IQWiG Reports – Commission No. A22-37

Pembrolizumab (oesophageal or gastroesophageal junction carcinoma) –

Addendum to Commission A21-144[1]

Addendum

Commission: A22-37
Version: 1.1
Status: 25 April 2022

[1] Translation of addendum A22-37 *Pembrolizumab (Karzinom des Ösophagus oder gastroösophagealen Übergangs) – Addendum zum Auftrag A21-144* (Version 1.1; Status: 25 April 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
Pembrolizumab (oesophageal or gastroesophageal junction carcinoma) – Addendum to Commission A21-144

Commissioning agency
Federal Joint Committee

Commission awarded on
29 March 2022

Internal Commission No.
A22-37

Address of publisher
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Keywords: Pembrolizumab, Esophageal Neoplasms, Benefit Assessment, NCT03189719, NCT02494583

Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
5-FU	5-fluorouracil
AE	adverse event
CPS	Combined Positive Score
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life – 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)
MedDRA	Medical Dictionary for Regulatory Activities
PD-L1	progammed cell death ligand 1
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire – Core 30
QLQ-OES18	Quality of Life Questionnaire – Oesophageal Cancer Module 18
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 29 March 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-144 (Pembrolizumab – Benefit assessment according to §35a Social Code Book V) [1].

The commission involves assessing the clarification presented by the company in the commenting procedure regarding the operationalization of the following outcomes of the KEYNOTE 590 study, taking into account the information provided in the dossier:

- time to first clinically relevant deterioration (European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire – Core 30 [QLQ-C30] and EORTC Quality of Life Questionnaire – Oesophageal Cancer Module 18 [QLQ-OES18])
- discontinuation due to adverse events (AEs): time to discontinuation of at least 1 drug component

For consistency reasons, the responder analyses of time to first deterioration by ≥ 7 or ≥ 10 points in patient group B1 are further presented as supplementary information in Appendix C.

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.

1.1 Changes in comparison with version 1.0

The present version 1.1 dated 21 April 2022 replaces version 1.0 of the addendum to commission A21-144 dated 14 April 2022. Version 1.1 contains the following change compared with version 1.0:

- Table 4 in version 1.0 of the addendum erroneously states the probability of a statistically significant effect in favour of pembrolizumab + cisplatin + 5-FU for the outcome of overall survival is an indication rather than a hint. This error has been corrected in Table 4 of the present version of the addendum.
- For patient group B1, Appendix C contains a supplementary presentation of responder analyses of the outcome of health status (European Quality of Life – 5 Dimensions visual analogue scale [EQ-5D VAS]) operationalized as time to first deterioration by ≥ 7 or ≥ 10 points.

These changes do not affect the conclusion of the benefit assessment.

2 Assessment

The benefit assessment of pembrolizumab used the randomized controlled trial (RCT) KEYNOTE 590 to investigate research question A of the dossier assessment (first-line treatment of adult patients with locally advanced or metastatic squamous cell carcinoma of the oesophagus which cannot be treated curatively and whose tumours express programmed cell death ligand 1 (PD-L1) tumours and a Combined Positive Score [CPS] ≥ 10). The KEYNOTE 590 and KEYNOTE 062 RCTs were used to investigate research question B1 (first-line treatment of adult patients with locally advanced or metastatic HER2-negative adenocarcinoma of the oesophagus or of the gastrooesophageal junction which cannot be treated curatively and whose tumours express PD-L1 and a CPS ≥ 10. The KEYNOTE 590 study compared pembrolizumab in combination with cisplatin and 5-fluorouracil (pembrolizumab + cisplatin + 5-FU) versus placebo in combination with cisplatin and 5-fluorouracil (placebo + cisplatin + 5FU). The KEYNOTE 062 study's comparisons relevant for the present benefit assessment are pembrolizumab in combination with cisplatin and either 5-fluorouracil or capecitabine (pembrolizumab + cisplatin + 5-FU/capecitabine) and placebo + cisplatin in combination with either 5-fluorouracil or capecitabine (placebo + cisplatin + 5-FU/capecitabine).

The sections below evaluate the clarifications provided in the company's comments regarding the operationalizations of the symptoms and health-related quality of life outcomes measured with the EORTC QLQ-C30 and EORTC QLQ-OES18 (Section 2.1) as well as discontinuation due to AEs (Section 2.2). In Sections 2.3 and 2.4, the results on these outcomes as well as their influence on the result of the benefit assessment are evaluated for each research question.

2.1 Time to first clinically relevant deterioration (EORTC QLQ-C30, EORTC QLQ-OES18)

The dossier's Module 4 A provides contradictory information on the operationalizations of the symptoms and health-related quality of life outcomes surveyed in the KEYNOTE 590 study using EORTC QLQ-C30 and EORTC QLQ-OES18. The company's dossier states that it provides analyses for the time to first deterioration by ≥10 points. However, the company occasionally refers to the operationalization of the analyses presented as time to first confirmed deterioration, without describing how a confirmed deterioration is defined. Results on time to first confirmed deterioration for individual scales of the EORTC QLQ-C30 and EORTC QLQ-OES18 can be found in the KEYNOTE 590 study report. These results presented in the study report differ from the results presented in Module 4 A for the corresponding scales. Overall, the benefit assessment left it unclear whether the discrepancies between the results presented in Module 4 A versus those in the study report might be explained solely by the 2 sources using different operationalizations.

For these reasons, the KEYNOTE 590 study's results on EORTC QLQ-C30 and EORTC QLQ-OES18 as presented in Module 4 A were deemed unusable in dossier assessment A21-144 and are disregarded in the present assessment [1].

With its comments [2], the company has now clarified that the analyses presented in the dossier‘s Module 4 A use the operationalization of time to first deterioration by ≥ 10 points (scale range of 0 to 100 in each case).

Neither in its written comments nor in its dossier does the company provide any reasoning as to why the analyses in Module 4 A use the operationalization of time to first deterioration by ≥ 10 points, unlike the company’s study report, which used time to first confirmed deterioration by ≥ 10 points. Since the operationalization of time to first deterioration by ≥ 10 points is generally suitable, however, the data submitted in Module 4 A with the clarification are deemed usable and were therefore included in the present addendum to assess the added benefit of pembrolizumab for research question A and research question B1.

2.2 Discontinuation due to AEs

For the outcome “discontinuation due to AEs”, it cannot be inferred from the information provided by the company in Module 4 A whether the analyses refer to the time to discontinuation of all drug components or to discontinuation of at least one drug component.

For these reasons, the results of the KEYNOTE 590 and KEYNOTE 062 studies on the outcome of discontinuation due to AEs presented in Module 4 A were deemed unusable and were disregarded in dossier assessment A21-144 [1].

The company’s comments clarify that the analyses take into account patients who discontinued treatment with at least 1 drug component.

The data submitted in Module 4 A with the clarification are deemed usable and are therefore taken into account in the present addendum to assess the added benefit of pembrolizumab concerning research question A and research question B1.

2.3 Research question A

2.3.1 Risk of bias

For the symptoms and health-related quality of life outcomes surveyed using EORTC QLQ-C30 and EORTC QLQ-OES18, the risk of bias is rated as high due to incomplete observation for potentially informative reasons. This results from discontinuation of treatment and subsequent discontinuation of follow-up observation being largely due to disease progression.

Despite a low risk of bias in the KEYNOTE 590 study, the certainty of results for the outcome of discontinuation due to AEs is reduced. Premature treatment discontinuation for reasons other than AEs represents a competing event for the outcome to be surveyed, discontinuation due to AEs. Consequently, after discontinuation for other reasons, AEs would have led to discontinuation may have occurred, but the criterion of discontinuation could no longer be applied to them. It is impossible to estimate the number of AEs to which this applies.

2.3.2 Results

Table 1 summarizes the results on the outcomes of symptoms, measured with the EORTC QLQ-C30 and EORTC QLQ-OES18, on the outcome of health-related quality of life, measured with the EORTC QLQ-C30, as well as on the outcome of discontinuation due to AEs.

Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier.

Results on all AEs which led to treatment discontinuation are presented in Appendix A. Kaplan-Meier curves on the time-to-event analyses can be found in Appendix B.

Table 1: Results (morbidity, health-related quality of life, side effects; time to event) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU versus cisplatin + 5-FU, subpopulation with squamous cell carcinoma of the oesophagus and CPS ≥ 10 (multipage table)

Study Outcome category Outcome	Pembrolizumab + cisplatin + 5-FU		Placebo + cisplatin + 5-FU		Pembrolizumab + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU
	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]
KEYNOTE 590					
Morbidity					
Symptoms (EORTC QLQ-C30)[b]					
Fatigue	138	1.7 [1.0; 2.6] 97 (70.3)	136	1.4 [1.3; 2.1] 100 (73.5)	0.87 [0.65; 1.15]; 0.318
Nausea and vomiting	138	3.1 [2.1; 4.2] 83 (60.1)	136	2.2 [1.8; 3.1] 84 (61.8)	0.79 [0.58; 1.08]; 0.140
Pain	138	6.6 [4.1; 8.4] 71 (51.4)	136	3.2 [2.4; 3.8] 87 (64.0)	0.60 [0.44; 0.84]; 0.002
Dyspnoea	138	25.3 [7.2; NC] 49 (35.5)	136	3.7 [2.9; 5.8] 71 (52.2)	0.50 [0.35; 0.74]; < 0.001
Insomnia	138	4.5 [3.0; 25.3] 67 (48.6)	136	4.9 [3.7; 7.4] 61 (44.9)	1.01 [0.71; 1.43]; 0.969
Appetite loss	138	3.5 [2.7; 4.9] 81 (58.7)	136	2.9 [2.1; 3.7] 81 (59.6)	0.81 [0.59; 1.12]; 0.202
Constipation	138	5.2 [3.8; NC] 60 (43.5)	136	4.4 [3.0; 7.1] 67 (49.3)	0.81 [0.57; 1.15]; 0.228
Diarrhoea	138	12.2 [3.3; NC] 57 (41.3)	136	NR [5.7; NC] 43 (31.6)	1.23 [0.83; 1.84]; 0.308
Symptoms (EORTC QLQ-OES18)[b]					
Food	137	7.2 [3.9; 11.2] 67 (48.9)	133	3.5 [2.9; 5.5] 69 (51.9)	0.75 [0.53; 1.06]; 0.103
Reflux[c]	137	7.6 [4.2; NC] 62 (45.3)	133	5.0 [3.4; 8.4] 63 (47.4)	0.89 [0.62; 1.27]; 0.506
Pain	137	5.2 [3.5; 12.3] 66 (48.2)	133	4.6 [2.9; 5.8] 66 (49.6)	0.79 [0.56; 1.13]; 0.195
Swallowing saliva	137	25.8 [4.9; NC] 53 (38.7)	133	5.5 [4.0; NC] 59 (44.4)	0.72 [0.49; 1.06]; 0.093
Choking	137	12.3 [8.9; NC] 46 (33.6)	133	5.5 [3.9; 10.1] 56 (42.1)	0.53 [0.35; 0.80]; 0.003
Dry mouth	137	4.0 [2.1; 8.1] 74 (54.0)	133	3.0 [2.3; 6.7] 69 (51.9)	1.03 [0.74; 1.44]; 0.846
Taste	137	4.0 [2.4; 10.2] 70 (51.1)	133	4.2 [3.0; 5.5] 63 (47.4)	1.07 [0.76; 1.51]; 0.686

Table 1: Results (morbidity, health-related quality of life, side effects; time to event) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU versus cisplatin + 5-FU, subpopulation with squamous cell carcinoma of the oesophagus and CPS ≥ 10 (multipage table)

Study Outcome category Outcome	Pembrolizumab + cisplatin + 5-FU		Placebo + cisplatin + 5-FU		Pembrolizumab + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU
	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]
Cough	137	NR [8.6; NC] 45 (32.8)	133	7.8 [5.3; NC] 49 (36.8)	0.73 [0.48; 1.10]; 0.131
Speech	137	25.3 [11.1; NC] 45 (32.8)	133	10.1 [5.5; NC] 46 (34.6)	0.83 [0.54; 1.26]; 0.384
Dysphagia[c]	137	2.8 [1.6; 3.8] 79 (57.7)	133	3.0 [2.3; 3.7] 81 (60.9)	0.92 [0.67; 1.26]; 0.593
Health-related quality of life					
Quality of life (EORTC QLQ-C30)[d]					
Global health status	138	3.2 [2.1; 4.2] 82 (59.4)	136	3.4 [2.1; 3.7] 81 (59.6)	0.97 [0.72; 1.33]; 0.868
Physical functioning	138	3.6 [2.8; 4.4] 83 (60.1)	136	2.9 [2.5; 3.6] 82 (60.3)	0.89 [0.65; 1.22]; 0.474
Role functioning	138	2.4 [1.4; 3.6] 89 (64.5)	136	2.3 [2.1; 3.0] 85 (62.5)	1.03 [0.76; 1.39]; 0.868
Emotional functioning	138	11.8 [7.2; NC] 53 (38.4)	136	5.5 [3.7; 8.4] 63 (46.3)	0.68 [0.47; 0.99]; 0.045
Cognitive functioning	138	3.3 [2.7; 4.6] 79 (57.2)	136	3.7 [2.8; 4.9] 78 (57.4)	0.92 [0.67; 1.27]; 0.609
Social functioning	138	4.4 [3.0; 5.7] 76 (55.1)	136	3.2 [2.3; 5.2] 72 (52.9)	0.84 [0.61; 1.17]; 0.312
Side effects					
Discontinuation due to AEs	143	NR 36 (25.2)	140	NR [46.4; NC] 37 (26.4)	0.88 [0.55; 1.39]; 0.571[e]

a. Unless stated otherwise: HR and CI from Cox proportional hazards model, stratified by region (Asia vs. rest of the world) and ECOG (0 vs. 1) with associated p-value from 2-sided Wald test.
b. Time to first deterioration; a score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
c. The KEYNOTE 590 study used an EORTC-generated Japanese version of the EORTC QLQ-OES18 questionnaire which was, in part, incorrectly translated. This resulted, firstly, in 3 items of the dysphagia scale being rated by patients in an opposite manner. Secondly, the reflux scale's item of heartburn was incorrectly translated into Japanese. After consultation with the EORTC, the company reanalysed the questionnaire. For the reflux symptom scale, the item of heartburn was treated as missing in the analysis. For the dysphagia symptom scale, the analysis of the 3 items in question was corrected. Overall, this approach was deemed acceptable.
d. Time to first deterioration; a score decrease by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 100).
e. HR and CI from Cox proportional hazards model, nonstratified with associated p-value from 2-sided Wald test.

Table 1: Results (morbidity, health-related quality of life, side effects; time to event) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU versus cisplatin + 5-FU, subpopulation with squamous cell carcinoma of the oesophagus and CPS ≥ 10 (multipage table)

Study Outcome category Outcome	Pembrolizumab + cisplatin + 5-FU		Placebo + cisplatin + 5-FU		Pembrolizumab + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU
	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]
5-FU: 5-fluorouracil; AE: adverse event; CI: confidence interval; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-OES18 : Quality of Life Questionnaire – Oesophageal Cancer Module 18; RCT: randomized controlled trial					

On the basis of the available information, at most hints, e.g. of an added benefit, can be determined from the available information for all outcomes; this is due to the high risk of bias of the results and the limited certainty of results (see A21-144 report [1]).

Morbidity

Symptoms

The symptoms outcomes were recorded with the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-OES18. Time to first deterioration by ≥ 10 points (scale range 0 to 100) was analysed.

EORTC QLQ-C30: fatigue, nausea and vomiting, insomnia, appetite loss, constipation, and diarrhoea

No statistically significant differences between treatment arms were shown for the outcomes of fatigue, nausea and vomiting, insomnia, appetite loss, constipation, or diarrhoea. This results in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU; an added benefit is therefore not proven.

EORTC QLQ-C30: pain

A statistically significant difference in favour of pembrolizumab + cisplatin + 5-FU in comparison with placebo + cisplatin + 5-FU was found for the outcome of pain, surveyed by the EORTC QLQ-C30. In addition, there is an effect modification by age at baseline (< 65 years versus ≥ 65 years). For patients < 65 years, this results in no hint of added benefit of pembrolizumab + cisplatin + 5FU in comparison with cisplatin + 5FU; an added benefit is therefore not proven for these patients. For patients ≥ 65 years, this results in a hint of an added benefit of pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU (see Section 2.3.3).

EORTC QLQ-C30: dyspnoea

A statistically significant difference in favour of pembrolizumab + cisplatin + 5-FU in comparison with placebo + cisplatin + 5-FU was found for the outcome of dyspnoea, surveyed by the EORTC QLQ-C30. This results in a hint of an added benefit of pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU.

EORTC QLQ-OES18: eating, reflux, pain, swallowing saliva, dry mouth, taste, cough, speech, and dysphagia

No statistically significant differences between treatment arms were shown for the outcomes of eating, reflux, pain, swallowing saliva, dry mouth, taste, cough, speech, or dysphagia. This results in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU; an added benefit is therefore not proven.

EORTC QLQ-OES18: choking

A statistically significant difference in favour of pembrolizumab + cisplatin + 5-FU in comparison with placebo + cisplatin + 5-FU was found for the outcome of choking, surveyed by the EORTC QLQ-OES18. This results in a hint of an added benefit of pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU.

Health-related quality of life

Health-related quality of life outcomes were surveyed using the disease-specific instrument of EORTC QLQ-C30. Time to first deterioration by ≥ 10 points (scale range 0 to 100) was analysed for the individual functional scales.

EORTC QLQ-C30: global health status, physical functioning, role functioning, cognitive functioning, and social functioning

No statistically significant difference between treatment arms was found for the EORTC QLQ-C30 scales of global health status, physical functioning, role functioning, cognitive functioning, or social functioning. This results in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU; an added benefit is therefore not proven.

EORTC QLQ-C30: emotional functioning

A statistically significant difference in favour of pembrolizumab + cisplatin + 5-FU in comparison with placebo + cisplatin + 5-FU was found for the emotional functioning scale, surveyed by the EORTC QLQ-C30. This results in a hint of an added benefit of pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU.

Side effects

According to the study protocol, progression events of the underlying oncological disease were not recorded as AEs. The Medical Dictionary for Regulatory Activities (MedDRA) terms “progression of neoplasms”, “progression of malignant neoplasms” and “disease progression”

were excluded from the AE recording. For the outcome of discontinuation due to AEs, time to discontinuation of at least 1 drug component was analysed.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, no statistically significant difference between treatment arms was found. This results in no hint of greater or lesser harm from pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU; greater or lesser harm is therefore not proven for this outcome.

2.3.3 Subgroups and other effect modifiers

For the present assessment, the following subgroup characteristics are relevant (see report A21-144 [1]):

- sex (male versus female)
- age (< 65 years versus ≥ 65 years)
- disease stage (locally advanced vs. metastatic)

The company's subgroup analyses were conducted post hoc for the patient-relevant outcomes in the morbidity, health-related quality of life, and side effects categories.

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

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

Table 2 presents the subgroup results found using the methods described in dossier assessment A21-144 based on the subsequently analysed results.

Table 2: Subgroups (morbidity, time to event) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU versus placebo + cisplatin + 5-FU, subpopulation with squamous cell carcinoma of the oesophagus and CPS ≥ 10 (multipage table)

Study Outcome Characteristic Subgroup	Pembrolizumab + cisplatin + 5-FU N	Pembrolizumab + cisplatin + 5-FU Median time to event in months [95% CI] Patients with event n (%)	Placebo + cisplatin + 5-FU N	Placebo + cisplatin + 5-FU Median time to event in months [95% CI] Patients with event n (%)	Pembrolizumab + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU HR [95% CI][a]	 p-value
KEYNOTE 590						
Morbidity						
Symptoms (EORTC QLQ-C30 – pain)[b]						
Age						
< 65	75	3.6 [1.9; 7.0] 46 (61.3)	82	3.0 [2.3; 4.9] 52 (63.4)	0.92 [0.61; 1.37]	0.666
≥ 65 years	63	9.5 [4.8; NC] 25 (39.7)	54	3.2 [2.1; 4.1] 35 (64.8)	0.35 [0.20; 0.59]	< 0.001
Total					Interaction[c]:	0.006

a. HR and CI from Cox proportional hazards model, nonstratified with associated p-value from 2-sided Wald test.
b. Time to first deterioration; a score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
c. Cox proportional hazards model with treatment and subgroup as covariates and interaction between treatment and subgroup (p-value based on likelihood ratio test).

5-FU: 5-fluorouracil; CI: confidence interval; CPS: Combined Positive Score; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NC: not calculable; NR: not reached; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-OES18 : Quality of Life Questionnaire – Oesophageal Cancer Module 18; RCT: randomized controlled trial

Morbidity

Symptoms

EORTC QLQ-C30: pain

An effect modification by the characteristic of age was found for the outcome of pain, surveyed with the EORTC QLQ-C30. No statistically significant difference between treatment groups was found for patients < 65 years. For these patients, this results in no hint of added benefit of pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU; an added benefit is therefore not proven for these patients. A statistically significant difference in favour of pembrolizumab + cisplatin + 5-FU in comparison with placebo + cisplatin + 5-FU was shown for patients ≥ 65 years. For these patients, this results in a hint of added benefit of pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU.

2.3.4 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Sections 2.3.2 and 2.3.3 (see Table 3).

Pain, dyspnoea (EORTC QLQ-C30); choking (EORTC QLQ-OES18)

Insufficient information is available for categorizing the severity of the outcomes of pain and dyspnoea, surveyed with the EORTC QLQ-C30 symptoms scales, as well as the outcome of choking, surveyed with the EORTC QLQ-OES18 symptom scales. Therefore, each of these outcomes was assigned to the outcome category of non-serious/non-severe symptoms.

Discontinuation due to AEs

Insufficient information is available for determining whether the outcome of discontinuation due to AEs is to be allocated to the outcome category of serious/severe side effects or non-serious/non-severe side effects. For the relevant subpopulation, no information is available on the severities of the individual AEs on which the discontinuation due to AEs was based. Therefore, this outcome was assigned to the outcome category of non-serious/non-severe side effects.

