6)
Autoimmune colitis	2 (0.4)	0 (0)
Nausea	2 (0.4)	4 (0.9)
Dysphagia	1 (0.2)	4 (0.9)

Table 14: Common discontinuation due to AEs[a] – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Nivolumab + chemotherapy (FOLFOX or XELOX)** **N = 468**	**Chemotherapy (FOLFOX or XELOX)** **N = 465**
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	27 (5.8)	19 (4.1)
Malignant neoplasm progression	22 (4.7)	19 (4.1)
Metastases to central nervous system	3 (0.6)	0 (0)
General disorders and administration site conditions	19 (4.1)	12 (2.6)
Fatigue	5 (1.1)	2 (0.4)
Asthenia	2 (0.4)	2 (0.4)
Oedema peripheral	2 (0.4)	0 (0)
Pyrexia	2 (0.4)	2 (0.4)
Sudden death	2 (0.4)	0 (0)
Mucosal inflammation	0 (0)	2 (0.4)
Blood and lymphatic system disorders	18 (3.8)	16 (3.4)
Thrombocytopenia	9 (1.9)	9 (1.9)
Neutropenia	6 (1.3)	4 (0.9)
Anaemia	4 (0.9)	4 (0.9)
Leukopenia	0 (0)	3 (0.6)
Respiratory, thoracic and mediastinal disorders	18 (3.8)	5 (1.1)
Pneumonitis	13 (2.8)	0 (0)
Interstitial lung disease	2 (0.4)	1 (0.2)
Chronic obstructive pulmonary disease	0 (0)	2 (0.4)
Immune system disorders	15 (3.2)	10 (2.2)
Drug hypersensitivity	6 (1.3)	4 (0.9)
Hypersensitivity	5 (1.1)	2 (0.4)
Anaphylactic reaction	4 (0.9)	3 (0.6)
Infections and infestations	11 (2.4)	7 (1.5)
Pneumonia	4 (0.9)	1 (0.2)
Injury, poisoning and procedural complications	11 (2.4)	4 (0.9)
Infusion related reaction	10 (2.1)	3 (0.6)
Hepatobiliary disorders	9 (1.9)	3 (0.6)
Immune-mediated hepatitis	2 (0.4)	0 (0)
Skin and subcutaneous tissue disorders	8 (1.7)	2 (0.4)
Palmar-plantar erythrodysaesthesia syndrome	6 (1.3)	1 (0.2)

Table 14: Common discontinuation due to AEs[a] – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Nivolumab + chemotherapy (FOLFOX or XELOX)** **N = 468**	**Chemotherapy (FOLFOX or XELOX)** **N = 465**
Cardiac disorders	7 (1.5)	4 (0.9)
Cardiac arrest	2 (0.4)	1 (0.2)
Metabolism and nutrition disorders	7 (1.5)	7 (1.5)
Decreased appetite	3 (0.6)	2 (0.4)
Renal and urinary disorders	5 (1.1)	3 (0.6)
Endocrine disorders	3 (0.6)	0 (0)
Hypothyroidism	2 (0.4)	0 (0)
Musculoskeletal and connective tissue disorders	3 (0.6)	1 (0.2)
Vascular disorders	2 (0.4)	2 (0.4)

a. Events which occurred in ≥ 0.4% of the patients in at least 1 study arm.
b. MedDRA version 23.0; SOC and PT notation taken from the documents pertaining to the comments.
c. AEs including events caused by progression of the underlying disease.