Table 3: Extent of added benefit at outcome level: pembrolizumab + cisplatin + 5-FU versus cisplatin + 5-FU (patients with squamous cell carcinoma of the oesophagus and CPS ≥ 10) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + cisplatin + 5-FU vs. cisplatin + 5-FU** **Median time to event (months) or MD** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	13.9 vs. 8.8 months HR: 0.57 [0.43; 0.75]; p < 0.001 Probability: "hint"	Outcome category: mortality CI_u < 0.85 Added benefit, extent: "major"
Morbidity		
Symptoms (EORTC QLQ-C30 – time to first deterioration by ≥ 10 points)		
Fatigue	**1.7 vs. 1.4 months** **HR: 0.87 [0.65; 1.15];** **p = 0.318**	**Lesser/added benefit not proven**
Nausea and vomiting	**3.1 vs. 2.2 months** **HR: 0.79 [0.58; 1.08];** **p = 0.140**	**Lesser/added benefit not proven**
Pain		
Age		
< 65 years	**3.6 vs. 3.0 months** **HR: 0.92 [0.61; 1.37];** **p = 0.666**	**Lesser/added benefit not proven**
≥ 65 years	**9.5 vs. 3.2 months** **HR: 0.35 [0.20; 0.59];** **p < 0.001** **Probability: hint**	**Outcome category: non-serious/non-severe symptoms / late complications** **CI_u < 0.80** **Added benefit, extent: considerable**
Dyspnoea	**25.3 vs. 3.7 months** **HR: 0.50 [0.35; 0.74];** **p < 0.001** **Probability: "hint"**	**Outcome category: non-serious/non-severe symptoms/late complications** **CI_u < 0.80** **Added benefit, extent: considerable**
Insomnia	**4.5 vs. 4.9 months** **HR: 1.01 [0.71; 1.43];** **p = 0.969**	**Lesser/added benefit not proven**
Appetite loss	**3.5 vs. 2.9 months** **HR: 0.81 [0.59; 1.12];** **p = 0.202**	**Lesser/added benefit not proven**
Constipation	**5.2 vs. 4.4 months** **HR: 0.81 [0.57; 1.15];** **p = 0.228**	**Lesser/added benefit not proven**

Table 3: Extent of added benefit at outcome level: pembrolizumab + cisplatin + 5-FU versus cisplatin + 5-FU (patients with squamous cell carcinoma of the oesophagus and CPS ≥ 10) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + cisplatin + 5-FU vs. cisplatin + 5-FU** **Median time to event (months) or MD** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Diarrhoea	**12.2 months vs. NR** **HR: 1.23 [0.83; 1.84];** **p = 0.308**	**Lesser/added benefit not proven**
Symptoms (EORTC QLQ-OES18 – time to first deterioration by ≥ 10 points)		
Food	**7.2 vs. 3.5 months** **HR: 0.75 [0.53; 1.06]; p = 0.103**	**Lesser benefit/added benefit not proven**
Reflux	**7.6 vs. 5.0 months** **HR: 0.89 [0.62; 1.27]; p = 0.506**	**Lesser/added benefit not proven**
Pain	**5.2 vs. 4.6 months** **HR: 0.79 [0.56; 1.13]; p = 0.195**	**Lesser/added benefit not proven**
Swallowing saliva	**25.8 vs. 5.5 months** **HR: 0.72 [0.49; 1.06]; p = 0.093**	**Lesser/added benefit not proven**
Choking	**12.3 vs. 5.5 months** **HR: 0.53 [0.35; 0.80]; p = 0.003** **Probability: hint**	**Outcome category: non-serious/non-severe symptoms/late complications** **CI_u < 0.90** **Added benefit, extent: minor**
Dry mouth	**4.0 vs. 3.0 months** **HR: 1.03 [0.74; 1.44]; p = 0.846**	**Lesser benefit/added benefit not proven**
Taste	**4.0 vs. 4.2 months** **HR: 1.07 [0.76; 1.51]; p = 0.686**	**Lesser/added benefit not proven**
Cough	**NA vs. 7.8 months** **HR: 0.73 [0.48; 1.10]; p = 0.131**	**Lesser/added benefit not proven**
Speech	**25.3 vs. 10.1 months** **HR: 0.83 [0.54; 1.26]; p = 0.384**	**Lesser/added benefit not proven**
Dysphagia	**2.8 vs. 3.0 months** **HR: 0.92 [0.67; 1.26]; p = 0.593**	**Lesser/added benefit not proven**
Health status (EQ-5D VAS – mean difference until Week 18)		
EQ-5D VAS	Mean (until week 18): -4.46 vs. -4.35 MD: -0.10 [-4.96; 4.76]; p = 0.967	Lesser/added benefit not proven
Health-related quality of life		
Quality of life (EORTC QLQ-C30 - time to first deterioration by ≥ 10 points)		
Global health status	**3.2 vs. 3.4 months** **HR: 0.97 [0.72; 1.33]; p = 0.868**	**Lesser/added benefit not proven**
Physical functioning	**3.6 vs. 2.9 months** **HR: 0.89 [0.65; 1.22]; p = 0.474**	**Lesser/added benefit not proven**

Table 3: Extent of added benefit at outcome level: pembrolizumab + cisplatin + 5-FU versus cisplatin + 5-FU (patients with squamous cell carcinoma of the oesophagus and CPS ≥ 10) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + cisplatin + 5-FU vs. cisplatin + 5-FU** **Median time to event (months) or MD** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Role functioning	**2.4 vs. 2.3 months** **HR: 1.03 [0.76; 1.39]; p = 0.868**	**Lesser/added benefit not proven**
Emotional functioning	**11.8 vs. 5.5 months** **HR: 0.68 [0.47; 0.99]; p = 0.045** **Probability: hint**	**Outcome category: health-related quality of life** **$0.90 \leq CI_u < 1.00$** **Added benefit; extent: minor**
Cognitive functioning	**3.3 vs. 3.7 months** **HR: 0.92 [0.67; 1.27]; p = 0.609**	**Lesser/added benefit not proven**
Social functioning	**4.4 vs. 3.2 months** **HR: 0.84 [0.61; 1.17]; p = 0.312**	**Lesser/added benefit not proven**
Side effects		
SAEs	35.6 vs. 25.7 months HR: 0.87 [0.64; 1.20]; p = 0.405	Greater/lesser harm not proven
Severe AEs	4.4 vs. 5.0 months HR: 1.01 [0.78; 1.30]; p = 0.952	Greater/lesser harm not proven
Discontinuation due to AEs	**NR vs. NR** **HR: 0.88 [0.55; 1.39]; p = 0.571**	**Lesser/added benefit not proven**
Immune-related SAEs	NA vs. NA HR: 5.36 [1.20; 24.00] HR: 0.19 [0.04; 0.83][c]; p = 0.028 Probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm, extent: "considerable"
Immune-related severe AEs	NA vs. NA HR: 3.30 [0.93; 11.77]; p = 0.065	Greater/lesser harm not proven
Musculoskeletal and connective tissue disorders (AEs)	NA vs. 53.1 months HR: 0.41 [0.25; 0.67]; p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
General disorders and administration site conditions (SAEs)	NA vs. NA HR: 0.11 [0.02; 0.47]; p = 0.003 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Platelet count decreased (severe AEs)	NA vs. NA HR: 0.25 [0.07; 0.90]; p = 0.033 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm; extent: minor

Table 3: Extent of added benefit at outcome level: pembrolizumab + cisplatin + 5-FU versus cisplatin + 5-FU (patients with squamous cell carcinoma of the oesophagus and CPS ≥ 10) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + cisplatin + 5-FU vs. cisplatin + 5-FU** **Median time to event (months) or MD** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Weight decreased (severe AEs)	NA vs. NA HR: 0.07 [0.01; 0.58]; p = 0.013 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Results printed in **bold** result from the data additionally analysed. 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. 5-FU: 5-fluorouracil; AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; EORTC: European Organization for Research and Treatment of Cancer; HR: hazard ratio; MD: mean difference; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-OE18: Quality of Life Questionnaire – Oesophageal Cancer Module 18; SAE: serious adverse event; VAS: visual analogue scale		

2.3.5 Overall conclusion on added benefit

Table 4 summarizes the results of the benefit assessment for commission A21-144 and the present addendum A22-37, both of which were used to inform the overall conclusion on the extent of added benefit.

Table 4: Favourable and unfavourable effects from the assessment of pembrolizumab + cisplatin + 5-FU versus cisplatin + 5-FU (patients with squamous cell carcinoma of the oesophagus and CPS ≥ 10)

Favourable effects	**Unfavourable effects**
Mortality ▪ Overall survival: hint of an added benefit – extent: "major"	–
Non-serious/non-severe symptoms / late complications ▪ **Pain:** ▫ **Age (≥ 65 years): hint of added benefit – extent: considerable** ▪ **Dyspnoea: hint of an added benefit – extent: considerable** ▪ **Choking: hint of an added benefit – extent: minor**	–
Health-related quality of life ▪ **Emotional functioning: hint of minor added benefit**	–
Serious/severe side effects ▪ General disorders and administration site conditions (SAEs): hint of lesser harm – extent: "major" ▪ Platelet count decreased (severe AEs): hint of lesser harm – extent: "minor" ▪ Weight decreased (severe AEs): hint of lesser harm – extent: "major"	Serious/severe side effects ▪ Immune-related AEs (SAEs): hint of greater harm – extent: considerable
Non-serious/non-severe side effects ▪ Musculoskeletal and connective tissue disorders (AEs); hint of lesser harm, extent: "considerable"	–
Results printed in **bold** result from the data additionally analysed. 5-FU: 5-fluorouracil; AEs: adverse events; CPS: combined positive score; SAEs: serious adverse events	

For patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10, the subsequently assessed results in combination with the effects presented in dossier assessment A21-144 result in 3 further favourable effects in the outcome category of nonserious/nonsevere symptoms as well as 1 favourable effect in the health-related quality of life dimension of emotional functioning. Each of these effects constitute hints of added benefit of minor to considerable extent.

The observed effects do not call into question the overall conclusions on added benefit drawn in dossier assessment A21-144 for patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10.

All things considered, this results in no change in the overall conclusion on the added benefit of pembrolizumab versus the ACT.

2.4 Research question B1

2.4.1 Risk of bias

In the KEYNOTE 590 and KEYNOTE 062 studies, the symptoms and health-related quality of life outcomes were surveyed using the EORTC QLQ-C30. In the KEYNOTE 590 study, symptoms were additionally surveyed using EORTC QLQ-OES18 (also see dossier assessment A21-144). The risk of bias for these outcomes was rated as high due to incomplete observation for potentially informative reasons. This results from discontinuation of treatment and subsequent discontinuation of follow-up observation being largely due to disease progression.

For the outcome of discontinuation due to AEs, the certainty of results in the KEYNOTE 590 and KEYNOTE 062 studies is reduced, despite a low risk of bias. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome to be surveyed, discontinuation due to AEs. Consequently, after discontinuation for other reasons, AEs would have led to discontinuation may have occurred, but the criterion of discontinuation could no longer be applied to them. It is impossible to estimate the number of AEs to which this applies.

2.4.2 Results

Table 5 summarizes the results on the outcomes of symptoms, measured with the EORTC QLQ-C30 and EORTC QLQ-OES18, on the outcome of health-related quality of life, measured with the EORTC QLQ-C30, as well as on the outcome of discontinuation due to AEs.

Where necessary, IQWiG calculations are provided in addition to the data from the company's dossier.

Results on all AEs which led to treatment discontinuation are presented in Appendix A. Kaplan-Meier curves on the time-to-event analyses as well as Forest plots on the metaanalyses calculated by IQWiG are presented in Appendix B.

Table 5: Results (morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine versus placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10 (multipage table)

Outcome category **Outcome** **Study**	**Pembrolizumab + cisplatin + 5-FU or capecitabine**		**Placebo + cisplatin + 5-FU or capecitabine**		**Pembrolizumab + cisplatin + 5-FU or capecitabine vs. placebo + cisplatin + 5-FU or capecitabine**
	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**
Morbidity					
Symptoms (EORTC QLQ-C30)[a]					
Fatigue					
KEYNOTE 590	41	1.6 [1.0; 4.3] 28 (68.3)	49	2.0 [1.0; 2.8] 34 (69.4)	0.88 [0.53; 1.46]; 0.627[b]
KEYNOTE 062	28	1.4 [1.0; 2.3] 24 (85.7)	20	0.8 [0.7; 3.0] 15 (75.0)	0.84 [0.44; 1.61]; 0.597[c]
Total[d]					0.86 [0.58; 1.29]; 0.475
Nausea and vomiting					
KEYNOTE 590	41	2.1 [1.4; 7.0] 26 (63.4)	49	2.3 [1.4; 4.1] 30 (61.2)	0.91 [0.53; 1.54]; 0.712[b]
KEYNOTE 062	28	1.9 [0.8; 5.3] 19 (67.9)	20	1.4 [0.7; 1.6] 17 (85.0)	0.56 [0.29; 1.08]; 0.085[c]
Total[d]					0.75 [0.50; 1.14]; 0.174
Pain					
KEYNOTE 590	41	3.3 [2.4; 14.1] 25 (61.0)	49	4.1 [1.9; NC] 22 (44.9)	1.11 [0.62; 2.01]; 0.723[b]
KEYNOTE 062	28	6.5 [2.4; 8.8] 16 (57.1)	20	3.3 [1.5; NC] 12 (60.0)	0.80 [0.38; 1.69]; 0.551[c]
Total[d]					0.98 [0.62; 1.55]; 0.929
Dyspnoea					
KEYNOTE 590	41	8.3 [3.2; NC] 19 (46.3)	49	5.1 [3.0; 12.0] 25 (51.0)	0.96 [0.51; 1.78]; 0.887[b]
KEYNOTE 062	28	8.6 [4.4; NC] 12 (42.9)	20	2.6 [0.8; 6.0] 13 (65.0)	0.43 [0.19; 0.94]; 0.035[c]
Total[d]					0.71 [0.43; 1.16]; 0.169

Table 5: Results (morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine versus placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10 (multipage table)

Outcome category **Outcome** **Study**	**Pembrolizumab + cisplatin + 5-FU or capecitabine**		**Placebo + cisplatin + 5-FU or capecitabine**		**Pembrolizumab + cisplatin + 5-FU or capecitabine vs. placebo + cisplatin + 5-FU or capecitabine**
	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**
Insomnia					
KEYNOTE 590	41	NR [7.0; NC] 15 (36.6)	49	4.6 [2.8; 12.9] 24 (49.0)	0.65 [0.34; 1.26]; 0.204[b]
KEYNOTE 062	28	NA [2.7; NC] 11 (39.3)	20	6.0 [0.7; NC] 10 (50.0)	0.64 [0.27; 1.52]; 0.315[c]
Total[d]					0.65 [0.38; 1.09]; 0.101
Appetite loss					
KEYNOTE 590	41	2.7 [1.3; 14.9] 24 (58.5)	49	3.0 [1.4; 4.1] 30 (61.2)	0.83 [0.48; 1.44]; 0.513[b]
KEYNOTE 062	28	5.8 [1.4; 10.2] 18 (64.3)	20	3.4 [1.5; 6.0] 13 (65.0)	0.65 [0.31; 1.37]; 0.257[c]
Total[d]					0.76 [0.49; 1.18]; 0.226
Constipation					
KEYNOTE 590	41	3.0 [1.4; NC] 22 (53.7)	49	3.5 [2.1; NC] 25 (51.0)	1.00 [0.56; 1.79]; 0.993[b]
KEYNOTE 062	28	3.0 [1.4; NC] 15 (53.6)	20	3.2 [1.4; 6.1] 14 (70.0)	0.76 [0.36; 1.57]; 0.454[c]
Total[d]					0.90 [0.57; 1.42]; 0.651
Diarrhoea					
KEYNOTE 590	41	3.0 [1.3; 10.6] 24 (58.5)	49	4.1 [1.8; NC] 23 (46.9)	1.17 [0.65; 2.11]; 0.591[b]
KEYNOTE 062	28	4.4 [1.4; NC] 15 (53.6)	20	NR [0.7; NC] 9 (45.0)	1.04 [0.45; 2.38]; 0.924[c]
Total[d]					1.12 [0.70; 1.82]; 0.631
Symptoms (EORTC QLQ-OES18)[a]					
Food					
KEYNOTE 590	41	5.3 [3.2; NC] 21 (51.2)	47	4.4 [3.0; NC] 23 (48.9)	0.88 [0.48; 1.60]; 0.669[b]
KEYNOTE 062	Instrument not surveyed				

Table 5: Results (morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine versus placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10 (multipage table)

Outcome category Outcome Study	Pembrolizumab + cisplatin + 5-FU or capecitabine		Placebo + cisplatin + 5-FU or capecitabine		Pembrolizumab + cisplatin + 5-FU or capecitabine vs. placebo + cisplatin + 5-FU or capecitabine
	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
Reflux[e]					
KEYNOTE 590	41	12.7 [2.3; NC] 18 (43.9)	47	2.6 [1.4; 10.2] 28 (59.6)	0.50 [0.27; 0.92]; 0.026[b]
KEYNOTE 062			Instrument not surveyed		
Pain					
KEYNOTE 590	41	3.9 [2.9; 14.9] 22 (53.7)	47	4.4 [3.1; 8.0] 27 (57.4)	0.94 [0.53; 1.66]; 0.827[b]
KEYNOTE 062			Instrument not surveyed		
Swallowing saliva					
KEYNOTE 590	41	8.3 [2.8; NC] 19 (46.3)	47	5.1 [2.6; NC] 21 (44.7)	0.93 [0.50; 1.75]; 0.823[b]
KEYNOTE 062			Instrument not surveyed		
Choking					
KEYNOTE 590	41	5.6 [2.6; NC] 20 (48.8)	47	12.2 [4.2; NC] 16 (34.0)	1.71 [0.86; 3.41]; 0.124[b]
KEYNOTE 062			Instrument not surveyed		
Dry mouth					
KEYNOTE 590	41	1.7 [1.4; 3.5] 28 (68.3)	47	3.4 [1.6; NC] 23 (48.9)	1.81 [1.00; 3.27] 0.048[b]
KEYNOTE 062			Instrument not surveyed		
Taste					
KEYNOTE 590	41	1.4 [1.3; 3.0] 28 (68.3)	47	2.0 [1.4; 2.8] 35 (74.5)	0.87 [0.52; 1.44]; 0.576[b]
KEYNOTE 062			Instrument not surveyed		
Cough					
KEYNOTE 590	41	4.7 [2.7; NC] 19 (46.3)	47	7.7 [4.2; NC] 19 (40.4)	1.32 [0.70; 2.52]; 0.393[b]
KEYNOTE 062			Instrument not surveyed		
Speech					
KEYNOTE 590	41	24.3 [2.8; NC] 15 (36.6)	47	NR [4.7; NC] 13 (27.7)	1.33 [0.62; 2.84]; 0.461[b]
KEYNOTE 062			Instrument not surveyed		

Table 5: Results (morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine versus placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10 (multipage table)

Outcome category **Outcome** **Study**	**Pembrolizumab + cisplatin + 5-FU or capecitabine**		**Placebo + cisplatin + 5-FU or capecitabine**		**Pembrolizumab + cisplatin + 5-FU or capecitabine vs. placebo + cisplatin + 5-FU or capecitabine**
	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**
Dysphagia[e]					
KEYNOTE 590	41	3.7 [1.6; NC] 22 (53.7)	47	3.5 [2.1; NC] 24 (51.1)	0.98 [0.55; 1.76]; 0.942[b]
KEYNOTE 062	Instrument not surveyed				
Health-related quality of life					
Quality of life (EORTC QLQ-C30)[f]					
Global health status					
KEYNOTE 590	41	3.7 [1.6; 7.8] 24 (58.5)	49	5.6 [4.1; 12.2] 24 (49.0)	1.14 [0.63; 2.04]; 0.665[b]
KEYNOTE 062	28	8.3 [2.4; 10.2] 16 (57.1)	20	2.4 [1.4; 7.4] 13 (65.0)	0.59 [0.28; 1.26]; 0.176[c]
Total[d]					0.89 [0.56; 1.41]; 0.616
Physical functioning					
KEYNOTE 590	41	4.1 [1.4; 10.9] 25 (61.0)	49	3.7 [2.8; 8.0] 29 (59.2)	1.16 [0.66; 2.02]; 0.608[b]
KEYNOTE 062	28	4.2 [1.4; 5.9] 21 (75.0)	20	1.4 [0.8; 2.2] 15 (75.0)	0.60 [0.31; 1.17]; 0.136[c]
Total[d]					0.88 [0.58; 1.35]; 0.566
Role functioning					
KEYNOTE 590	41	3.0 [1.2; 5.5] 28 (68.3)	49	2.8 [1.2; 8.0] 29 (59.2)	1.05 [0.61; 1.81]; 0.847[b]
KEYNOTE 062	28	2.1 [1.4; 5.1] 23 (82.1)	20	2.2 [0.7; NC] 13 (65.0)	1.10 [0.56; 2.17]; 0.785[c]
Total[d]					1.07 [0.70; 1.63]; 0.757

Table 5: Results (morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine versus placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10 (multipage table)

Outcome category **Outcome** **Study**	**Pembrolizumab + cisplatin + 5-FU or capecitabine**		**Placebo + cisplatin + 5-FU or capecitabine**		**Pembrolizumab + cisplatin + 5-FU or capecitabine vs. placebo + cisplatin + 5-FU or capecitabine**
	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**
Emotional functioning					
KEYNOTE 590	41	3.3 [1.6; 14.1] 24 (58.5)	49	8.0 [4.2; 17.1] 22 (44.9)	1.34 [0.73; 2.44]; 0.342[b]
KEYNOTE 062	28	5.9 [1.4; NC] 15 (53.6)	20	6.1 [1.4; NC] 8 (40.0)	1.21 [0.51; 2.85]; 0.670[c]
Total[d]					1.30 [0.79; 2.12]; 0.304
Cognitive functioning					
KEYNOTE 590	41	2.8 [1.6; 4.3] 27 (65.9)	49	3.7 [2.3; 5.3] 31 (63.3)	0.94 [0.55; 1.61]; 0.832[b]
KEYNOTE 062	28	3.4 [1.4; 9.7] 17 (60.7)	20	1.5 [0.7; NC] 12 (60.0)	0.75 [0.35; 1.57]; 0.442[c]
Total[d]					0.87 [0.56; 1.35]; 0.535
Social functioning					
KEYNOTE 590	41	3.2 [1.6; 7.1] 25 (61.0)	49	3.7 [1.6; 4.2] 28 (57.1)	0.94 [0.54; 1.62]; 0.811[b]
KEYNOTE 062	28	4.4 [1.6; NC] 16 (57.1)	20	1.9 [1.0; 4.7] 15 (75.0)	0.62 [0.31; 1.27]; 0.191[c]
Total[d]					0.80 [0.52; 1.24]; 0.322
Side effects					
Discontinuation due to AEs					
KEYNOTE 590	42	NR 10 (23.8)	53	NR 3 (5.7)	4.35 [1.20; 15.82]; 0.025[c]
KEYNOTE 062	30	NR [20.0; NC] 11 (36.7)	20	NR [21.1; NC] 4 (20.0)	1.83 [0.58; 5.74]; 0.303[c]
Total[d]					2.68 [1.14; 6.32]; 0.024

Table 5: Results (morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine versus placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10 (multipage table)

Outcome category Outcome Study	Pembrolizumab + cisplatin + 5-FU or capecitabine		Placebo + cisplatin + 5-FU or capecitabine		Pembrolizumab + cisplatin + 5-FU or capecitabine vs. placebo + cisplatin + 5-FU or capecitabine
	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. Time to first deterioration; a score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
b. HR and CI from Cox proportional hazards model, stratified by region (Asia vs. rest of the world) and ECOG (0 vs. 1) with associated p-value from 2-sided Wald test.
c. HR and CI from Cox proportional hazards model, nonstratified with associated p-value from 2-sided Wald test.
d. IQWiG calculation; metaanalysis with fixed effect (method with inverse variance).
e. The KEYNOTE 590 study used an EORTC-generated Japanese version of the EORTC QLQ-OES18 questionnaire which was, in part, incorrectly translated. This resulted, firstly, in 3 items of the dysphagia scale being rated by patients in an opposite manner. Secondly, the reflux scale's item of heartburn was incorrectly translated into Japanese. After consultation with the EORTC, the company reanalysed the questionnaire. For the reflux symptom scale, the item of heartburn was treated as missing in the analysis. For the dysphagia symptom scale, the analysis of the 3 items in question was corrected. Overall, this approach was deemed acceptable.
f. Time to first deterioration; a score decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).

5-FU: 5-fluorouracil; AE: adverse event; CI: confidence interval; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-OES18: Quality of Life Questionnaire – Oesophageal Cancer Module 18; RCT: randomized controlled trial

On the basis of the available information, at most indications, e.g. of an added benefit, can be determined for all outcomes due to high risk of bias of results or due to limited certainty of results (see report A21-144 [1]). For the symptoms outcomes, measured with EORTC QLQ-OES18, which were surveyed only in the KEYNOTE 590 study, at most hints, e.g. of added benefit, can be derived to the high outcome-specific risk of bias.

Morbidity

Symptoms

The outcomes on symptoms were recorded with the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-OES18. Time to first deterioration by ≥ 10 points (scale range 0 to 100) was analysed.

EORTC QLQ-C30: fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea

No statistically significant differences between treatment arms were shown for the outcomes of fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, or diarrhoea, surveyed with the EORTC QLQ-C30. This results in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine; an added benefit is therefore not proven.

EORTC QLQ-OES18: eating, pain, swallowing saliva, choking, taste, cough, speech, and dysphagia

No statistically significant difference between treatment arms was found for the outcomes of eating, pain, swallowing saliva, choking, taste, cough, speech, and dysphagia, which were surveyed using the EORTC QLQ-OES18. This results in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine; an added benefit is therefore not proven.

EORTC QLQ-OES18: reflux

A statistically significant difference in favour of pembrolizumab + cisplatin + 5-FU/capecitabine was found in comparison with placebo + cisplatin + 5-FU/capecitabine for the outcome of reflux, which was surveyed with the EORTC QLQ-OES18. For an outcome of the category of non-serious/non-severe symptoms / late complications, the present effect is no more than marginal. This resulted in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine; an added benefit is therefore not proven.

EORTC QLQ-OES18: dry mouth

A statistically significant difference to the disadvantage of pembrolizumab + cisplatin + 5-FU/capecitabine was found in comparison with placebo + cisplatin + 5-FU/capecitabine for the outcome of dry mouth, which was surveyed with the EORTC QLQ-OES18. In addition, there is an effect modification by the attribute of sex (male versus female). For women, this resulted in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine; an added benefit is therefore not proven for women. For men, this resulted in a hint of minor benefit of pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine (see Section 2.4.3).

Health-related quality of life

Health-related quality of life outcomes were surveyed using the disease-specific instrument of EORTC QLQ-C30. Time to first deterioration by ≥ 10 points (scale range 0 to 100) was analysed for the individual functional scales.

EORTC QLQ-C30: global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning

No statistically significant difference between treatment arms was found for the outcomes of global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning, surveyed with the EORTC QLQ-C30. This results in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine; an added benefit is therefore not proven.

Side effects

According to the study protocol, progression events of the underlying oncological disease were not recorded as AEs. The MedDRA terms "progression of neoplasms", "progression of malignant neoplasms" and "disease progression" were excluded from the AE recording. For the outcome of discontinuation due to AEs, time to discontinuation of at least 1 drug component was analysed.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of pembrolizumab + cisplatin + 5-FU/capecitabine was found for the outcome of discontinuation due to AEs. This results in a hint of greater harm from pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine.