AE: adverse event; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; XELOX: capecitabine + oxaliplatin

Appendix B Supplementary presentation of results, on categories of immune-related AEs, severe immune-related AEs (CTCAE grade ≥ 3), and immune-related SAEs

Table 15: Categories of immune-related AEs[a] – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population

Study	Patients with event n (%)	
Category[b]	Nivolumab + chemotherapy (FOLFOX or XELOX) N = 468	Chemotherapy (FOLFOX or XELOX) N = 465
CheckMate 649 (3rd data cut-off)		
Overall rate of immune-related AEs	376 (80.3)	285 (61.3)
PATIENTS WITH ENDOCRINE AES	85 (18.2)	15 (3.2)
PATIENTS WITH GASTROINTESTINAL AES	187 (40.0)	170 (36.6)
PATIENTS WITH HEPATIC AES	172 (36.8)	119 (25.6)
PATIENTS WITH PULMONARY AES	25 (5.3)	4 (0.9)
PATIENTS WITH RENAL AES	49 (10.5)	19 (4.1)
PATIENTS WITH SKIN AES	172 (36.8)	82 (17.6)
PATIENTS WITH HYPERSENSITIVITY/ INFUSION REACTIONS AES	70 (15.0)	26 (5.6)

a. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of select AEs is used.
b. Category notation taken from the documents pertaining to the comments.

AE: adverse event; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; XELOX: capecitabine + oxaliplatin

Table 16: Categories of immune-related severe AEs[a] (CTCAE grade ≥ 3) – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population

Study	**Patients with event n (%)**	
Category[b]	**Nivolumab + chemotherapy (FOLFOX or XELOX)**	**Chemotherapy (FOLFOX or XELOX)**
	N = 468	**N = 465**
CheckMate 649 (3rd data cut-off)		
Overall rate of immune-related severe AEs (CTCAE grade ≥ 3)	114 (24.4)	58 (12.5)
PATIENTS WITH ENDOCRINE AES	7 (1.5)	2 (0.4)
PATIENTS WITH GASTROINTESTINAL AES	25 (5.3)	16 (3.4)
PATIENTS WITH HEPATIC AES	38 (8.1)	23 (4.9)
PATIENTS WITH PULMONARY AES	11 (2.4)	1 (0.2)
PATIENTS WITH RENAL AES	9 (1.9)	5 (1.1)
PATIENTS WITH SKIN AES	20 (4.3)	6 (1.3)
PATIENTS WITH HYPERSENSITIVITY/ INFUSION REACTIONS AES	13 (2.8)	9 (1.9)

a. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of select AEs is used.
b. Category notation taken from the documents pertaining to the comments.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; XELOX: capecitabine + oxaliplatin

Table 17: Categories of immune-related SAEs[a] – RCT, direct comparison: nivolumab + chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX), PD-L1-positive population

Study / **Category**[b]	**Patients with event n (%)**	
	Nivolumab + chemotherapy (FOLFOX or XELOX) **N = 468**	**Chemotherapy (FOLFOX or XELOX)** **N = 465**
CheckMate 649 (3rd data cut-off)		
Total rate of immune-mediated SAEs	63 (13.5)	24 (5.2)
PATIENTS WITH ENDOCRINE AES	8 (1.7)	2 (0.4)
PATIENTS WITH GASTROINTESTINAL AES	21 (4.5)	9 (1.9)
PATIENTS WITH HEPATIC AES	11 (2.4)	2 (0.4)
PATIENTS WITH PULMONARY AES	14 (3.0)	3 (0.6)
PATIENTS WITH RENAL AES	6 (1.3)	5 (1.1)
PATIENTS WITH SKIN AES	4 (0.9)	1 (0.2)
PATIENTS WITH HYPERSENSITIVITY/ INFUSION REACTIONS AES	6 (1.3)	2 (0.4)

a. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of select AEs is used.
b. Category notation taken from the documents pertaining to the comments.

AE: adverse event; FOLFOX: 5-fluorouracil + folinic acid + oxaliplatin; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; XELOX: capecitabine + oxaliplatin

Appendix C Kaplan-Meier curves on results of the PD-L1-positive population of the CheckMate 649 study

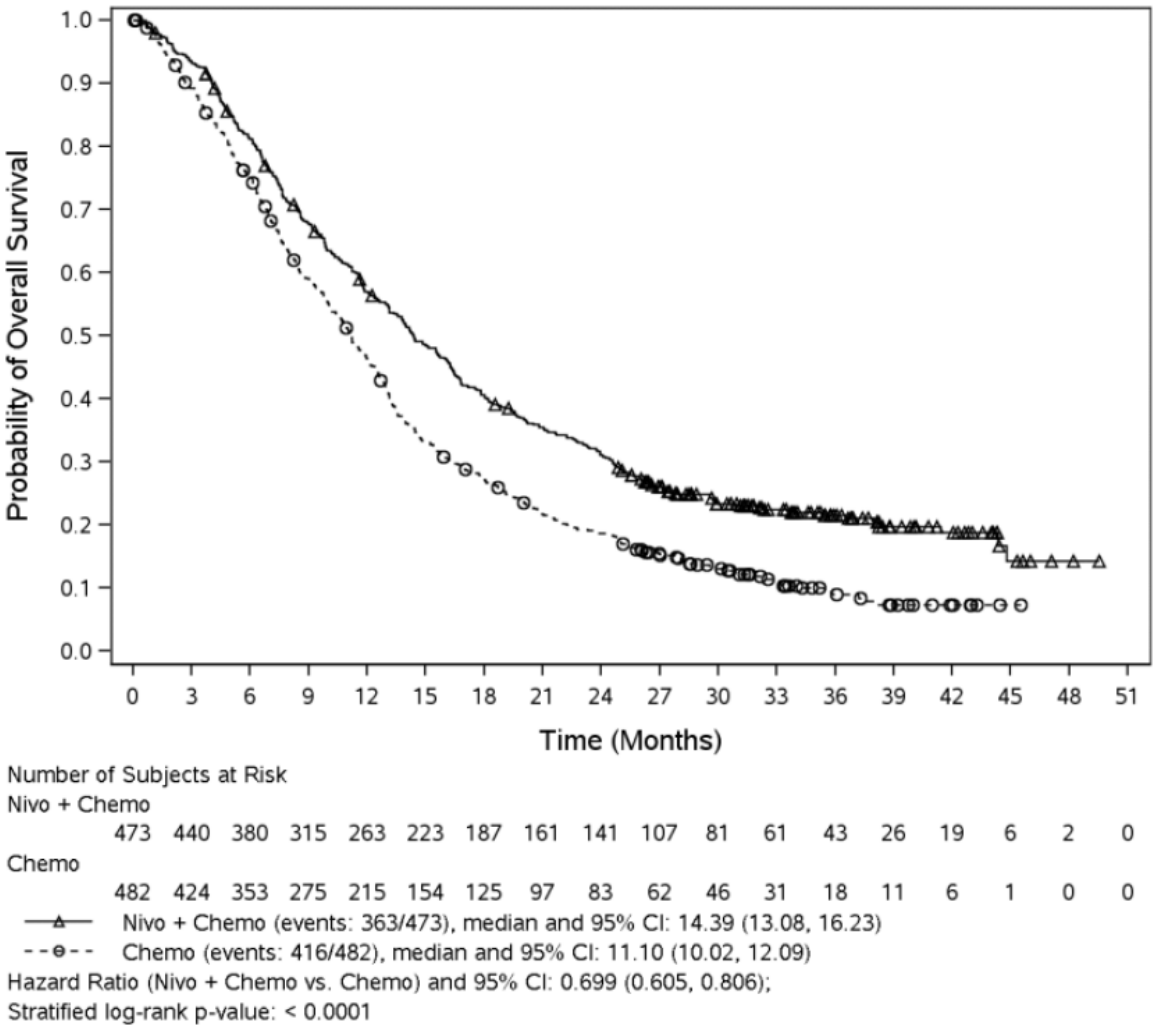

Figure 1: Kaplan-Meier curves for the outcome of overall survival; 3rd data cut-off (CheckMate 649 study, PD-L1-positive population)