2.4.3 Subgroups and other effect modifiers

For the present assessment, the following subgroup characteristics are relevant (see report A21-144 [1]):

- sex (male versus female)
- age (< 65 years versus ≥ 65 years)
- disease stage (locally advanced vs. metastatic)

The company's subgroup analyses were conducted post hoc for the patient-relevant outcomes of the morbidity, health-related quality of life, and side effects categories.

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

For each of the analyses on the symptoms and health-related quality of life outcomes and those of the side effects category, the company conducted interaction tests separately for each study. The company performed no joint consideration of the subgroup results of both studies. Hence, the present benefit assessment checked whether a significant effect modification at the level of 0.2 was present in both studies. If this was the case, an interaction test was conducted at the meta-level of both studies using Q test. Hereinafter, 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.

Table 6 shows the subgroup results found using the methods described in dossier assessment A21-144 on the basis of the subsequently analysed results.

Table 6: Subgroups (morbidity, time to event) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine versus placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

Outcome Characteristic Study Subgroup	Pembrolizumab + cisplatin + 5-FU/capecitabine		Placebo + cisplatin + 5-FU/capecitabine		Pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine	
	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
Morbidity						
Symptoms (EORTC QLQ–OES18 – dry mouth)[b]						
Sex						
KEYNOTE 590						
Women	4	NR [2.6; NC] 1 (25.0)	9	1.5 [0.7; 2.8] 7 (77.8)	0.19 [0.02; 1.58]	0.125
Men	37	1.5 [1.0; 3.5] 27 (73.0)	38	5.6 [1.6; NC] 16 (42.1)	2.36 [1.26; 4.44]	0.007
Total					Interaction:	0.003[c]
KEYNOTE 062	Instrument not surveyed					

a. HR and CI from Cox proportional hazards model, nonstratified with associated p-value from 2-sided Wald test.
b. Time to first deterioration; a score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
c. Cox proportional hazards model with treatment and subgroup as covariates and interaction between treatment and subgroup (p-value based on likelihood ratio test).

5-FU: 5-fluorouracil; CI: confidence interval; CPS: Combined Positive Score; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; QLQ-OES18 : Quality of Life Questionnaire – Oesophageal Cancer Module 18; RCT: randomized controlled trial

Morbidity

Symptoms

EORTC QLQ-OES18: dry mouth

There was an effect modification by the characteristic of sex for this outcome surveyed with the EORTC QLQ-C30. For women, there was no statistically significant difference between

treatment groups. For women, this results in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine; an added benefit is therefore not proven for women. For men, there is a statistically significant difference to the disadvantage of pembrolizumab + cisplatin + 5-FU/capecitabine. This results in a hint of minor benefit of pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine for men.

2.4.4 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Sections 2.4.2 and 2.4.3 (see Table 7).

Reflux, dry mouth (EORTC QLQ-OES18)

Insufficient information is available on the classification of the severity category for the outcomes of reflux and dry mouth, surveyed with the EORTC QLQ-OES18 symptom scales. Therefore, each of these outcomes was assigned to the outcome category of non-serious/non-severe symptoms.

Discontinuation due to AEs

Insufficient information is available for determining whether the outcome of discontinuation due to AEs is to be allocated to the outcome category of serious/severe side effects or non-serious/non-severe side effects. For the relevant subpopulation, no information is available on the severities of the individual AEs on which the discontinuation due to AEs was based. Therefore, the outcome was assigned to the outcome category of non-serious/non-severe side effects.

Table 7: Extent of added benefit at outcome level: pembrolizumab + cisplatin + 5-FU/capecitabine versus cisplatin + 5-FU/capecitabine (patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + cisplatin + 5-FU vs. cisplatin + 5-FU** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	11.8−12.1 vs. 10.4−10.7 months[c] HR: 0.87 [0.60; 1.27]; p = 0.476	Lesser/added benefit not proven
Morbidity		
Symptoms (EORTC QLQ-C30 – time to first deterioration by ≥ 10 points)		
Fatigue	**1.4−1.6 vs. 0.8−2.0 months[c]** **HR: 0.86 [0.58; 1.29]; p = 0.475**	**Lesser/added benefit not proven**
Nausea and vomiting	**1.9−2.1 vs. 1.4−2.3 months[c]** **HR: 0.75 [0.50; 1.14]; p = 0.174**	**Lesser/added benefit not proven**
Pain	**3.3−6.5 vs. 3.3−4.1 months[c]** **HR: 0.98 [0.62; 1.55]; p = 0.929**	**Lesser/added benefit not proven**
Dyspnoea	**8.3−8.6 vs. 2.6−5.1 months[c]** **HR: 0.71 [0.43; 1.16]; p = 0.169**	**Lesser/added benefit not proven**
Insomnia	**NR vs. 4.6–6.0 months[c]** **HR: 0.65 [0.38; 1.09]; p = 0.101**	**Lesser/added benefit not proven**
Appetite loss	**2.7−5.8 vs. 3.0−3.4 months[c]** **HR: 0.76 [0.49; 1.18]; p = 0.226**	**Lesser/added benefit not proven**
Constipation	**3.0 vs. 3.2−3.5 months[c]** **HR: 0.90 [0.57; 1.42]; p = 0.651**	**Lesser/added benefit not proven**
Diarrhoea	**3.0–4.4 months versus 4.1 months – NR[c]** **HR: 1.12 [0.70; 1.82]; p = 0.631**	**Lesser/added benefit not proven**
Symptoms (EORTC QLQ-OES18 – time to first deterioration by ≥ 10 points)		
Food	**5.3 vs. 4.4 months** **HR: 0.88 [0.48; 1.60]; p = 0.669**	**Lesser/added benefit not proven**
Reflux	**12.7 vs. 2.6 months** **HR: 0.50 [0.27; 0.92]; p = 0.026**	**Outcome category: non-serious/non-severe symptoms / late complications** **$0.90 \leq CI_u < 1.00$** **Lesser/added benefit not proven[d]**
Pain	**3.9 vs. 4.4 months** **HR: 0.94 [0.53; 1.66]; p = 0.827**	**Lesser/added benefit not proven**
Swallowing saliva	**8.3 vs. 5.1 months** **HR: 0.93 [0.50; 1.75]; p = 0.823**	**Lesser/added benefit not proven**
Choking	**5.6 vs. 12.2 months** **HR: 1.71 [0.86; 3.41]; p = 0.124**	**Lesser/added benefit not proven**

Table 7: Extent of added benefit at outcome level: pembrolizumab + cisplatin + 5-FU/capecitabine versus cisplatin + 5-FU/capecitabine (patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + cisplatin + 5-FU vs. cisplatin + 5-FU** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Dry mouth **Sex**		
Women	**NR vs. 1.5 months** **HR: 0.19 [0.02; 1.58]** **p = 0.125**	**Lesser/added benefit not proven**
Men	**1.5 vs. 5.6 months** **HR: 2.36 [1.26; 4.44]** **HR: 0.42 [0.23; 0.79]**[c] **p = 0.007** **Probability: hint**	**Outcome category: non-serious/non-severe symptoms / late complications** **CI_u < 0.80** **Lesser benefit; extent: considerable**
Taste	**1.4 vs. 2.0 months** **HR: 0.87 [0.52; 1.44]; p = 0.576**	**Lesser/added benefit not proven**
Cough	**4.7 vs. 7.7 months** **HR: 1.32 [0.70; 2.52]; p = 0.393**	**Lesser/added benefit not proven**
Speech	**24.3 months vs. NA** **HR: 1.33 [0.62; 2.84]; p = 0.461**	**Lesser/added benefit not proven**
Dysphagia	**3.7 vs. 3.5 months** **HR: 0.98 [0.55; 1.76]; p = 0.942**	**Lesser/added benefit not proven**
Health status (EQ-5D VAS)		
EQ-5D VAS	No usable data[f]	Lesser/added benefit not proven
Health-related quality of life		
Quality of life (EORTC QLQ-C30 - time to first deterioration by ≥ 10 points)		
Global health status	**3.7−8.3 vs. 2.4−5.6 months**[c] **HR: 0.89 [0.56; 1.41]; p = 0.616**	**Lesser/added benefit not proven**
Physical functioning	**4.1−4.2 vs. 1.4−3.7 months**[c] **HR: 0.88 [0.58; 1.35]; p = 0.566**	**Lesser/added benefit not proven**
Role functioning	**2.1−3.0 vs. 2.2−2.8 months**[c] **HR: 1.07 [0.70; 1.63]; p = 0.757**	**Lesser/added benefit not proven**
Emotional functioning	**3.3−5.9 vs. 6.1−8.0 months**[c] **HR: 1.30 [0.79; 2.12]; p = 0.304**	**Lesser/added benefit not proven**
Cognitive functioning	**2.8−3.4 vs. 1.5−3.7 months**[c] **HR: 0.87 [0.56; 1.35]; p = 0.535**	**Lesser/added benefit not proven**
Social functioning	**3.2−4.4 vs. 1.9−3.7 months**[c] **HR: 0.80 [0.52; 1.24]; p = 0.322**	**Lesser/added benefit not proven**

Table 7: Extent of added benefit at outcome level: pembrolizumab + cisplatin + 5-FU/capecitabine versus cisplatin + 5-FU/capecitabine (patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + cisplatin + 5-FU vs. cisplatin + 5-FU** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	11.6−15.6 vs. 31.1−36.7 months[c] HR: 1.42 [0.92; 2.20]; p = 0.112	Greater/lesser harm not proven
Severe AEs	4.7−5.4 vs. 5.6−6.3 months[c] HR: 1.19 [0.83; 1.72]; p = 0.344	Greater/lesser harm not proven
Discontinuation due to AEs	**NR vs. NR** **HR: 2.68 [1.14; 6.32]** **HR: 0.37 [0.16; 0.88][e];** **p = 0.024** **Probability: indication**	**Outcome category: non-serious/non-severe side effects** **$0.80 \leq CI_u < 0.90$** **Greater harm; extent: minor**
Immune-related SAEs	NA vs. NA HR: 2.22 [0.43; 11.51]; p = 0.343	Greater/lesser harm not proven
Immune-related severe AEs	NA vs. NA HR: 2.00 [0.38; 10.50]; p = 0.411	Greater/lesser harm not proven
Endocrine disorders (AEs)	16.7–19.0% vs. 0–3.8%[c] RR: 5.65 [1.48; 21.58] RR: 0.18 [0.05; 0.68][e]; p = 0.011 Probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: “considerable”

Results printed in **bold** result from the data additionally analysed.
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. Minimum and maximum proportions of events or months to event in each treatment arm in the studies included.
d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
e. IQWiG calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
f. For reasons, see report A21-144 [1].

5-FU: 5-fluorouracil; AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; EORTC: European Organization for Research and Treatment of Cancer; HR: hazard ratio; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-OES18: Quality of Life Questionnaire – Oesophageal Cancer Module 18; VAS: visual analogue scale

2.4.5 Overall conclusion on added benefit

Table 8 summarizes the results of the benefit assessment for commission A21-144 and the present addendum A22-37, both of which were used to inform the overall conclusion on the extent of added benefit.

Table 8: Favourable and unfavourable effects from the assessment of pembrolizumab + cisplatin + 5-FU/capecitabine versus cisplatin + 5-FU/capecitabine (patients with squamous cell carcinoma of the oesophagus or gastrooesophageal junction and CPS ≥ 10)

Favourable effects	Unfavourable effects
▪ –	**Non-serious/non-severe symptoms / late complications** ▪ **Dry mouth:** ▫ **Sex (men): hint of lesser benefit – extent: considerable**
▪ –	Non-serious/non-severe side effects ▪ **Discontinuation due to AEs: indication of greater harm – extent: minor** ▪ Endocrine disorders (AEs): indication of greater harm – extent: "considerable"
Results printed in **bold** result from the data additionally analysed. 5-FU: 5-fluorouracil; AEs: adverse events; CPS: Combined Positive Score	

For patients with adenocarcinoma of the oesophagus or of the gastrooesophageal junction and CPS ≥ 10, taking into account the subsequently assessed results in combination with the effects presented in dossier assessment A21-144 results in 2 additional unfavourable effects: (1) a hint of lesser benefit of considerable extent for the subgroup of male patients in the outcome category of morbidity and (2) a hint of greater harm of minor extent in the outcome of discontinuation due to AEs.

The observed effects do not call into question the overall conclusion on added benefit drawn in dossier assessment A21-144 for patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10.

All things considered, there is therefore no change regarding the respective overall conclusion on the added benefit of pembrolizumab versus the ACT.

2.5 Summary

The data presented in this addendum do not change the conclusion drawn in dossier assessment A21-144 on the added benefit of pembrolizumab.

Table 9 below shows the result of the benefit assessment of pembrolizumab taking into account dossier assessment A21-144 and the present addendum.

Table 9: Pembrolizumab in combination with platinum-based and fluoropyrimidine-based chemotherapy – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
A	Adult patients with locally advanced or metastatic squamous cell carcinoma of the oesophagus which cannot be treated curatively[b] and whose tumours express PD-L1 (CPS ≥ 10); first-line treatment	Cisplatin in combination with 5-FU[c]	Hint of major added benefit[d]
B1	Adult patients with locally advanced or metastatic HER2-negative adenocarcinoma of the oesophagus or of the gastroesophageal junction that cannot be treated curatively[b] and whose tumours express PD-L1 (CPS ≥ 10); first-line treatment	Treatment of physician's choice[e]	Added benefit not proven[d,f]
B2	Adult patients with locally advanced or metastatic HER2-positive adenocarcinoma of the oesophagus that cannot be treated curatively[b] and whose tumours express PD-L1 (CPS ≥ 10); first-line treatment	HER2-targeted therapy according to physician's choice[g]	Added benefit not proven[d]

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, it is assumed for the present therapeutic indication that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer.
c. According to the G-BA, it is assumed that cisplatin-containing chemotherapy is suitable for the patients.
d. The studies KEYNOTE 590 and KEYNOTE 062 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.
e. Guidelines mention several platinum- and fluoropyrimidine-based combination chemotherapies: S-1 (tegafur/gimeracil/oteracil) + cisplatin or capecitabine + cisplatin [XP], 5-FU + cisplatin, 5-FU + oxaliplatin + folinic acid [FLO and FOLFOX], capecitabine + oxaliplatin, infusional 5-FU + folinic acid + cisplatin [PLF], epirubicin + cisplatin + capecitabine [ECX], epirubicin + oxaliplatin + capecitabine [EOX], epirubicin + cisplatin + infusional 5-FU [ECF], docetaxel + cisplatin + infusional 5-FU [DCF], 5-FU + oxaliplatin + epirubicin, infusional 5-FU + folinic acid + oxaliplatin + docetaxel [FLOT regimen]. However, only the drugs 5-FU, docetaxel as well as cisplatin are approved in the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those recommended in the guidelines. In the context of treatment of physician's choice, the treatment options cited here are considered to be suitable comparators. The added benefit can be assessed versus one of the cited treatment options within the framework of a single-comparator study. The choice of the used comparator has to be justified in the dossier.
f. Data are only available for patients for whom cisplatin + 5-FU or cisplatin + capecitabine is a suitable treatment option according to physician's choice. No data are available for patients for whom another treatment option is suitable according to physician's choice.
g. Guidelines recommend the combination therapy of the anti-HER2 antibody trastuzumab with cisplatin and fluoropyrimidines (5-FU or capecitabine), but this is not (explicitly) approved for the present therapeutic indication. Only the drugs 5-FU as well as cisplatin are approved in the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those recommended in the guidelines. Within the framework of the HER2-targeted therapy according to physician's choice, trastuzumab in combination with cisplatin and capecitabine or 5-FU is considered to be a suitable comparator. The added benefit can be assessed versus one of the cited treatment options within the framework of a single-comparator study. The choice of the used comparator has to be justified in the dossier.

5-FU: 5-fluorouracil; ACT: appropriate comparator therapy; CPS: Combined Positive Score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Pembrolizumab (Karzinom des Ösophagus oder gastroösophagealen Übergangs) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2022 [Accessed: 08.04.2022]. URL: https://www.iqwig.de/download/a21-144_pembrolizumab_nutzenbewertung-35a-sgb-v_v1-1.pdf.

2. MSD Sharp & Dohme. Stellungnahme zum IQWiG-Bericht Nr. 1292: Pembrolizumab (Karzinom des Ösophagus oder gastroösophagealen Übergangs) – Nutzenbewertung gemäß § 35a SGB V. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/756/#beschluesse in the document "Zusammenfassende Dokumentation"].

Appendix A Results on discontinuation due to AEs

The tables below provide a complete presentation of all events related to System Organ Classes (SOCs) and Preferred Terms (PTs) according to the MedDRA for the outcome of discontinuation due to AEs.

Table 10: Discontinuation due to AEs – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU versus cisplatin + 5-FU, subpopulation with squamous cell carcinoma CPS ≥ 10 (multipage table)

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Pembrolizumab + cisplatin + 5-FU N = 143**	**Cisplatin + 5-FU N = 140**
KEYNOTE 590		
Overall rate of discontinuations due to AEs	36 (25.2)	37 (26.4)
Blood and lymphatic system disorders	4 (2.8)	3 (2.1)
Anaemia	1 (0.7)	0 (0)
Febrile neutropenia	3 (2.1)	2 (1.4)
Neutropenia	0 (0)	1 (0.7)
Cardiac disorders	2 (1.4)	3 (2.1)
Cardiac arrest	0 (0)	2 (1.4)
Cardiac failure	2 (1.4)	1 (0.7)
Congenital, familial, and genetic disorders	1 (0.7)	0 (0)
Oesophagotracheal fistula	1 (0.7)	0 (0)
Ear and labyrinth disorders	2 (1.4)	2 (1.4)
Eustachian tube disorder	0 (0)	1 (0.7)
Hypoacusis	0 (0)	1 (0.7)
Tinnitus	2 (1.4)	1 (0.7)
Vertigo	0 (0)	1 (0.7)
Gastrointestinal disorders	6 (4.2)	4 (2.9)
Enterocolitis	1 (0.7)	0 (0)
Haematemesis	1 (0.7)	0 (0)
Nausea	2 (1.4)	1 (0.7)
Oesophageal fistula	1 (0.7)	0 (0)
Upper gastrointestinal haemorrhage	1 (0.7)	2 (1.4)
Vomiting	0 (0)	1 (0.7)

Table 10: Discontinuation due to AEs – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU versus cisplatin + 5-FU, subpopulation with squamous cell carcinoma CPS ≥ 10 (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Pembrolizumab + cisplatin + 5-FU** **N = 143**	**Cisplatin + 5-FU** **N = 140**
General disorders and administration site conditions	4 (2.8)	5 (3.6)
Asthenia	0 (0)	1 (0.7)
Death	0 (0)	3 (2.1)
Fatigue	2 (1.4)	0 (0)
Malaise	1 (0.7)	0 (0)
Mucosal inflammation	1 (0.7)	0 (0)
Multiorgan failure	0 (0)	1 (0.7)
Hepatobiliary disorders	1 (0.7)	0 (0)
Autoimmune hepatitis	1 (0.7)	0 (0)
Infections and infestations	3 (2.1)	5 (3.6)
Clostridium difficile colitis	0 (0)	1 (0.7)
Extradural abscess	0 (0)	1 (0.7)
Pneumonia	1 (0.7)	3 (2.1)
Pulmonary sepsis	2 (1.4)	0 (0)
Injury, poisoning, and procedural complications	1 (0.7)	0 (0)
Infusion-related reaction	1 (0.7)	0 (0)
Investigations	5 (3.5)	6 (4.3)
Blood creatinine increased	4 (2.8)	6 (4.3)
Platelet count decreased	1 (0.7)	0 (0)
White blood cell count decreased	1 (0.7)	0 (0)
Metabolism and nutrition disorders	3 (2.1)	1 (0.7)
Cachexia	1 (0.7)	0 (0)
Decreased appetite	1 (0.7)	0 (0)
Dehydration	0 (0)	1 (0.7)
Hypochloraemia	1 (0.7)	0 (0)
Hypokalaemia	1 (0.7)	0 (0)
Hyponatraemia	1 (0.7)	0 (0)
Musculoskeletal and connective tissue disorders	0 (0)	1 (0.7)
Hypercreatinaemia	0 (0)	1 (0.7)
Nervous system disorders	4 (2.8)	1 (0.7)
Ischaemic stroke	0 (0)	1 (0.7)
Dizziness	1 (0.7)	0 (0)
Encephalopathy	1 (0.7)	0 (0)
Peripheral sensory neuropathy	2 (1.4)	0 (0)

Table 10: Discontinuation due to AEs – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU versus cisplatin + 5-FU, subpopulation with squamous cell carcinoma CPS ≥ 10 (multipage table)

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Pembrolizumab + cisplatin + 5-FU N = 143**	**Cisplatin + 5-FU N = 140**
Renal and urinary disorders	2 (1.4)	2 (1.4)
Acute kidney injury	1 (0.7)	1 (0.7)
Proteinuria	0 (0)	1 (0.7)
Renal impairment	1 (0.7)	0 (0)
Respiratory, thoracic and mediastinal disorders	7 (4.9)	3 (2.1)
Aspiration	0 (0)	1 (0.7)
Interstitial lung disease	1 (0.7)	1 (0.7)
Aspiration pneumonia	2 (1.4)	1 (0.7)
Pneumonitis	3 (2.1)	0 (0)
Pulmonary embolism	1 (0.7)	0 (0)
Skin and subcutaneous tissue disorders	1 (0.7)	1 (0.7)
Palmar-plantar erythrodysaesthesia syndrome	1 (0.7)	1 (0.7)
Vascular disorders	1 (0.7)	3 (2.1)
Aortic thrombosis	0 (0)	1 (0.7)
Dry gangrene	0 (0)	1 (0.7)
Subclavian vein thrombosis	1 (0.7)	0 (0)
Vasculitis	0 (0)	1 (0.7)

a. MedDRA version 23; SOCs and PTs taken from Module 4.

5-FU: 5-fluorouracil; AE: adverse event; CPS: Combined Positive Score; 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 11: Discontinuation due to AEs – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU versus cisplatin + 5-FU, subpopulation with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10, KEYNOTE 590 study

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Pembrolizumab + cisplatin + 5-FU** **N = 42**	**Cisplatin + 5-FU** **N = 53**
KEYNOTE 590		
Overall rate of discontinuations due to AEs	10 (23.8)	3 (5.7)
Cardiac disorders	2 (4.8)	0 (0)
Acute coronary syndrome	1 (2.4)	0 (0)
Angina, unstable	1 (2.4)	0 (0)
Ear and labyrinth disorders	1 (2.4)	0 (0)
Tinnitus	1 (2.4)	0 (0)
Gastrointestinal disorders	1 (2.4)	1 (1.9)
Duodenitis	1 (2.4)	0 (0)
Pneumatosis intestinalis	0 (0)	1 (1.9)
Hepatobiliary disorders	1 (2.4)	0 (0)
Hepatitis	1 (2.4)	0 (0)
Infections and infestations	0 (0)	2 (3.8)
Pneumonia	0 (0)	1 (1.9)
Sepsis	0 (0)	1 (1.9)
Investigations	3 (7.1)	0 (0)
Alanine aminotransferase increased	1 (2.4)	0 (0)
Aspartate aminotransferase increased	1 (2.4)	0 (0)
Blood creatinine increased	2 (4.8)	0 (0)
Renal and urinary disorders	1 (2.4)	0 (0)
Acute kidney injury	1 (2.4)	0 (0)
Respiratory, thoracic and mediastinal disorders	1 (2.4)	0 (0)
Pneumonitis	1 (2.4)	0 (0)

a. MedDRA version 23; SOCs and PTs taken from Module 4.

5-FU: 5-fluorouracil; AE: adverse event; CPS: Combined Positive Score; 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 12: Discontinuation due to AEs – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine versus cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the gastrooesophageal junction and CPS ≥ 10, KEYNOTE 062 study

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Pembrolizumab + cisplatin + 5-FU** **N = 30**	**Cisplatin + 5-FU** **N = 20**
KEYNOTE 062		
Overall rate of discontinuations due to AEs	11 (36.7)	4 (20.0)
Blood and lymphatic system disorders	1 (3.3)	2 (10.0)
Febrile neutropenia	0 (0)	1 (5.0)
Neutropenia	1 (3.3)	0 (0)
Thrombocytopenia	0 (0)	1 (5.0)
Cardiac disorders	1 (3.3)	0 (0)
Right ventricular dysfunction	1 (3.3)	0 (0)
Tricuspid valve disease	1 (3.3)	0 (0)
Gastrointestinal disorders	3 (10.0)	1 (5.0)
Diarrhoea	1 (3.3)	0 (0)
Nausea	2 (6.7)	0 (0)
Vomiting	0 (0)	1 (5.0)
General disorders and administration site conditions	2 (6.7)	0 (0)
Death	1 (3.3)	0 (0)
Fatigue	1 (3.3)	0 (0)
Infections and infestations	1 (3.3)	0 (0)
Sepsis	1 (3.3)	0 (0)
Investigations	1 (3.3)	0 (0)
Blood creatinine increased	1 (3.3)	0 (0)
Nervous system disorders	2 (6.7)	0 (0)
Peripheral sensory neuropathy	1 (3.3)	0 (0)
Syncope	1 (3.3)	0 (0)
Renal and urinary disorders	1 (3.3)	1 (5.0)
Acute kidney injury	0 (0)	1 (5.0)
Autoimmune nephritis	1 (3.3)	0 (0)
Respiratory, thoracic and mediastinal disorders	1 (3.3)	0 (0)
Pulmonary hypertension	1 (3.3)	0 (0)

a. MedDRA version 21.2; SOCs and PTs taken from Module 4.