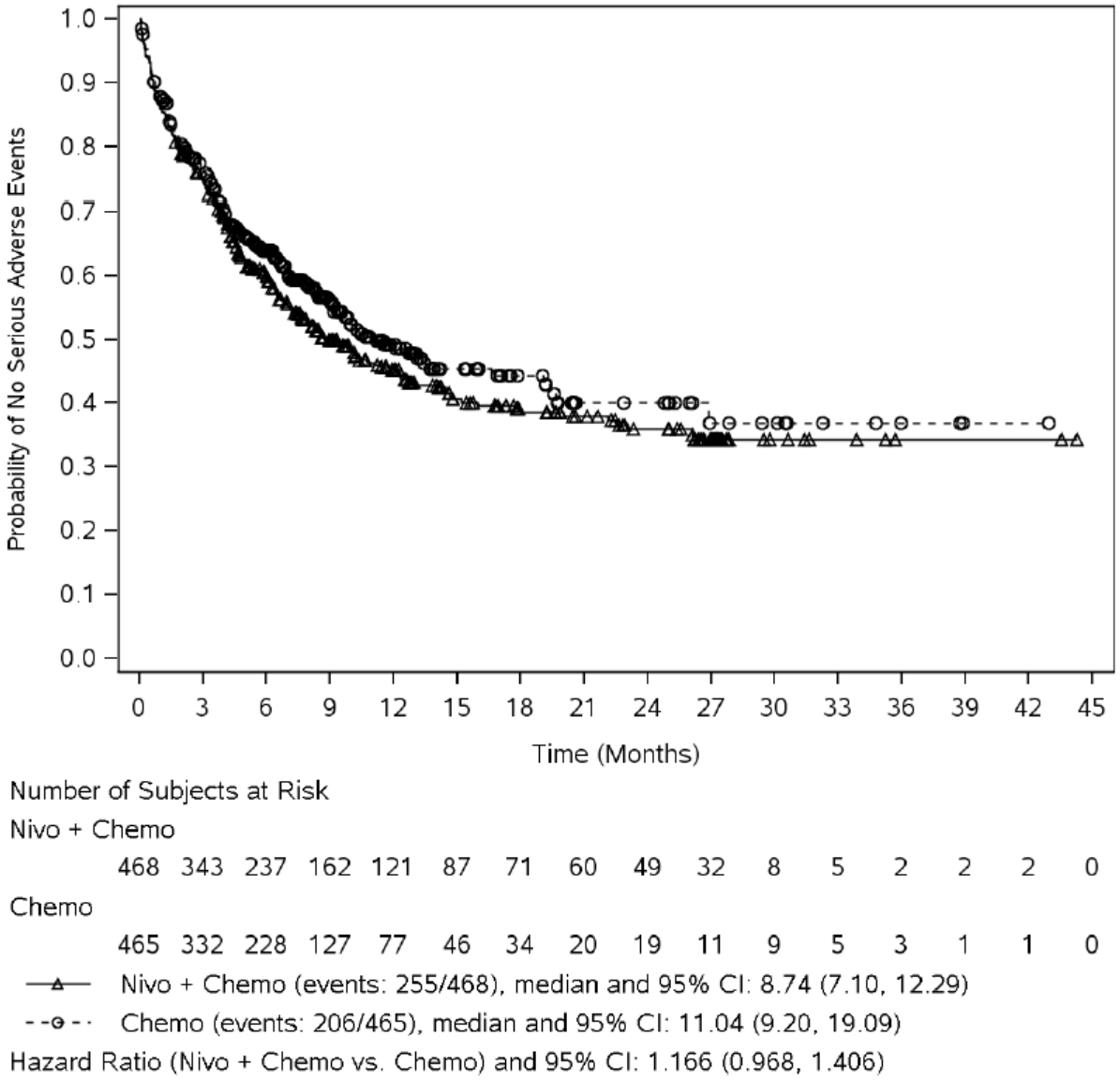

Figure 2: Kaplan-Meier curves for the outcome of SAEs; 3rd data cut-off (CheckMate 649 study, PD-L1-positive population)

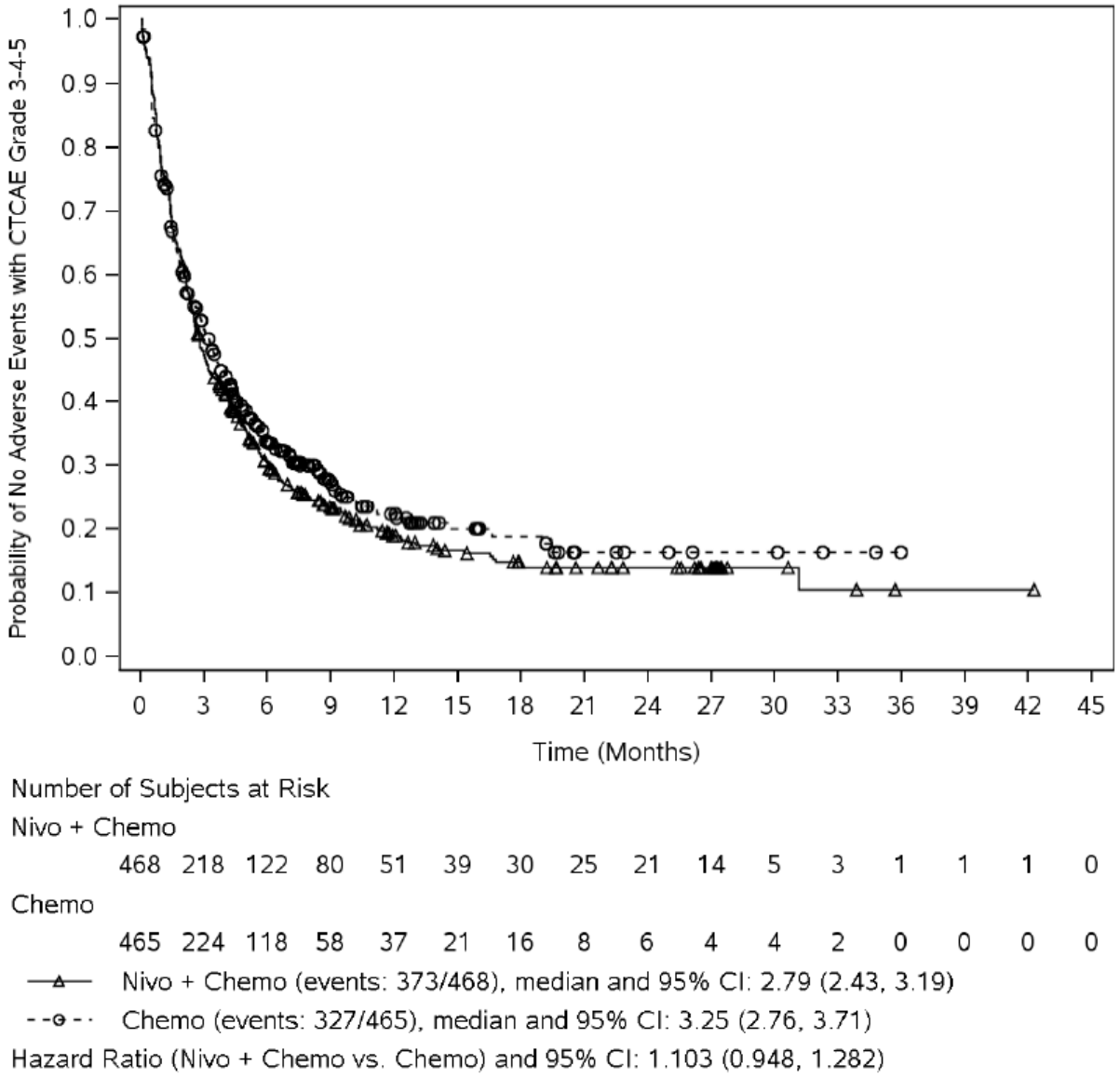

Figure 3: Kaplan-Meier curves for the outcome of severe AEs; 3rd data cut-off (CheckMate 649 study, PD-L1-positive population)