5-FU: 5-fluorouracil; AE: adverse event; CPS: Combined Positive Score; 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 B Figures on outcome analyses

B.1 Research question A

B.1.1 Morbidity

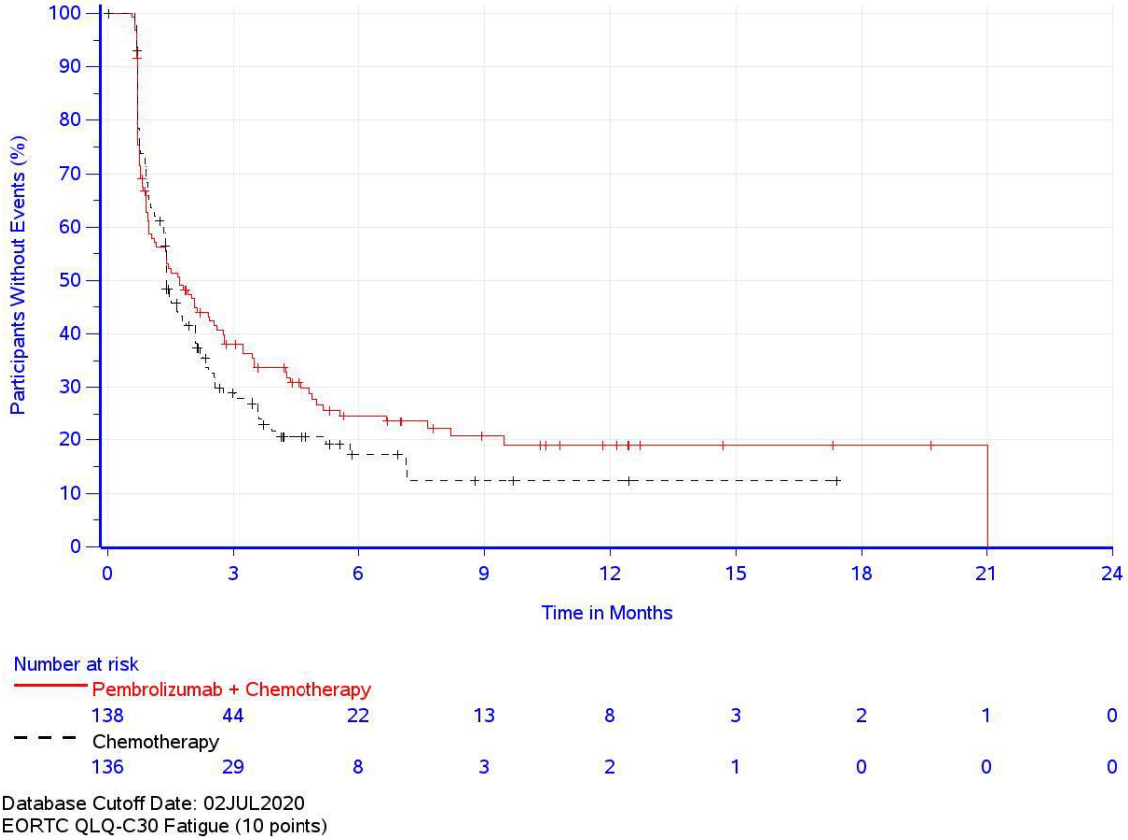

Figure 1: Kaplan-Meier curves for the outcome of fatigue (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

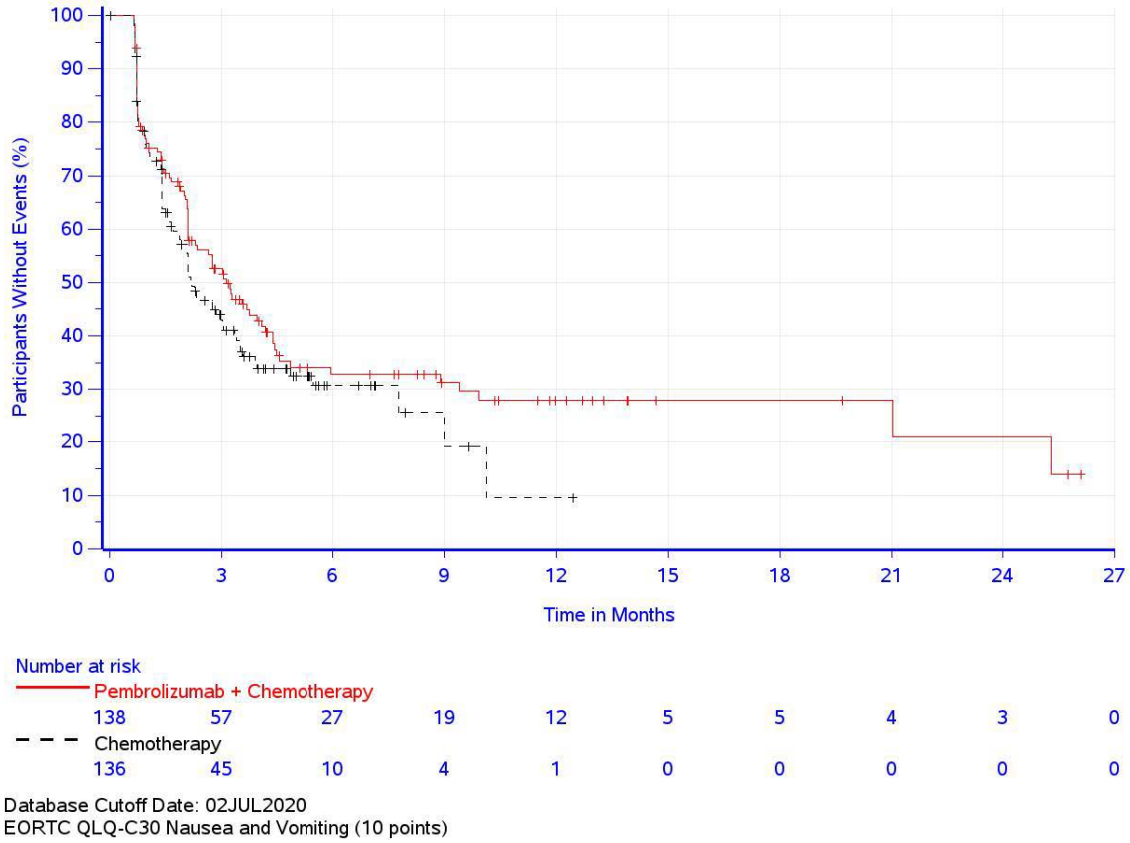

Figure 2: Kaplan-Meier curves for the outcome of nausea and vomiting (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

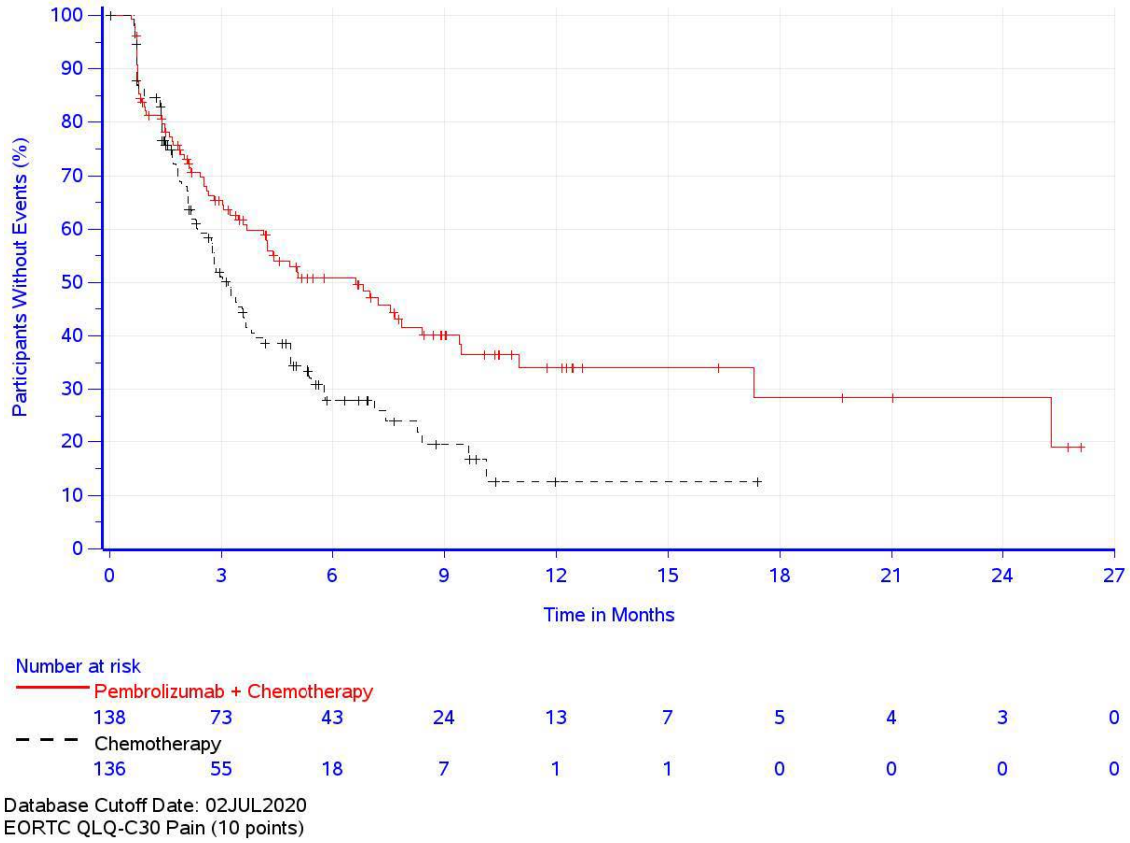

Figure 3: Kaplan-Meier curves for the outcome of pain (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

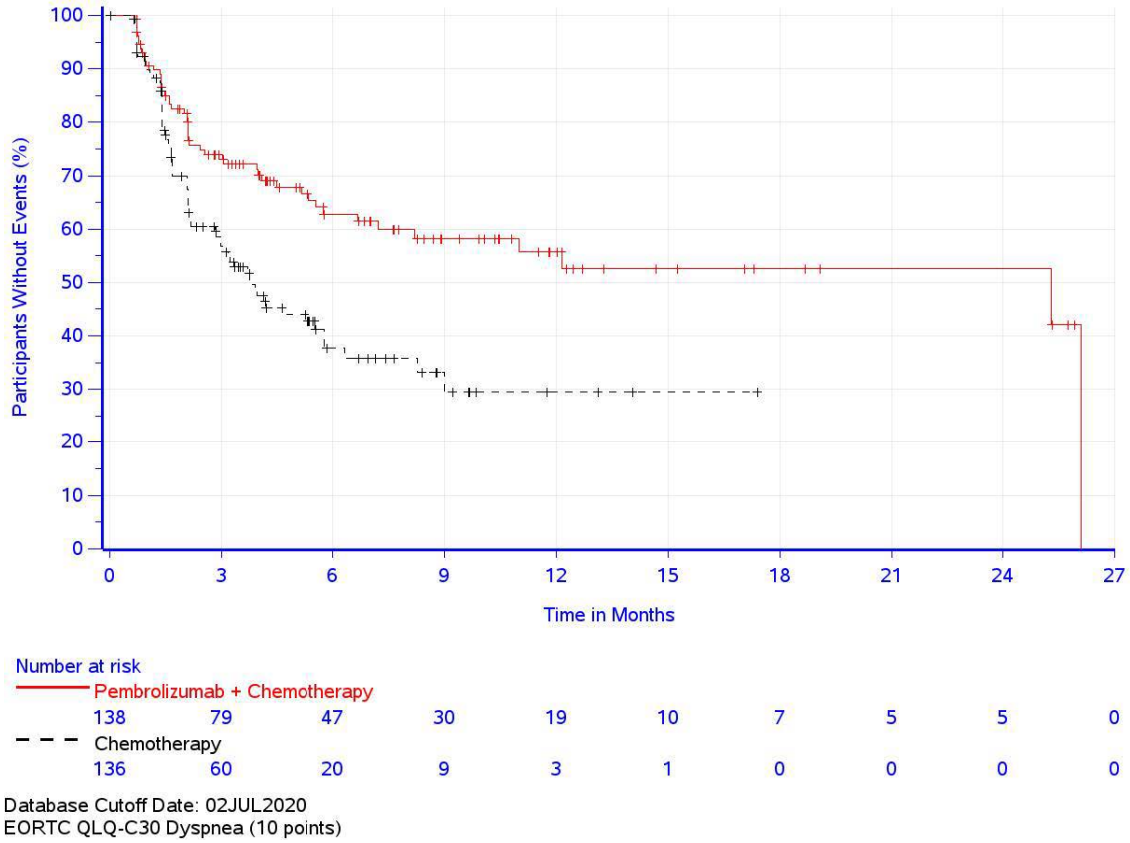

Figure 4: Kaplan-Meier curves for the outcome of dyspnoea (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

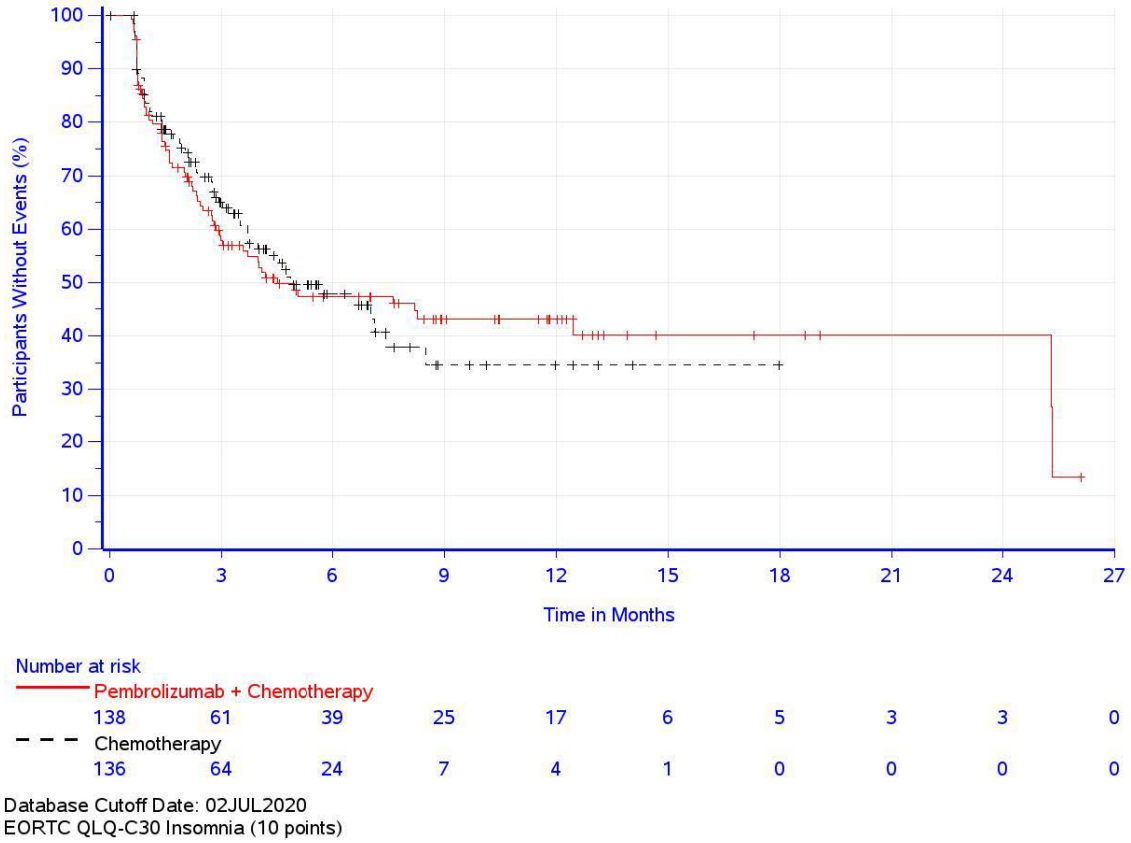

Figure 5: Kaplan-Meier curves for the outcome of insomnia (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

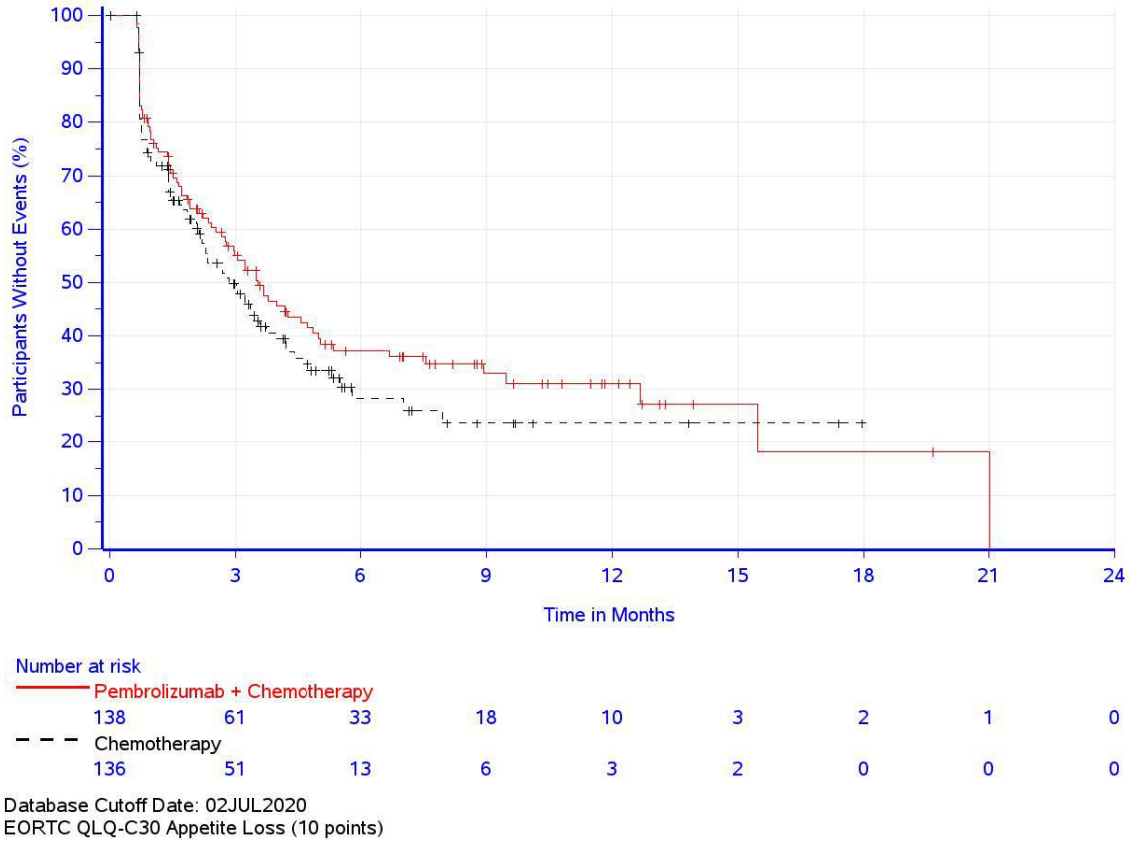

Figure 6: Kaplan-Meier curves for the outcome of appetite loss (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

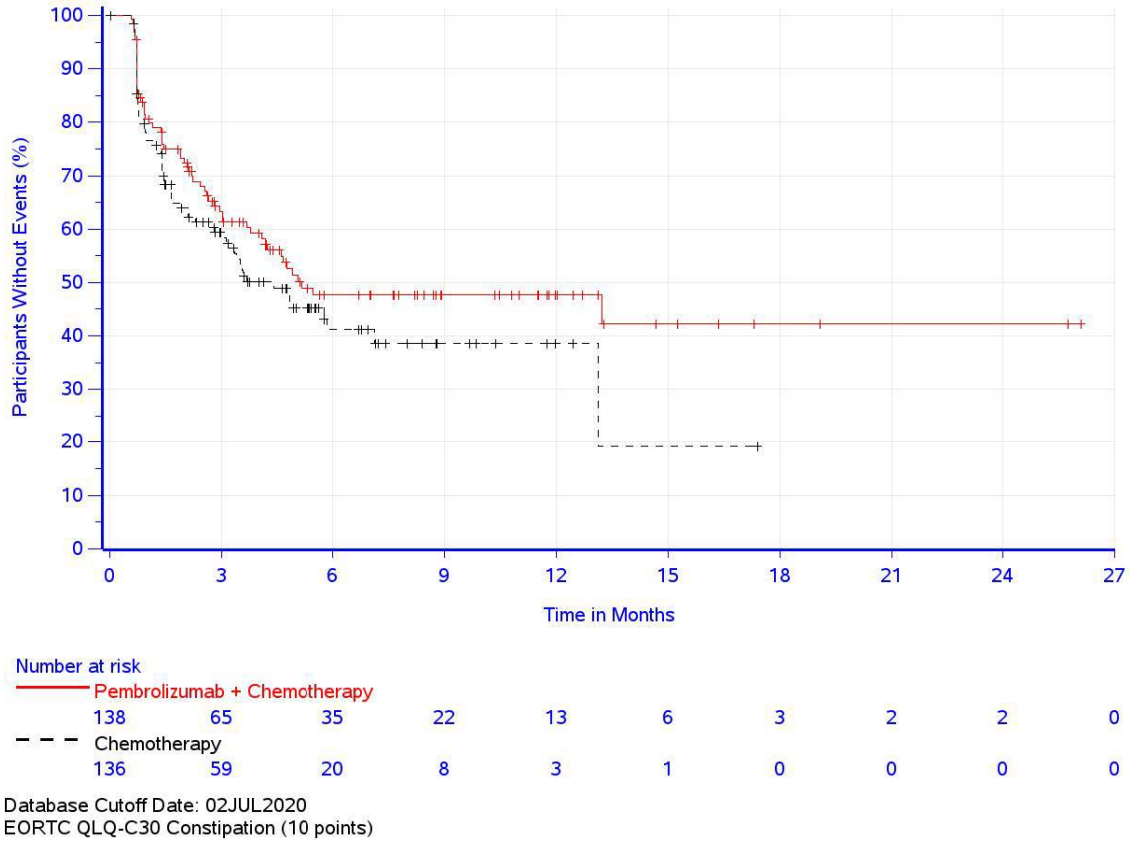

Figure 7: Kaplan-Meier curves for the outcome of constipation (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

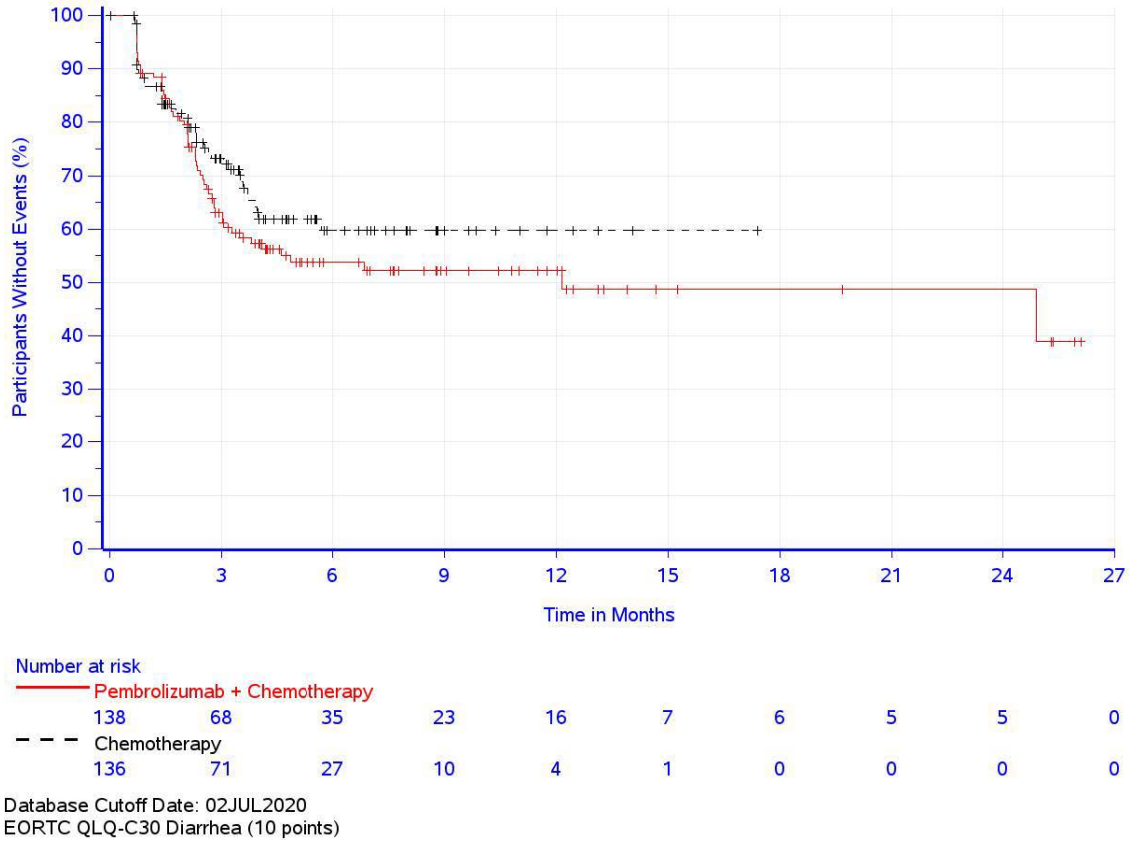

Figure 8: Kaplan-Meier curves for the outcome of diarrhoea (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