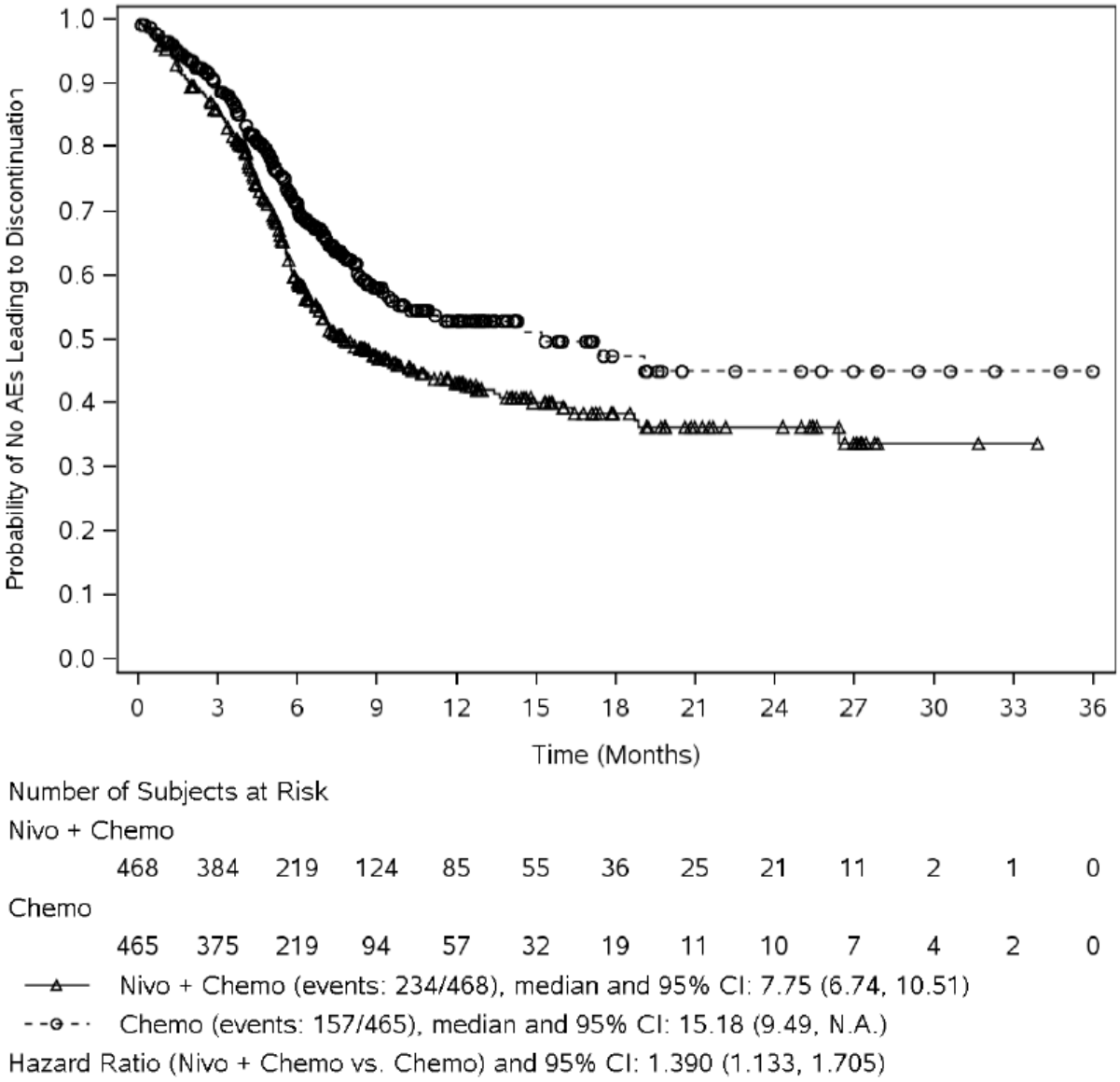

Figure 4: Kaplan-Meier curves for the outcome of discontinuation due to AEs; 3rd data cut-off (CheckMate 649 study, PD-L1-positive population)