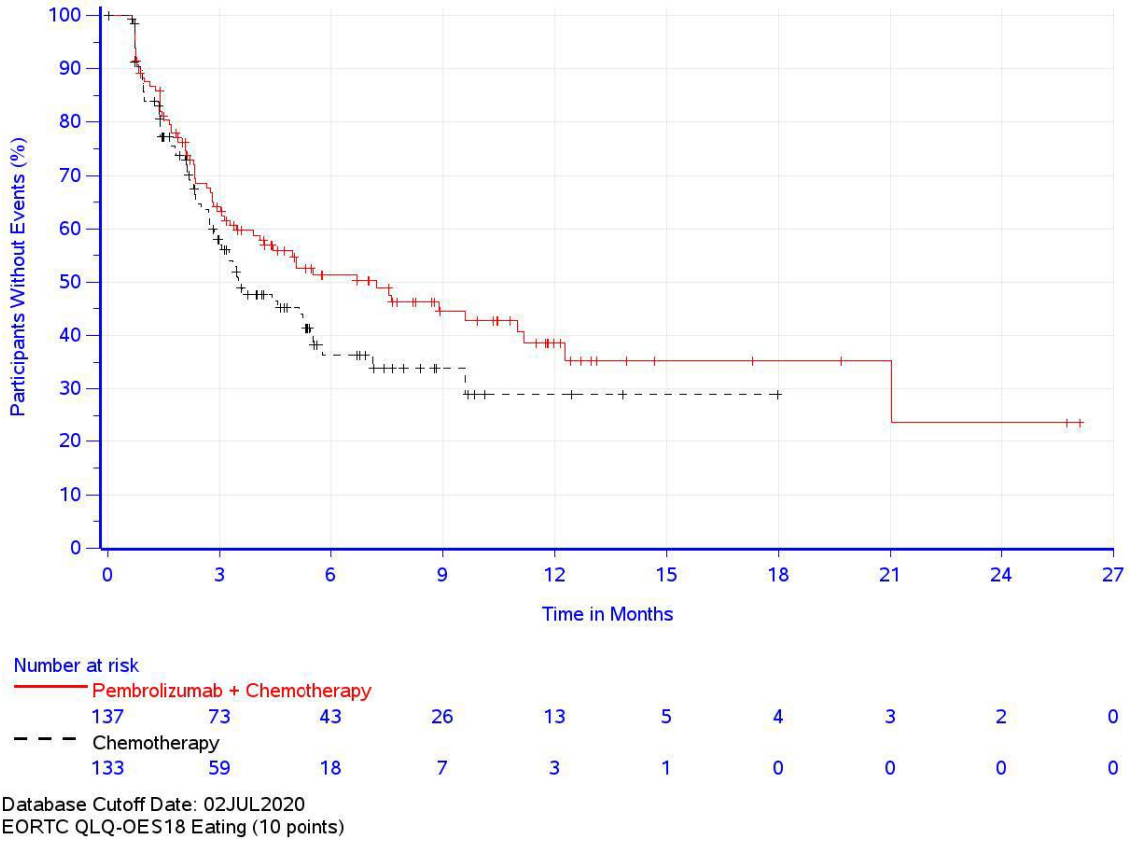

Figure 9: Kaplan-Meier curves for the outcome of eating (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

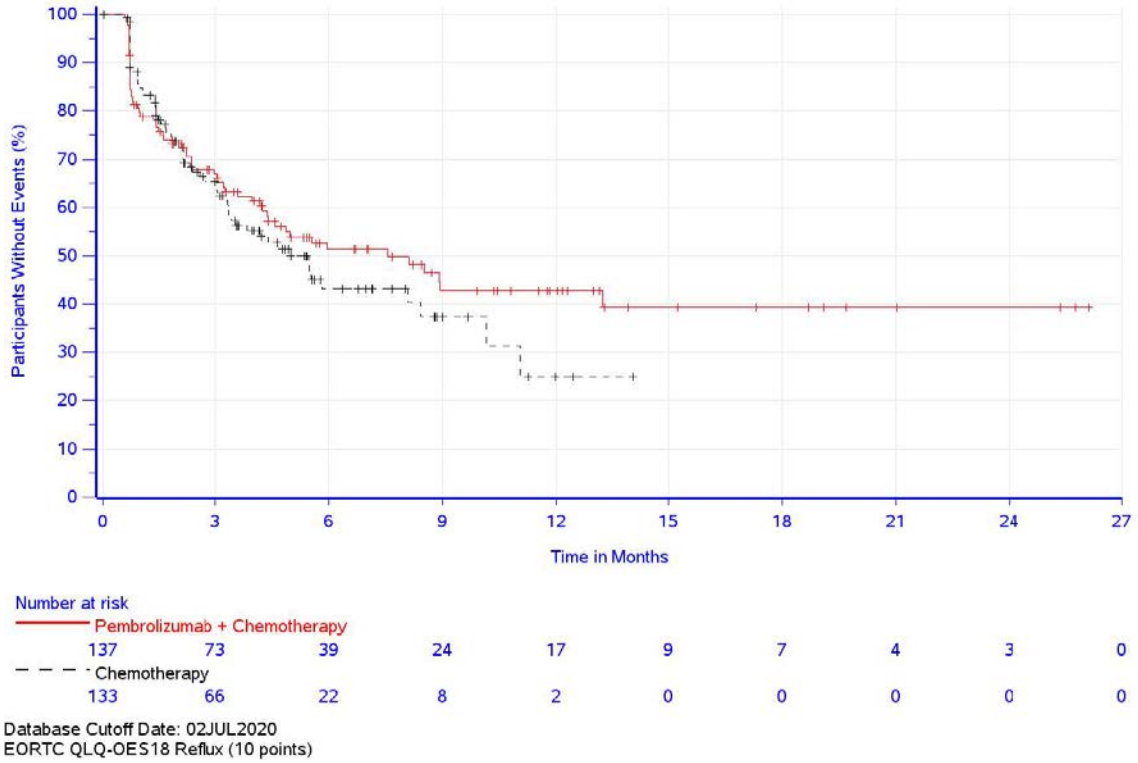

Figure 10: Kaplan-Meier curves for the outcome of reflux (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

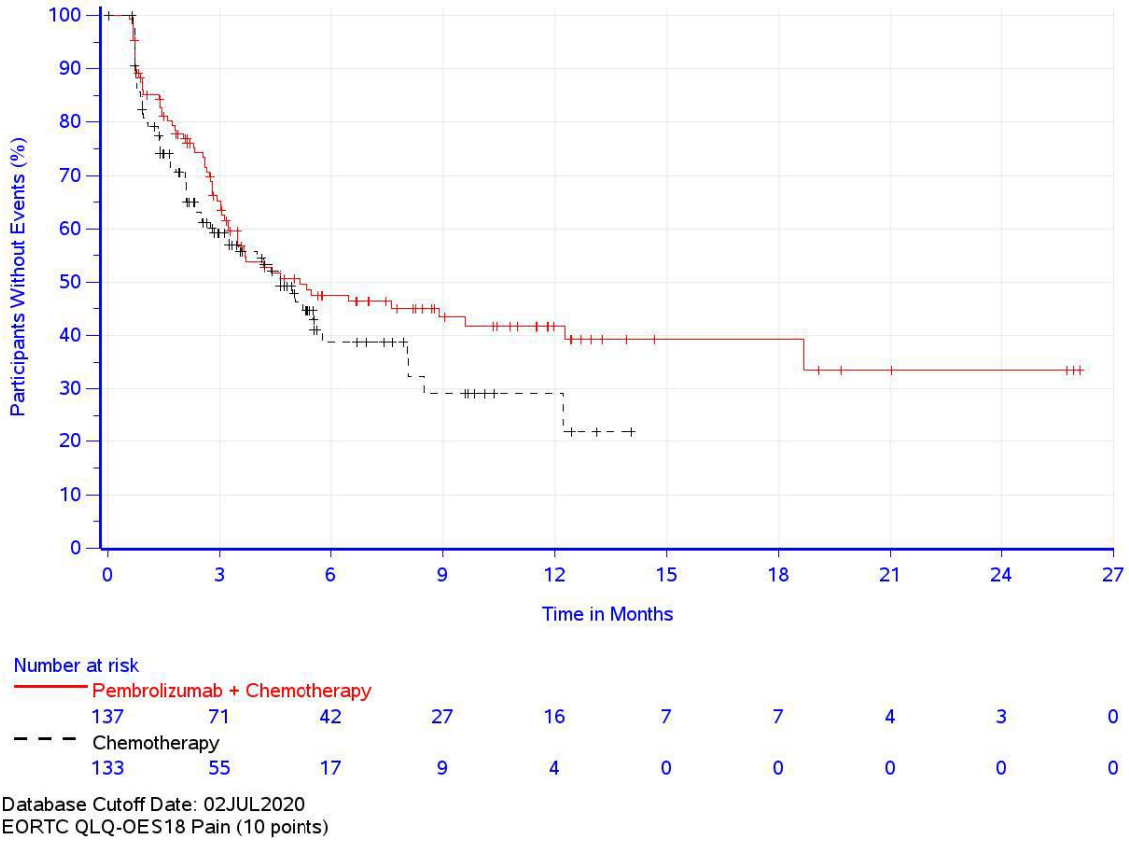

Figure 11: Kaplan-Meier curves for the outcome of pain (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

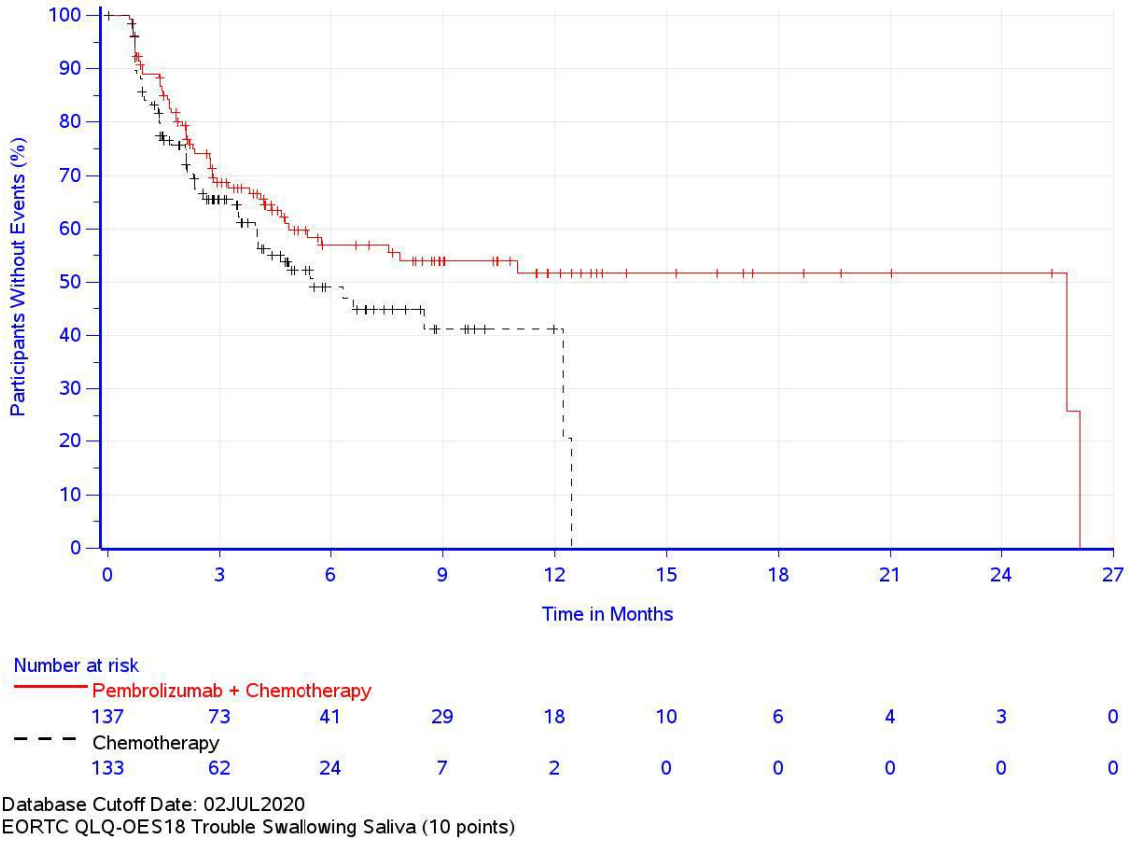

Figure 12: Kaplan-Meier curves for the outcome of swallowing saliva (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

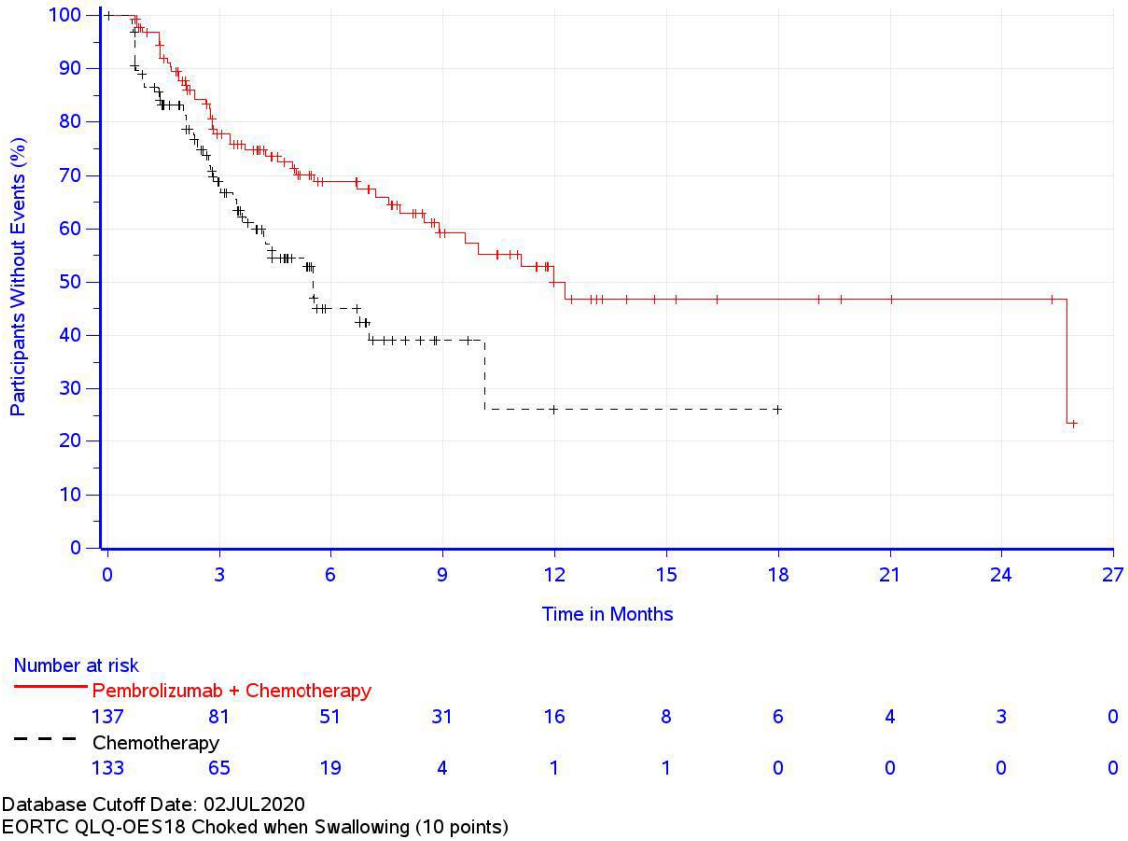

Figure 13: Kaplan-Meier curves for the outcome of choking (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

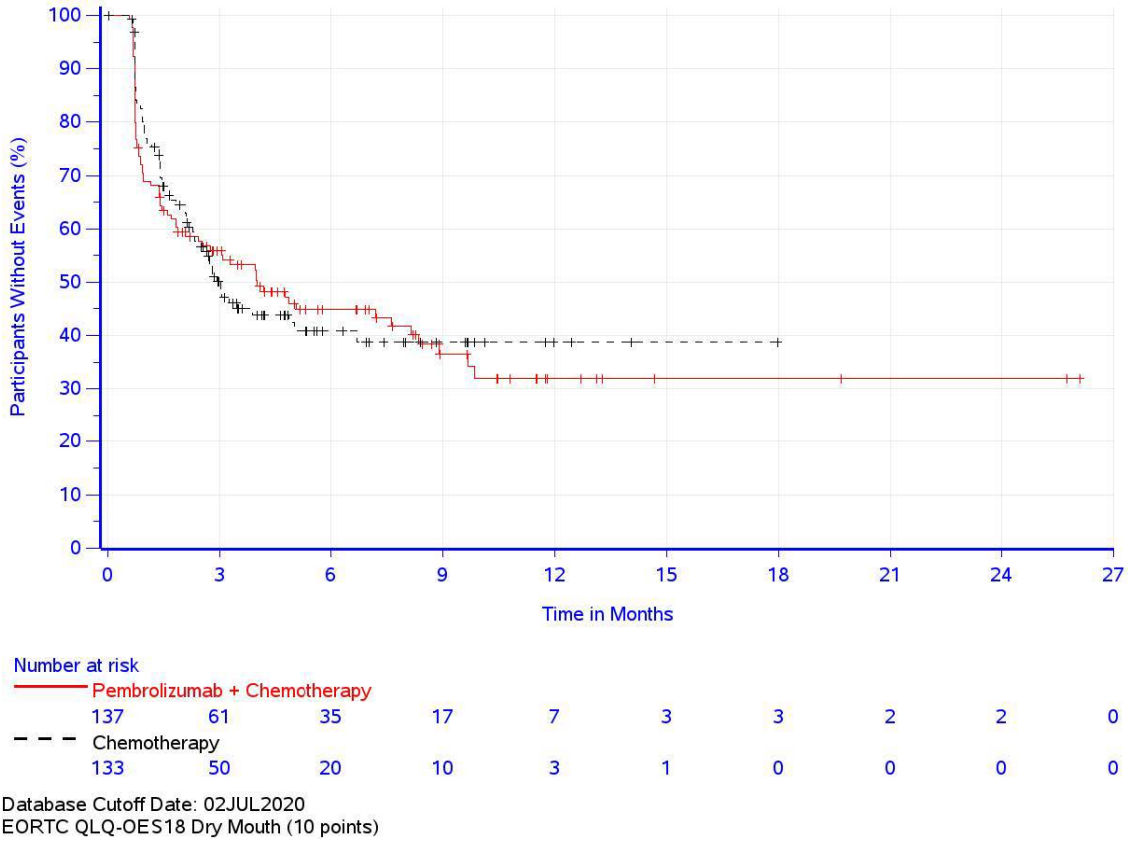

Figure 14: Kaplan-Meier curves for the outcome of dry mouth (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

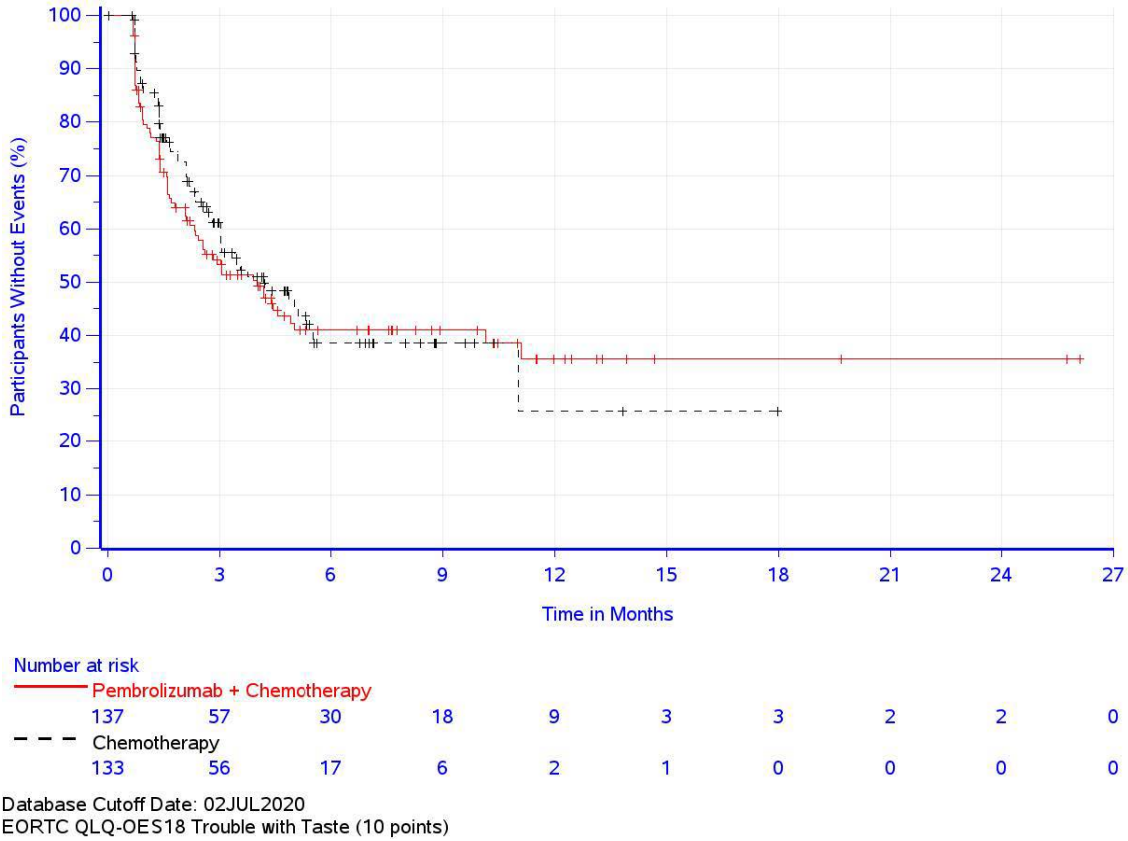

Figure 15: Kaplan-Meier curves for the outcome of taste (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

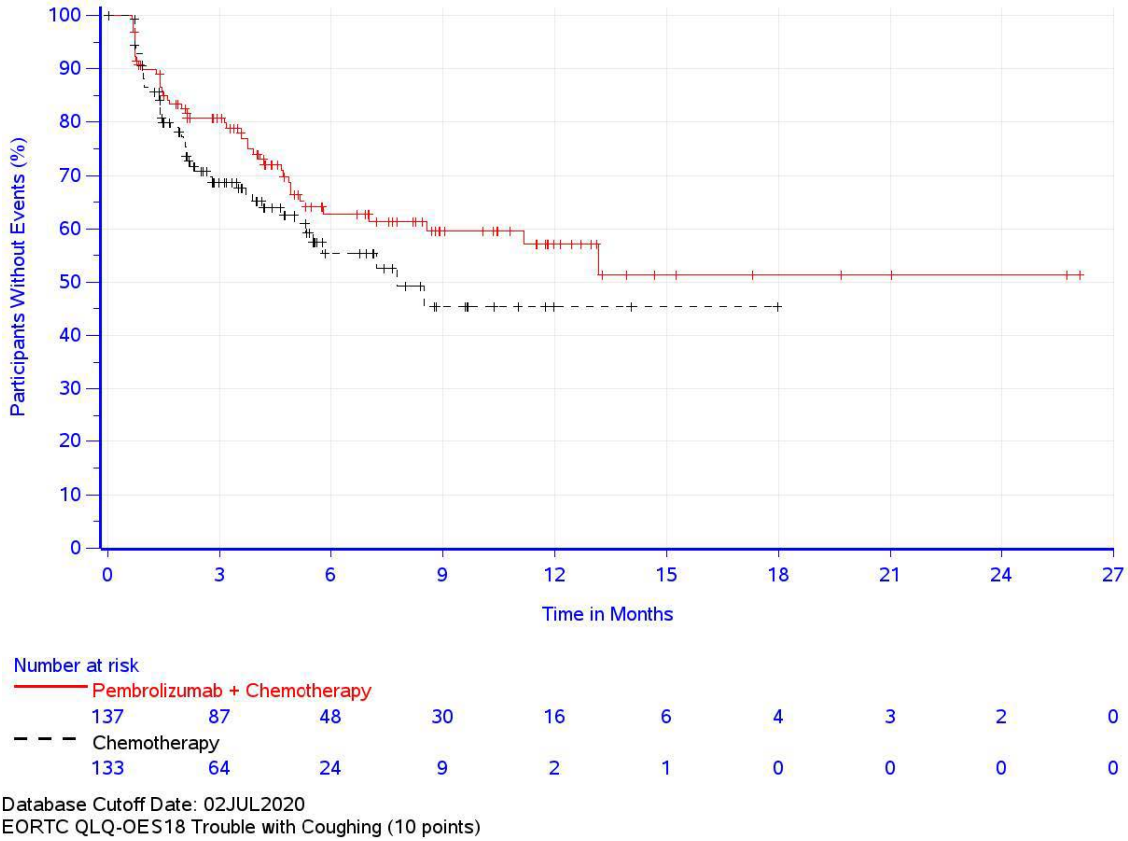

Figure 16: Kaplan-Meier curves for the outcome of cough (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

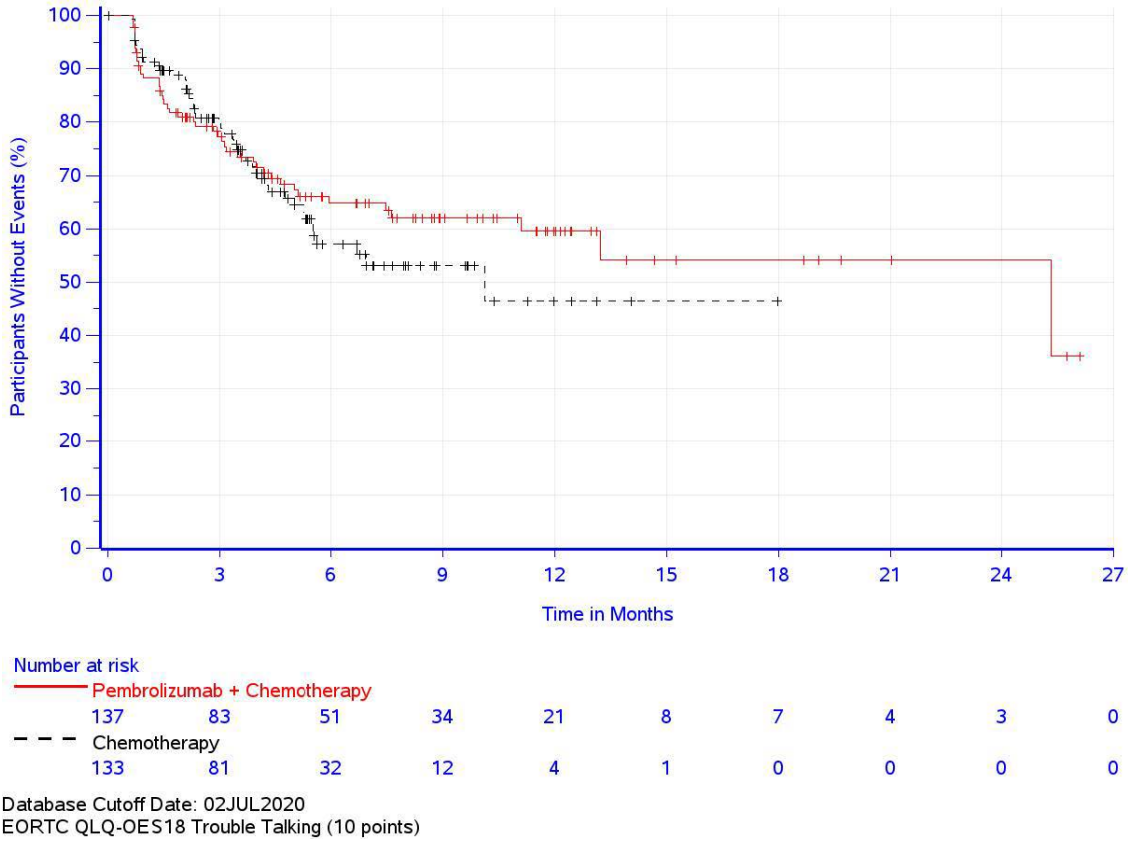

Figure 17: Kaplan-Meier curves for the outcome of speech (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

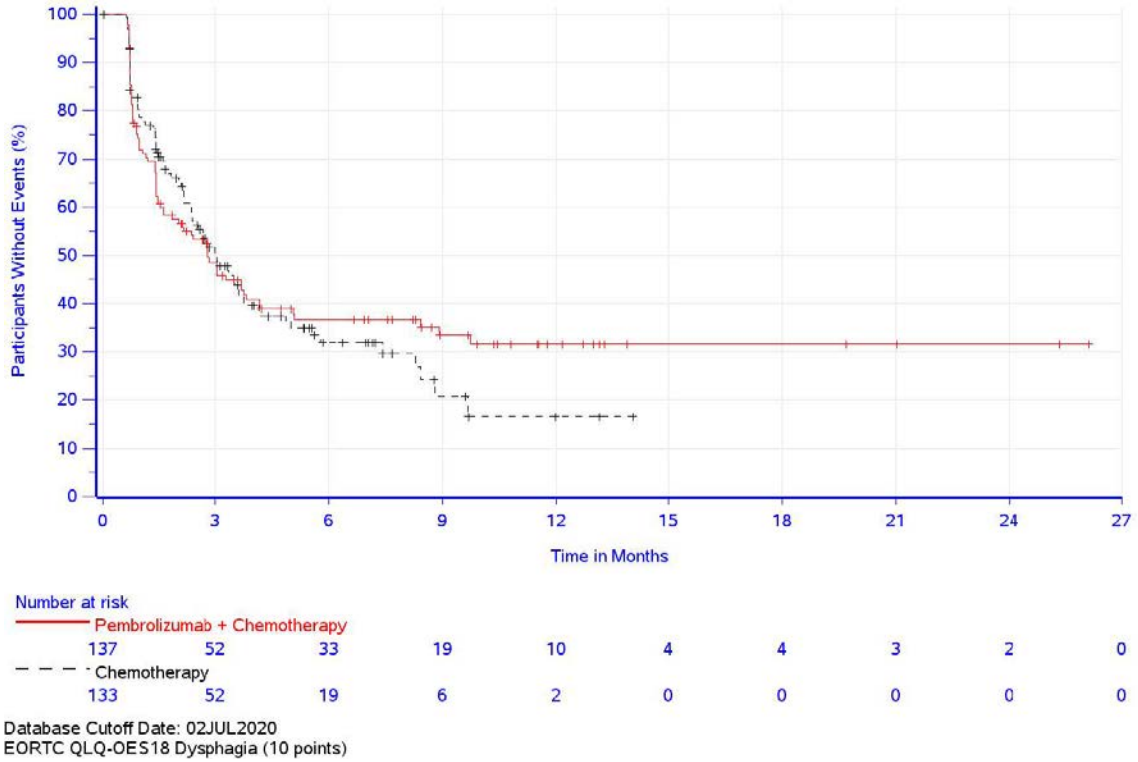

Figure 18: Kaplan-Meier curves for the outcome of dysphagia (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

B.1.2 Health-related quality of life

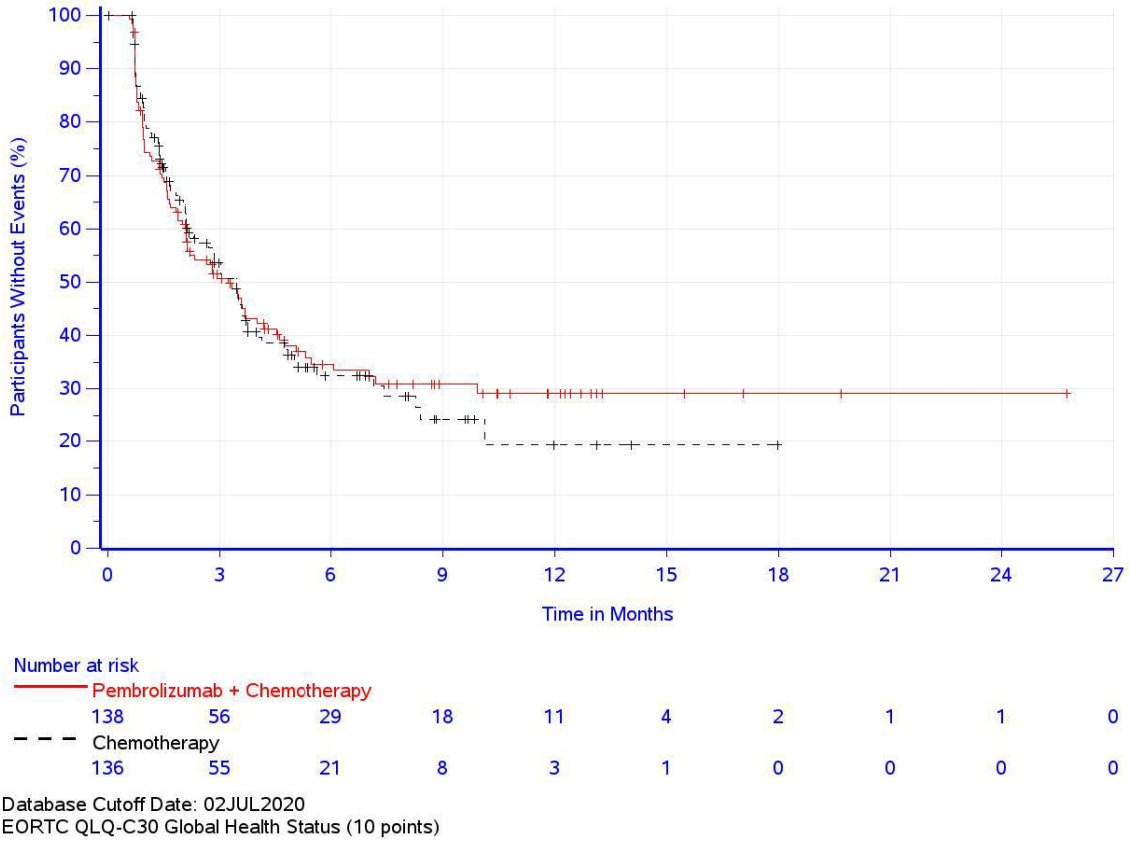

Figure 19: Kaplan-Meier curves for the outcome of global health status (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

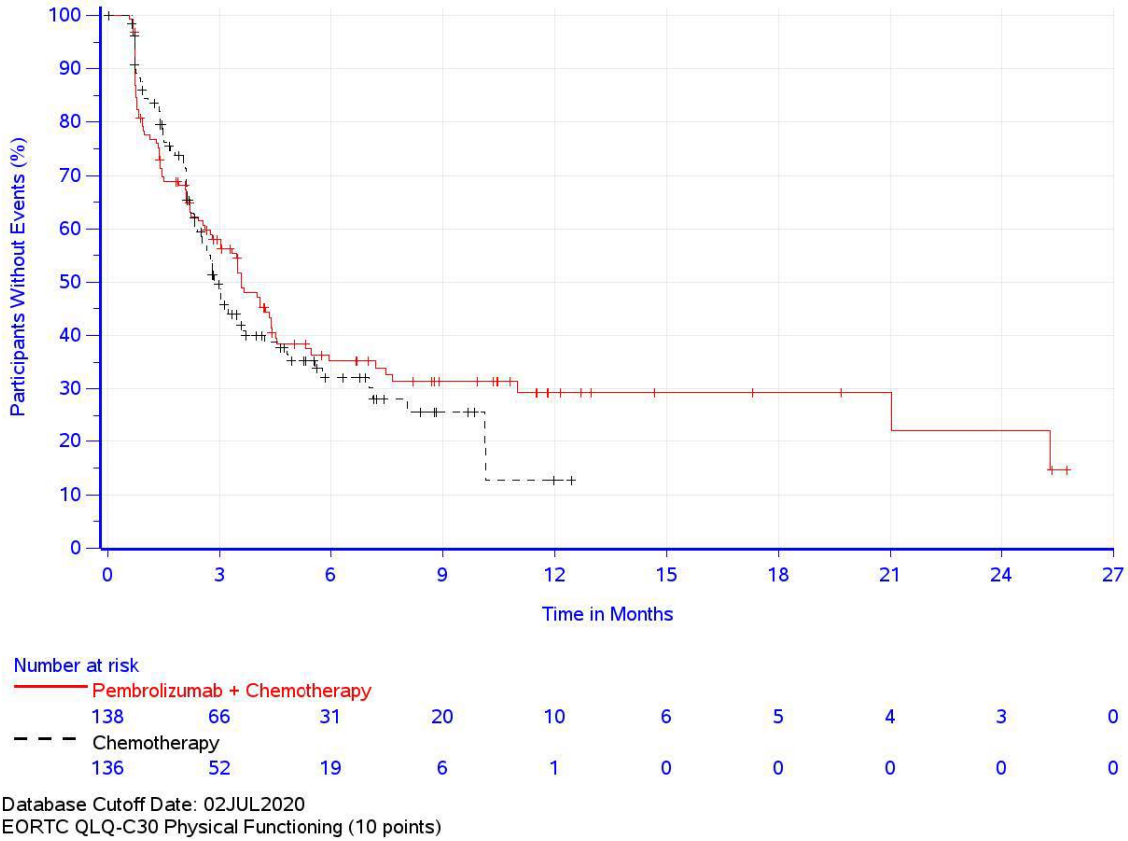

Figure 20: Kaplan-Meier curves for the outcome of physical functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

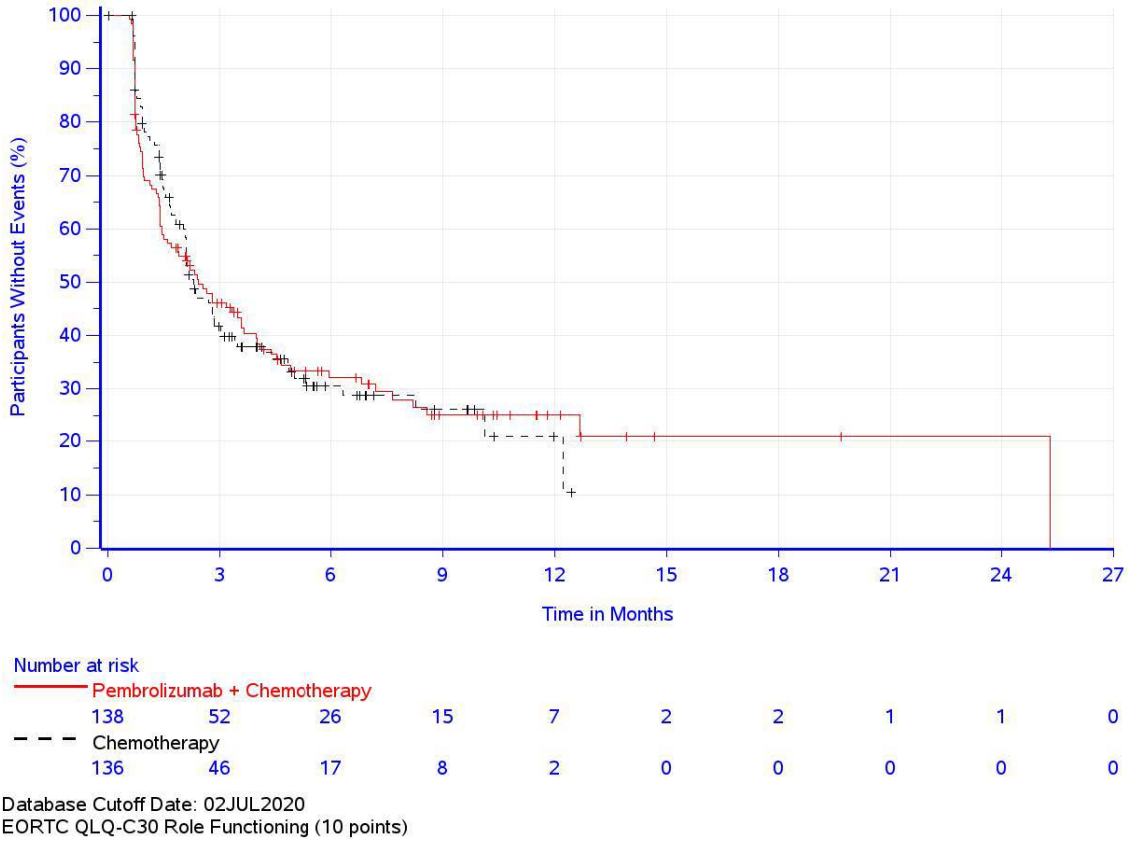

Figure 21: Kaplan-Meier curves for the outcome of role functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

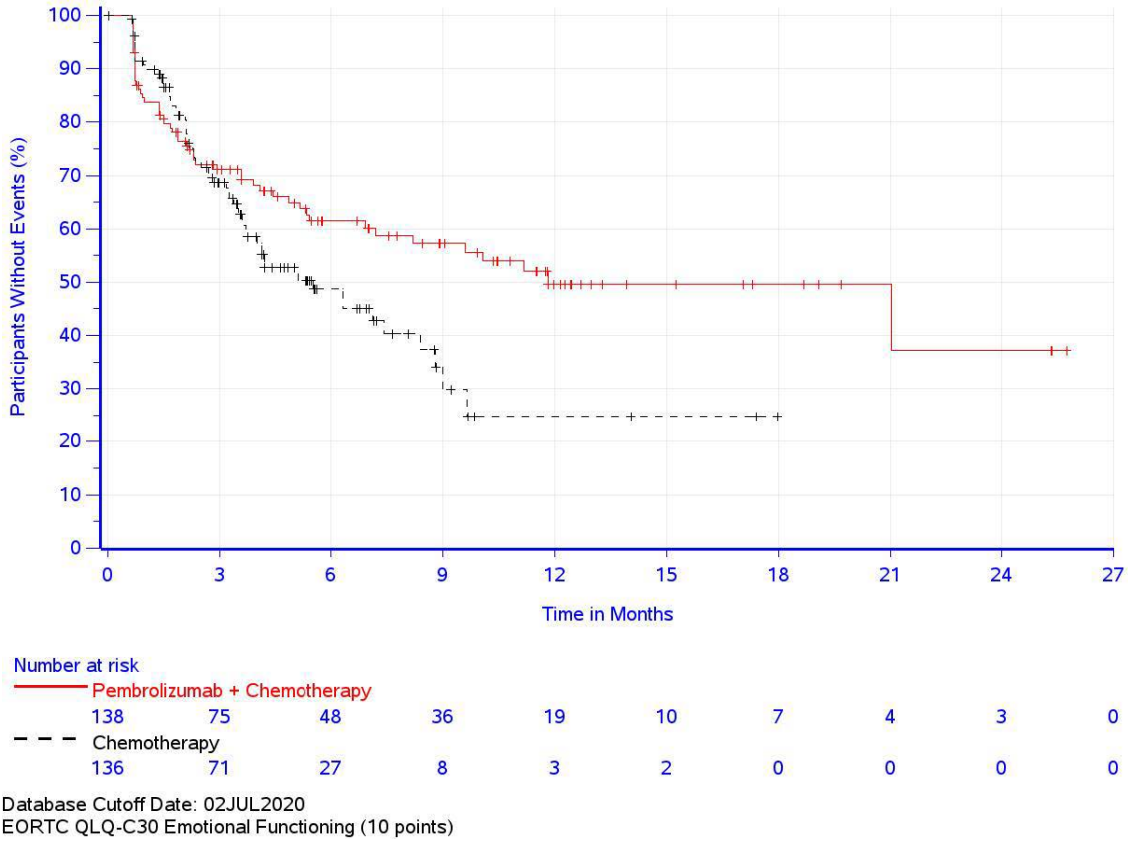

Figure 22: Kaplan-Meier curves for the outcome of emotional functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

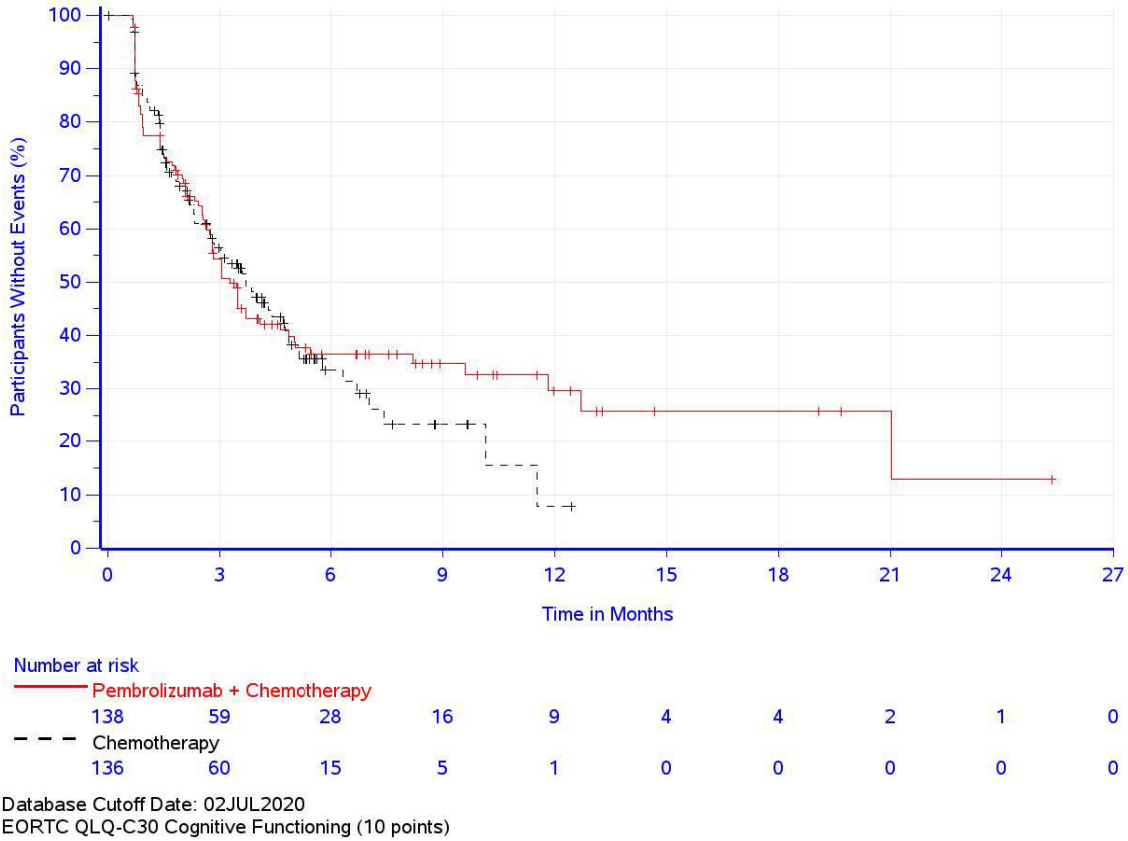

Figure 23: Kaplan-Meier curves for the outcome of cognitive functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

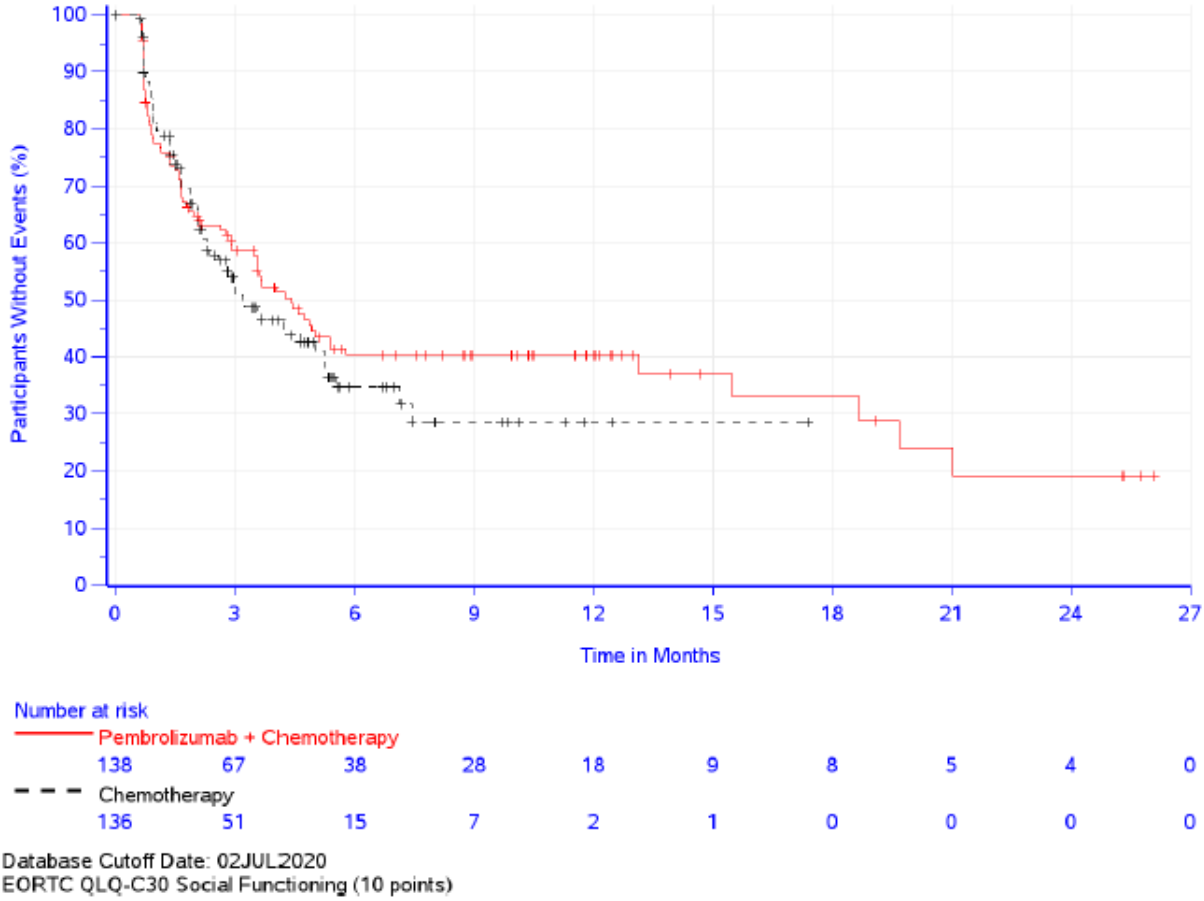

Figure 24: Kaplan-Meier curves for the outcome of social functioning (EORTC QLQ-C30 functional scales), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

B.1.3 Discontinuation due to AEs

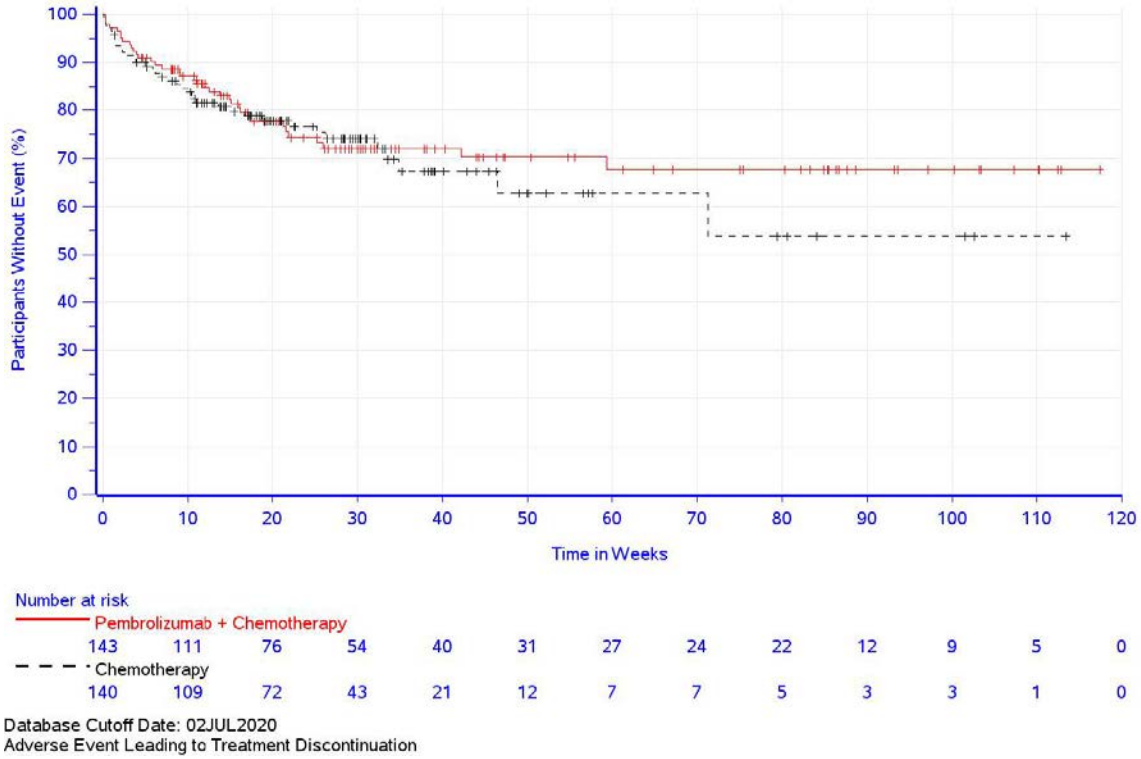

Figure 25: Kaplan-Meier curves for the outcome of discontinuation due to AEs, KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

B.1.4 Subgroup analyses

Age (< 65 years versus ≥ 65 years)

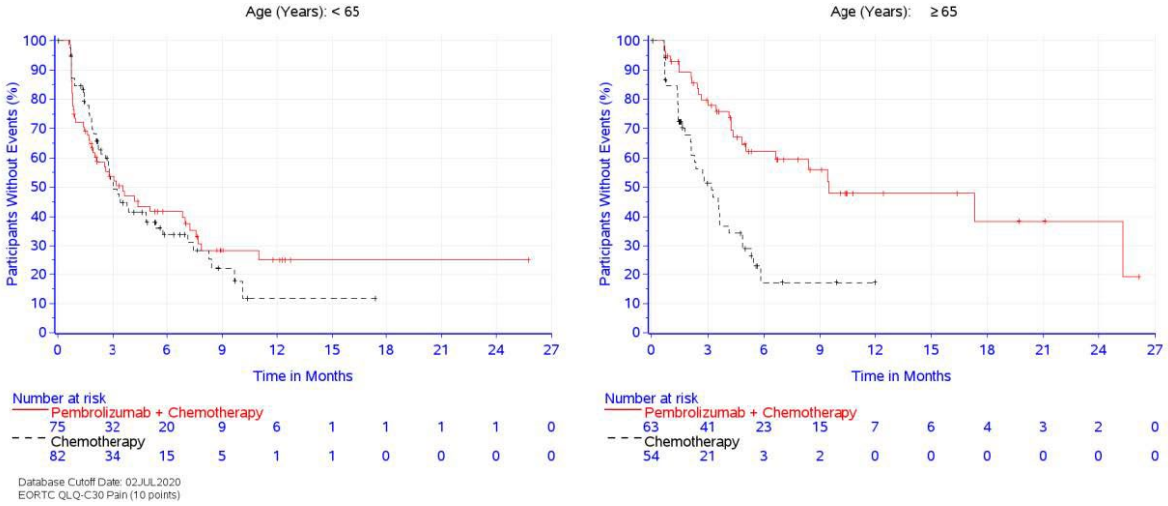

Figure 26: Kaplan-Meier curves for the outcome of pain (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, subgroup analysis by age (< 65 versus ≥ 65 years), KEYNOTE 590 study, subpopulation of patients with squamous epithelial carcinoma of the oesophagus and CPS ≥ 10

B.2 Research question B1

B.2.1 Morbidity

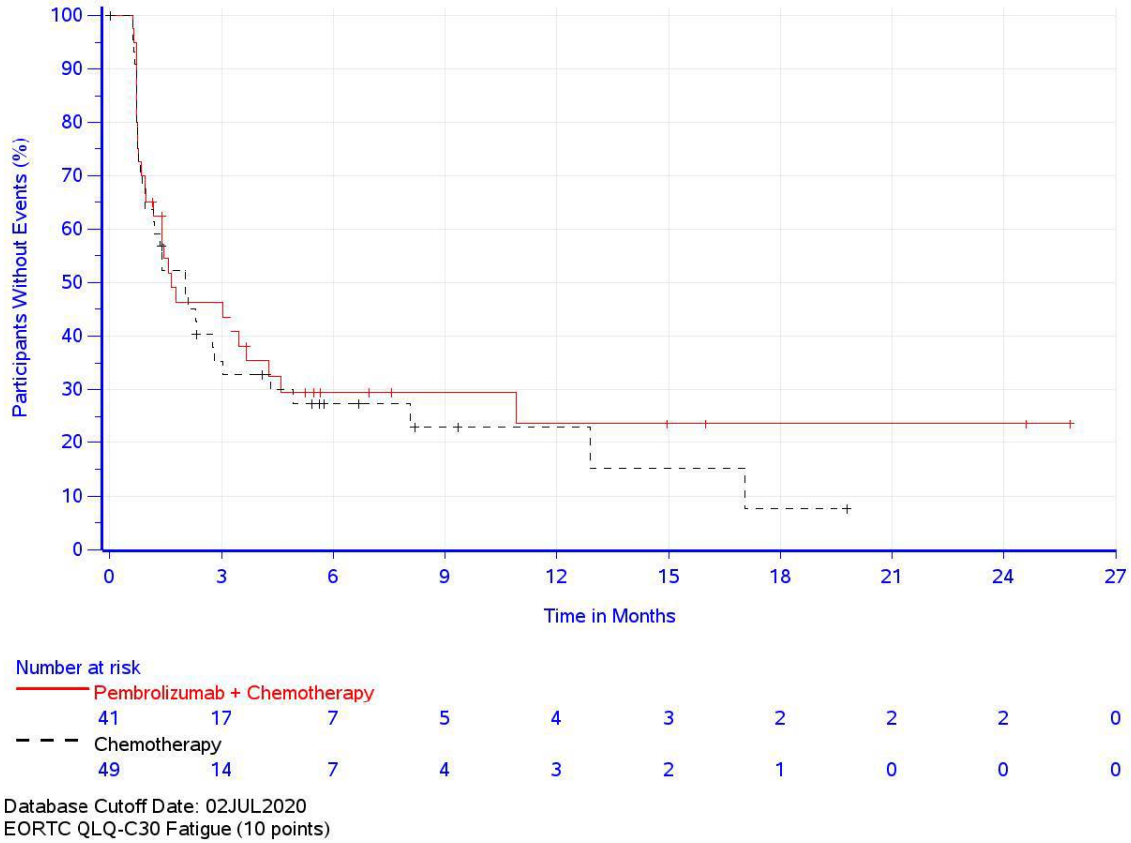

Figure 27: Kaplan-Meier curves for the outcome of fatigue (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

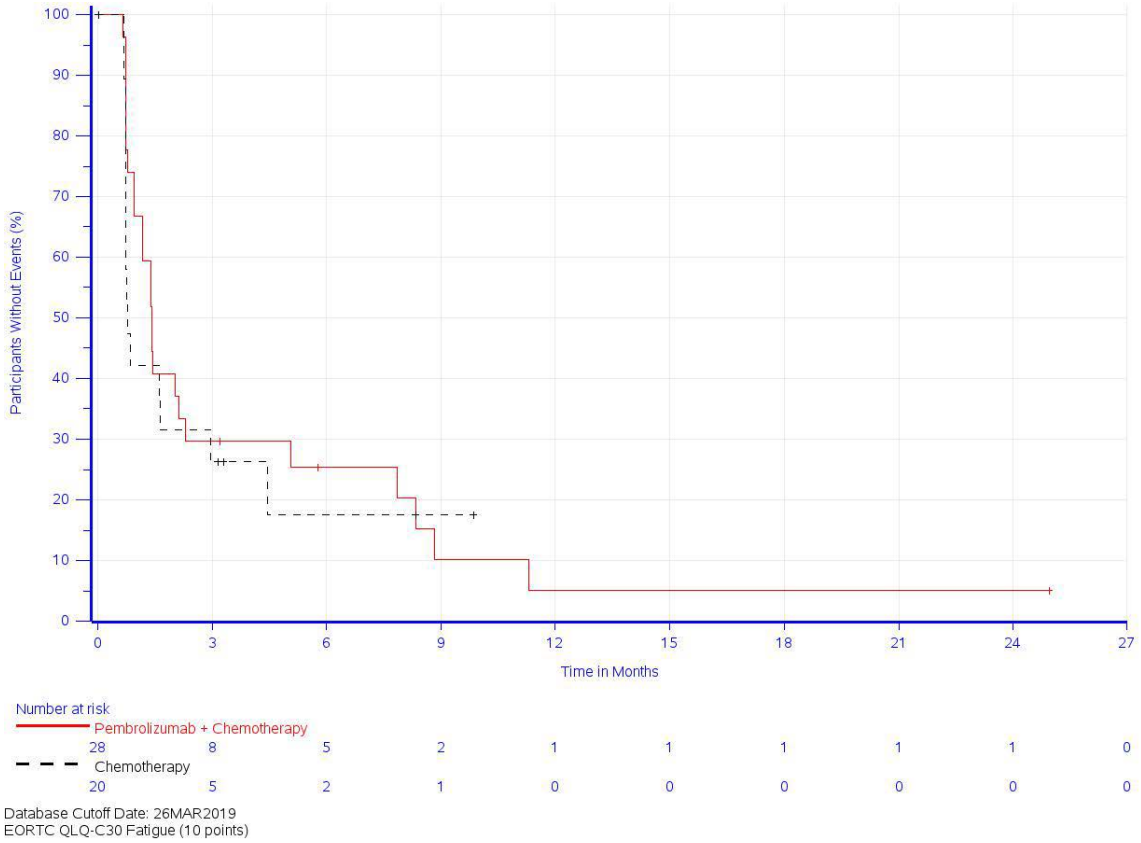

Figure 28: Kaplan-Meier curves for the outcome of fatigue (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 062 study, subpopulation of patients with adenocarcinoma of the oesophagus and CPS ≥ 10

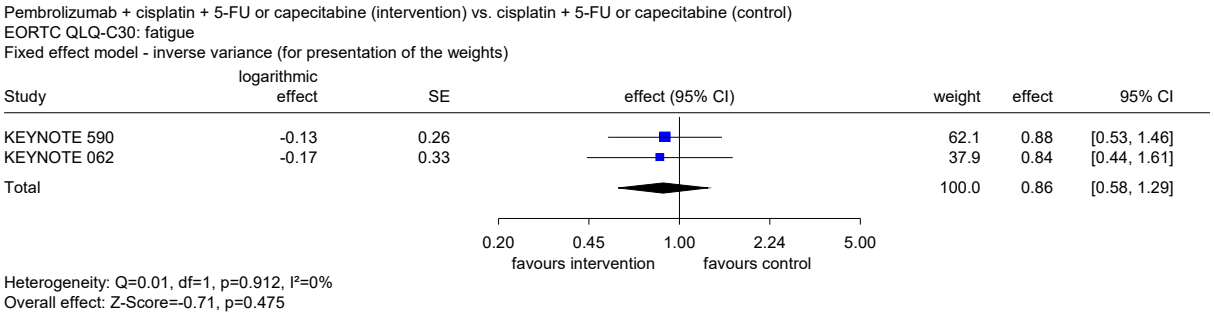

Figure 29: Metaanalysis with fixed effect for the outcome of fatigue (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, effect measure of HR, KEYNOTE 590 and KEYNOTE 062 studies, subpopulations of patients with adenocarcinoma of the oesophagus or gastrooesophageal junction and CPS ≥ 10

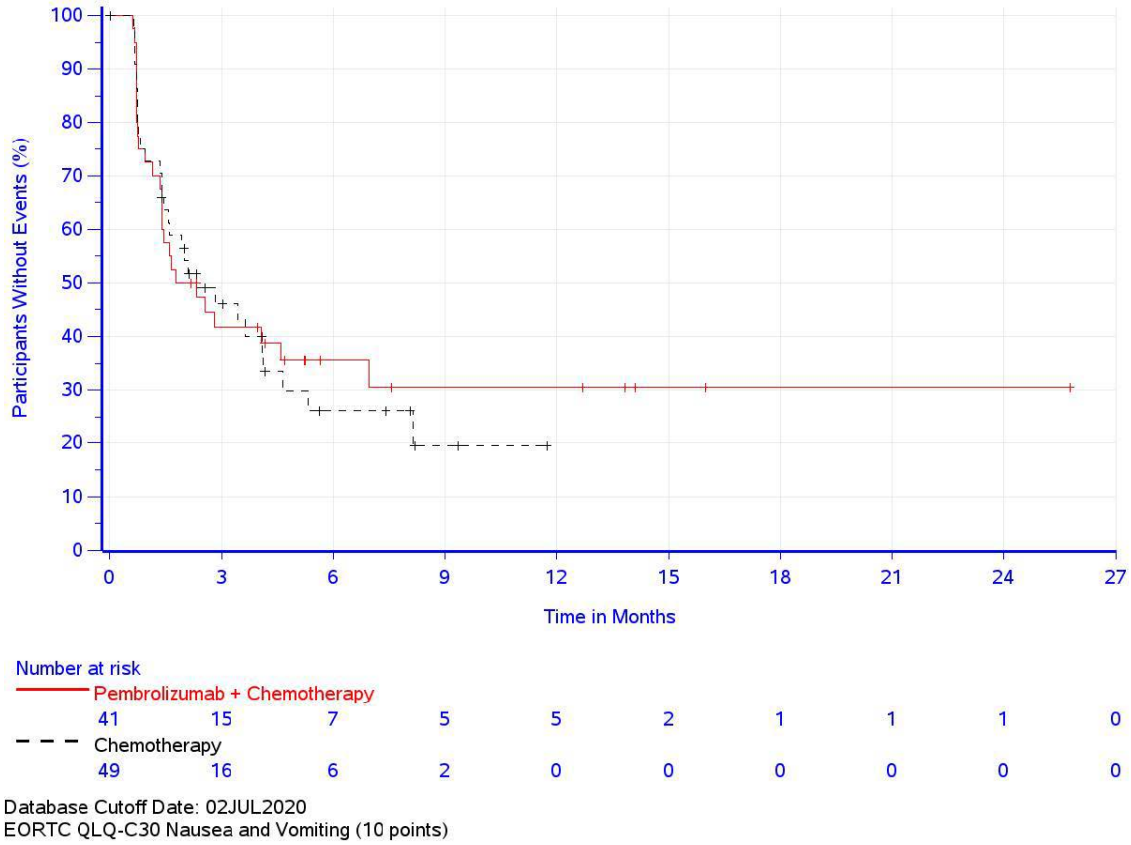

Figure 30: Kaplan-Meier curves for the outcome of nausea and vomiting (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

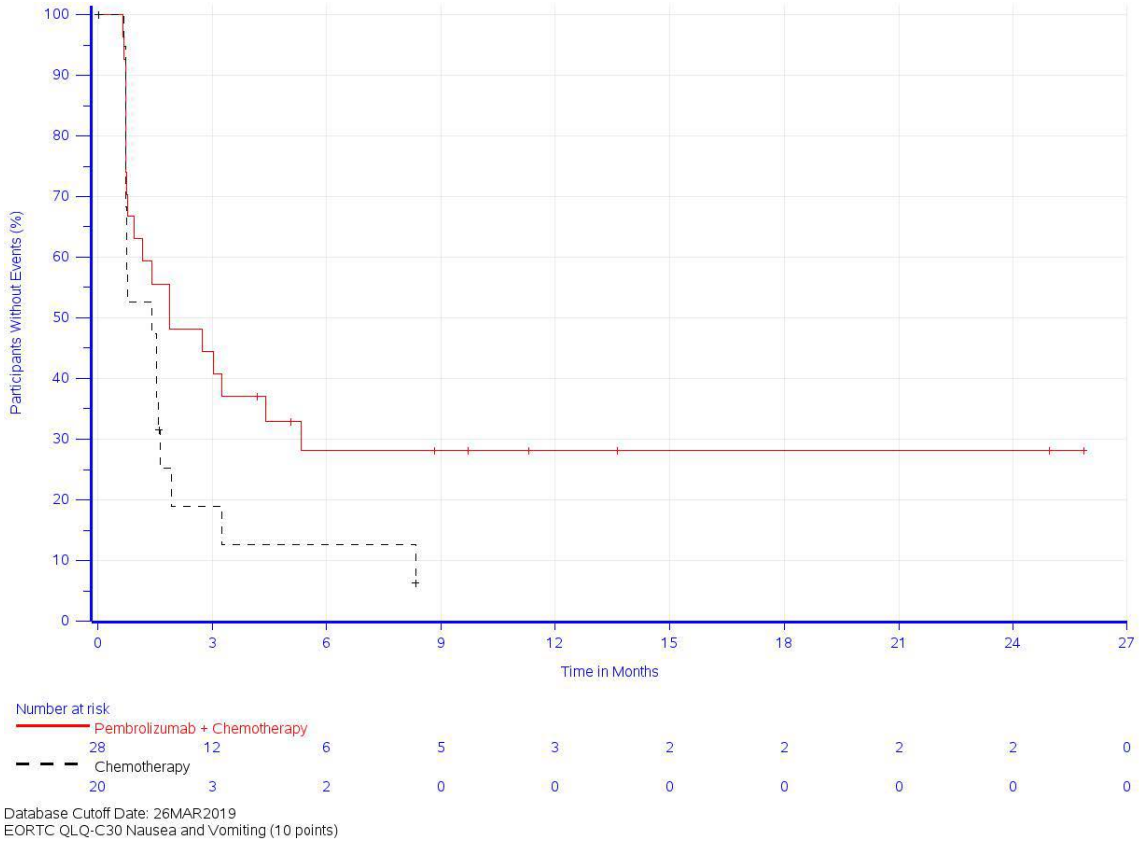

Figure 31: Kaplan-Meier curves for the outcome of nausea and vomiting (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 062 study, subpopulation of patients with adenocarcinoma of the gastrooesophageal junction and CPS ≥ 10

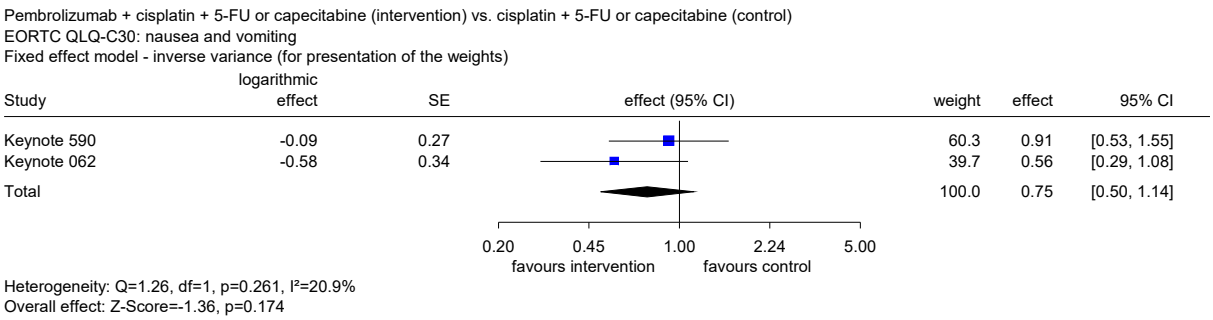

Figure 32: Metaanalysis with fixed effect for the outcome of nausea and vomiting (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, effect measure of HR, KEYNOTE 590 and KEYNOTE 062 studies, subpopulations of patients with adenocarcinoma of the oesophagus or gastrooesophageal junction and CPS ≥ 10

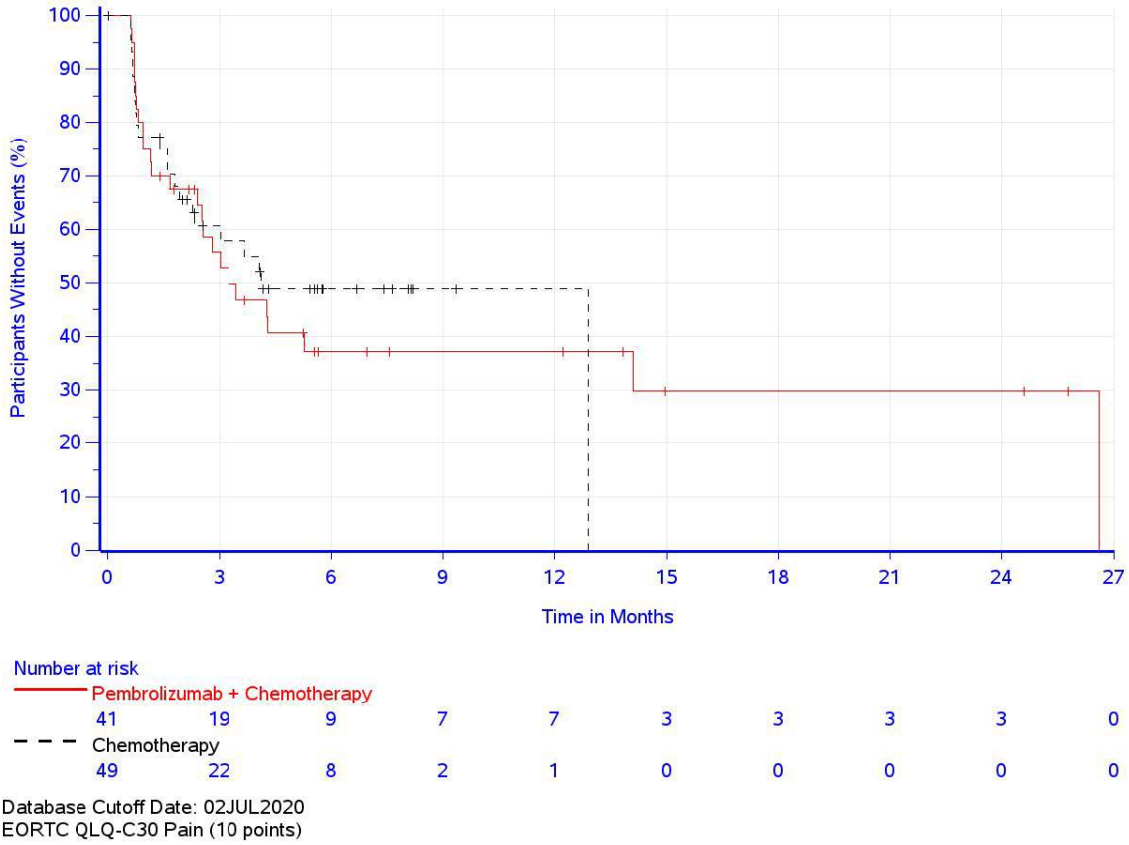

Figure 33: Kaplan-Meier curves for the outcome of pain (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

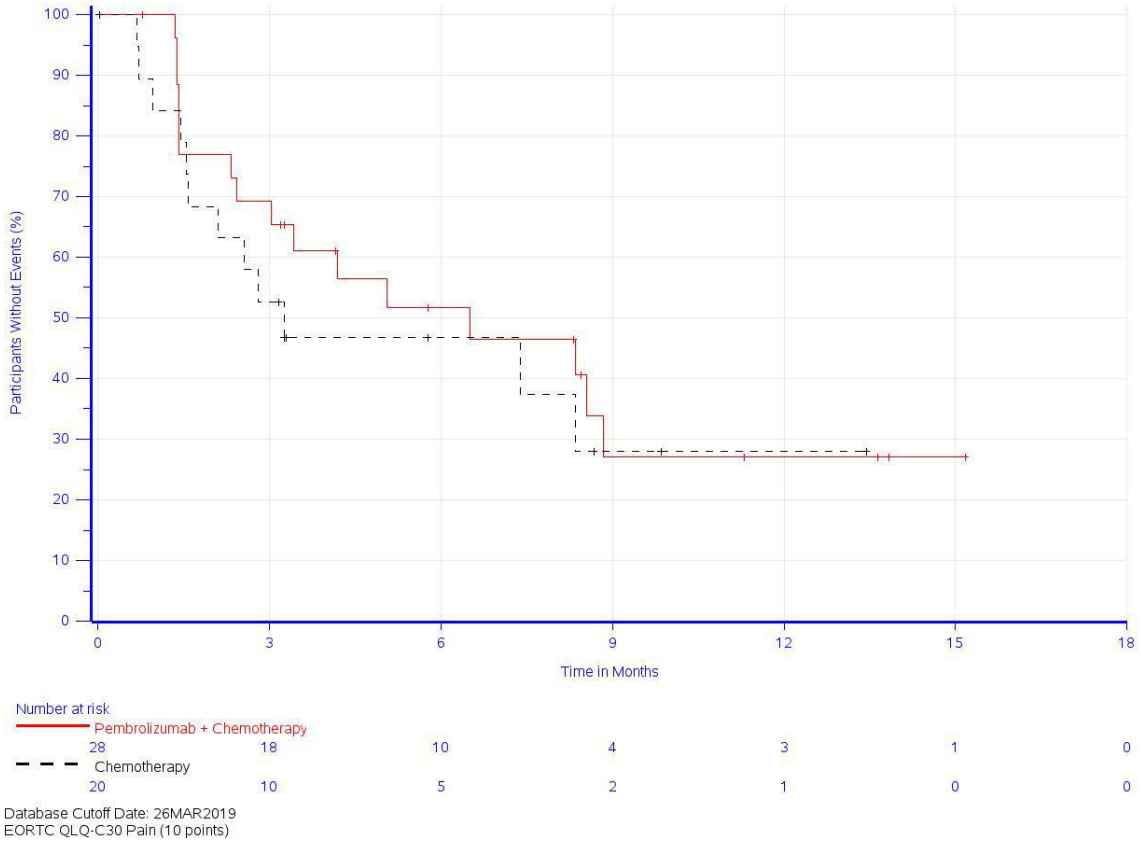

Figure 34: Kaplan-Meier curves for the outcome of pain (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 062 study, subpopulation of patients with adenocarcinoma of the gastrooesophageal junction and CPS ≥ 10

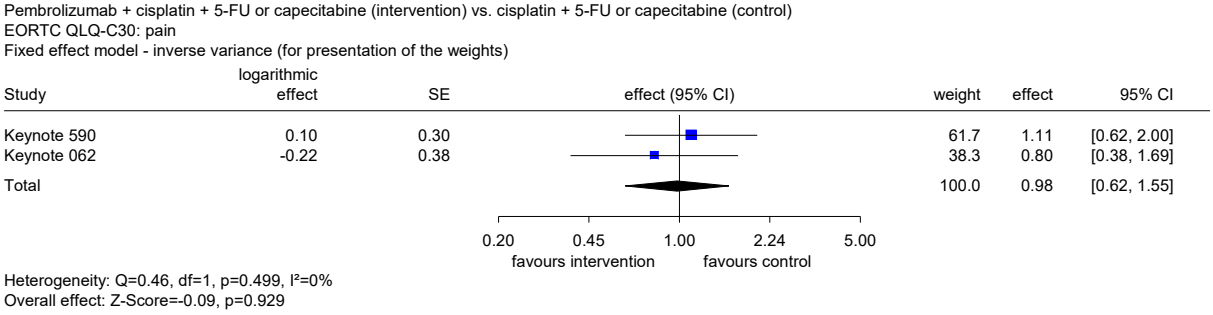

Figure 35: Metaanalysis with fixed effect for the outcome of pain (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, effect measure of HR, KEYNOTE 590 and KEYNOTE 062 studies, subpopulations of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

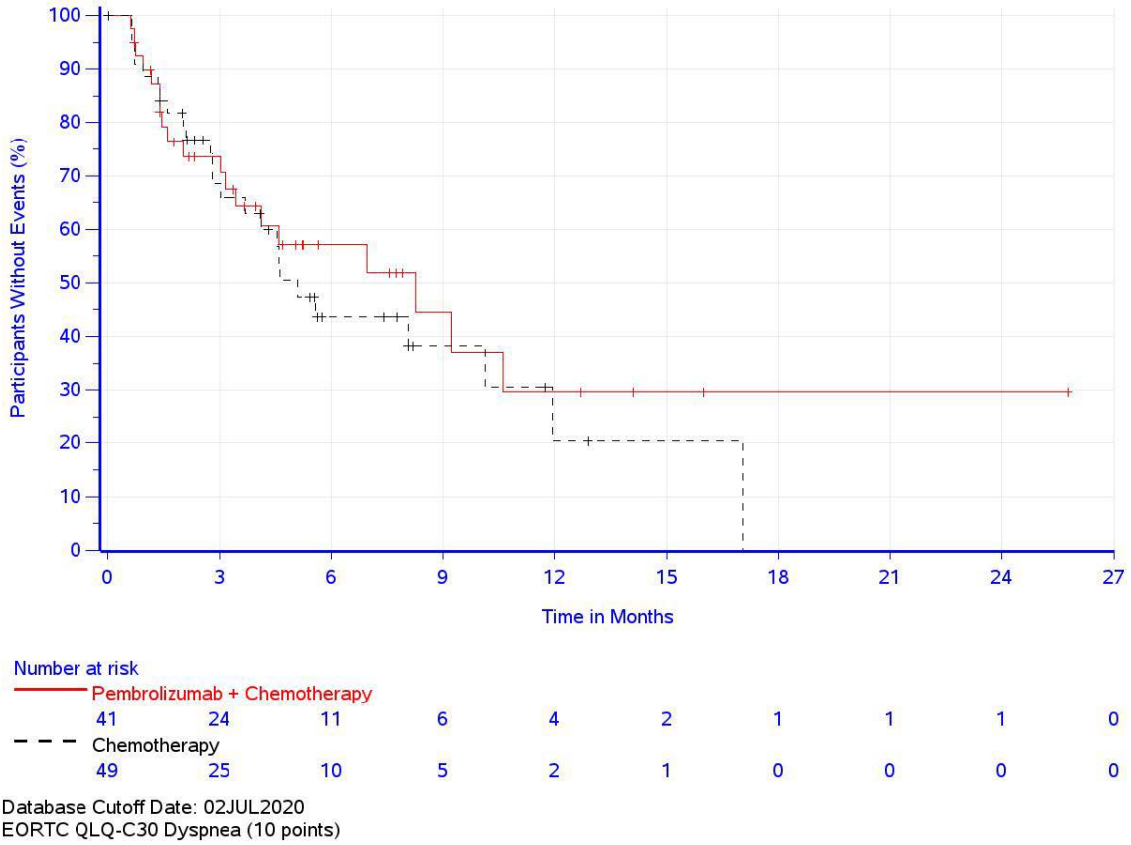

Figure 36: Kaplan-Meier curves for the outcome of dyspnoea (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

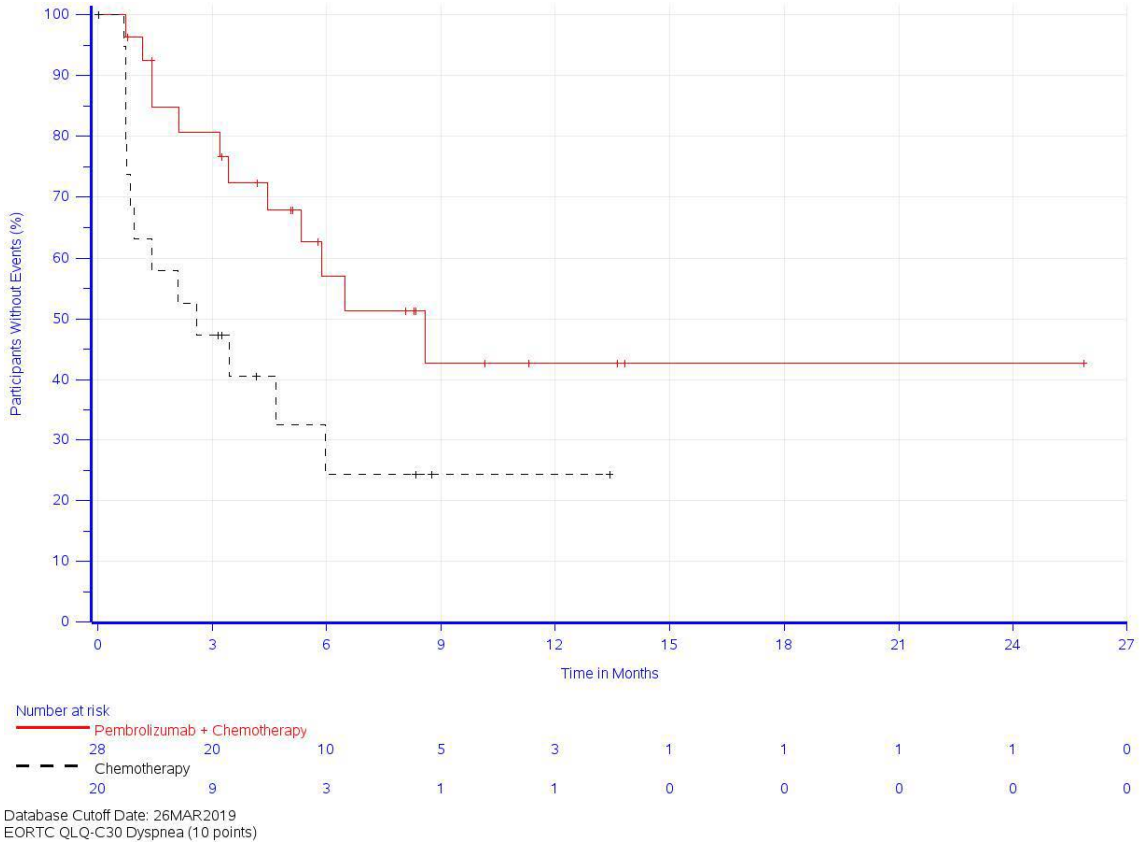

Figure 37: Kaplan-Meier curves for the outcome of dyspnoea (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 062 study, subpopulation of patients with adenocarcinoma of the gastrooesophageal junction and CPS ≥ 10

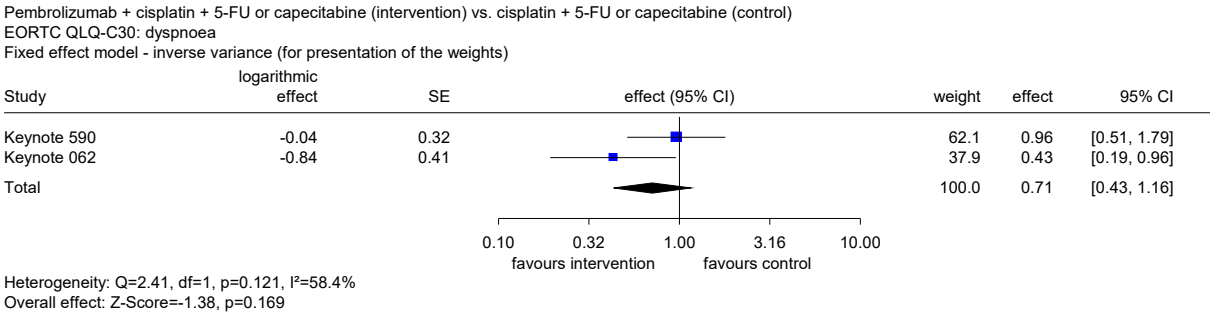

Figure 38: Metaanalysis with fixed effect for the outcome of dyspnoea (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, effect measure of HR, KEYNOTE 590 and KEYNOTE 062 studies, subpopulations of patients with adenocarcinoma of the oesophagus or gastrooesophageal junction and CPS ≥ 10

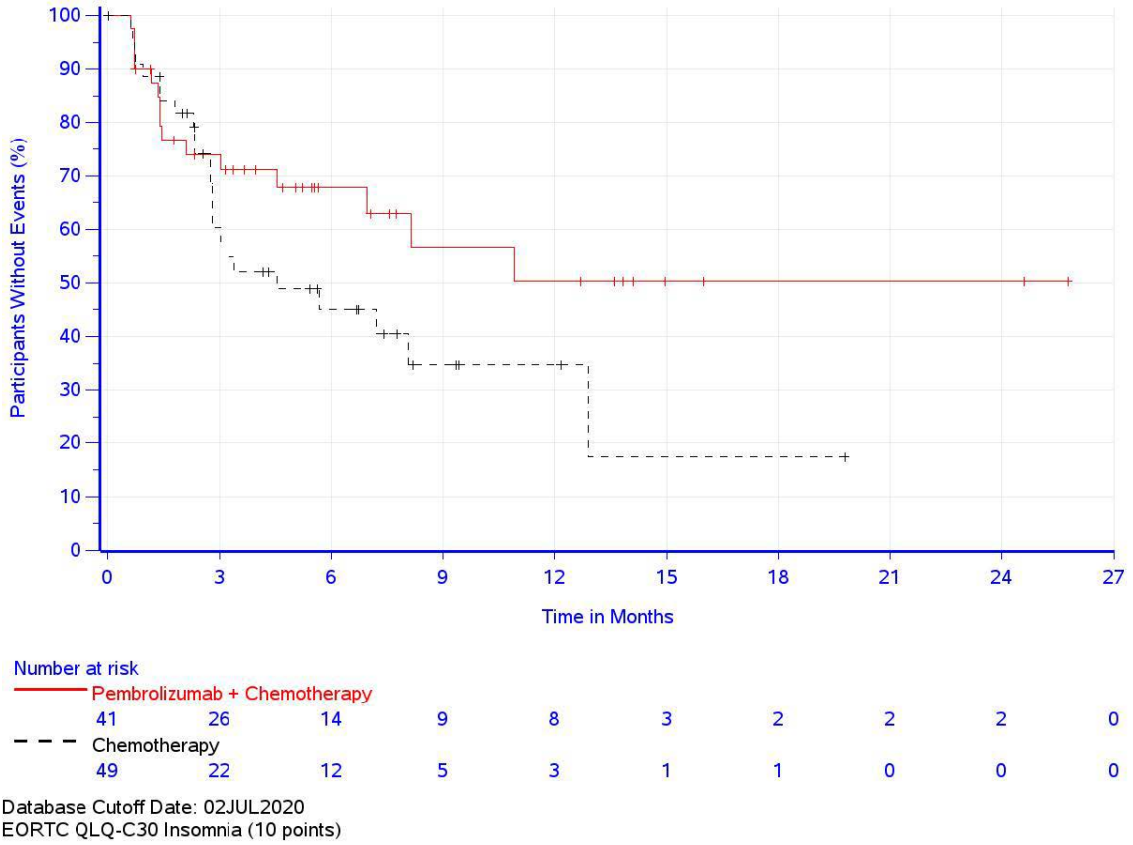

Figure 39: Kaplan-Meier curves for the outcome of insomnia (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

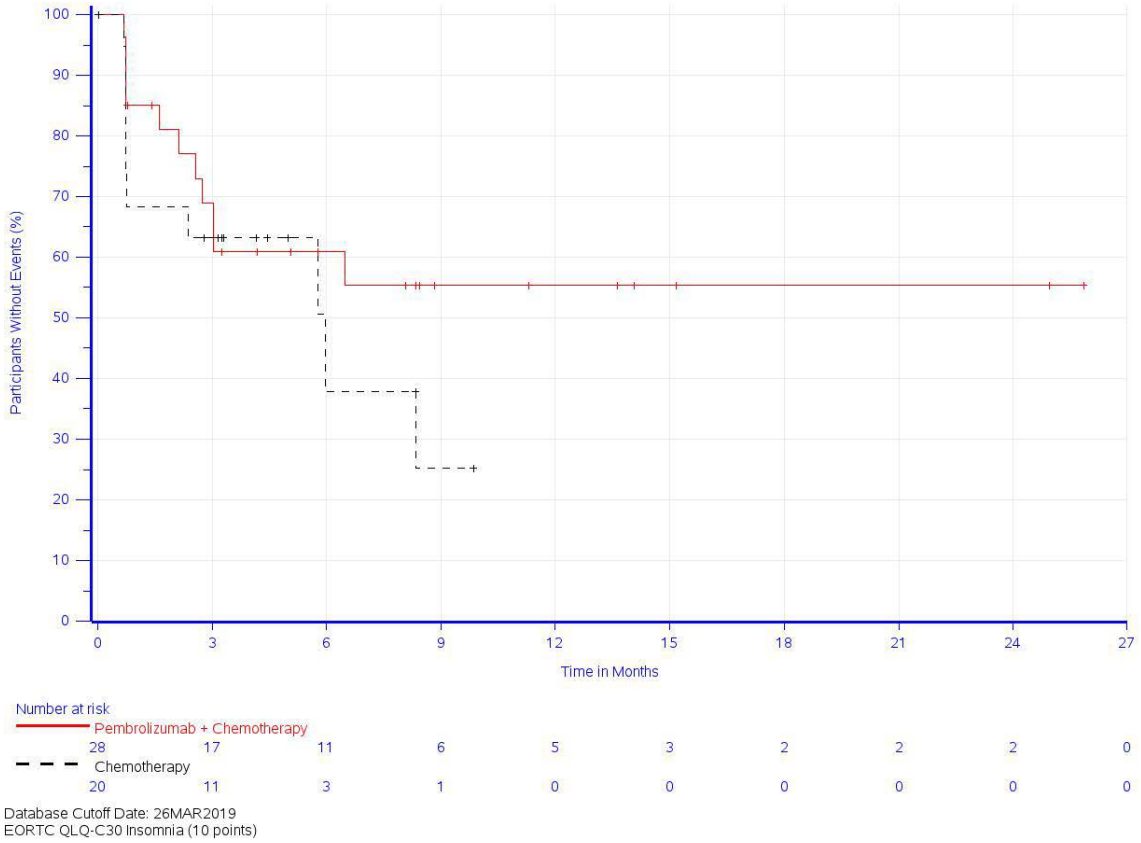

Figure 40: Kaplan-Meier curves for the outcome of insomnia (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 062 study, subpopulation of patients with adenocarcinoma of the gastrooesophageal junction and CPS ≥ 10

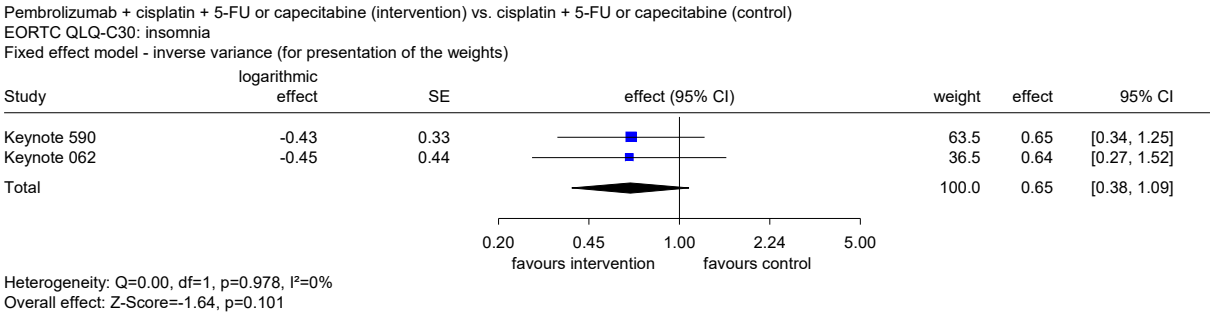

Figure 41: Metaanalysis with fixed effect for the outcome of insomnia (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, effect measure of HR, KEYNOTE 590 and KEYNOTE 062 studies, subpopulations of patients with adenocarcinoma of the oesophagus or gastrooesophageal junction and CPS ≥ 10

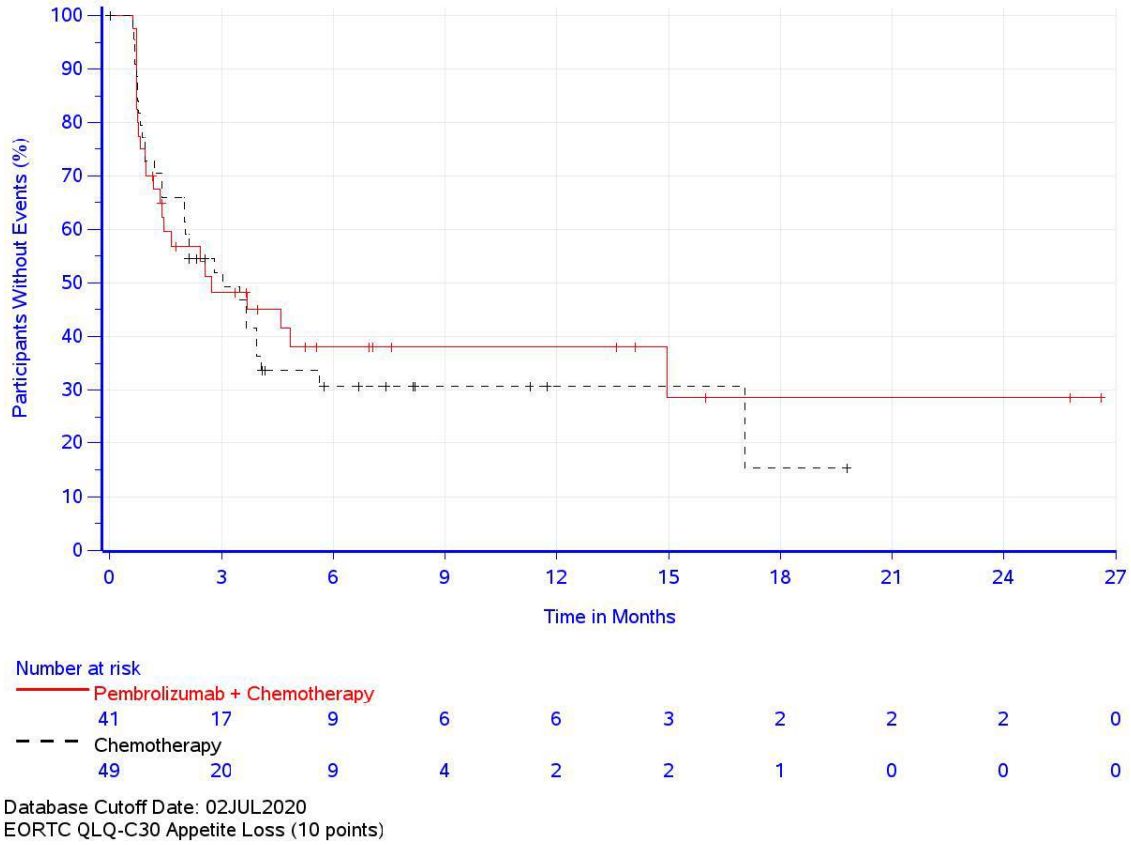

Figure 42: Kaplan-Meier curves for the outcome of appetite loss (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

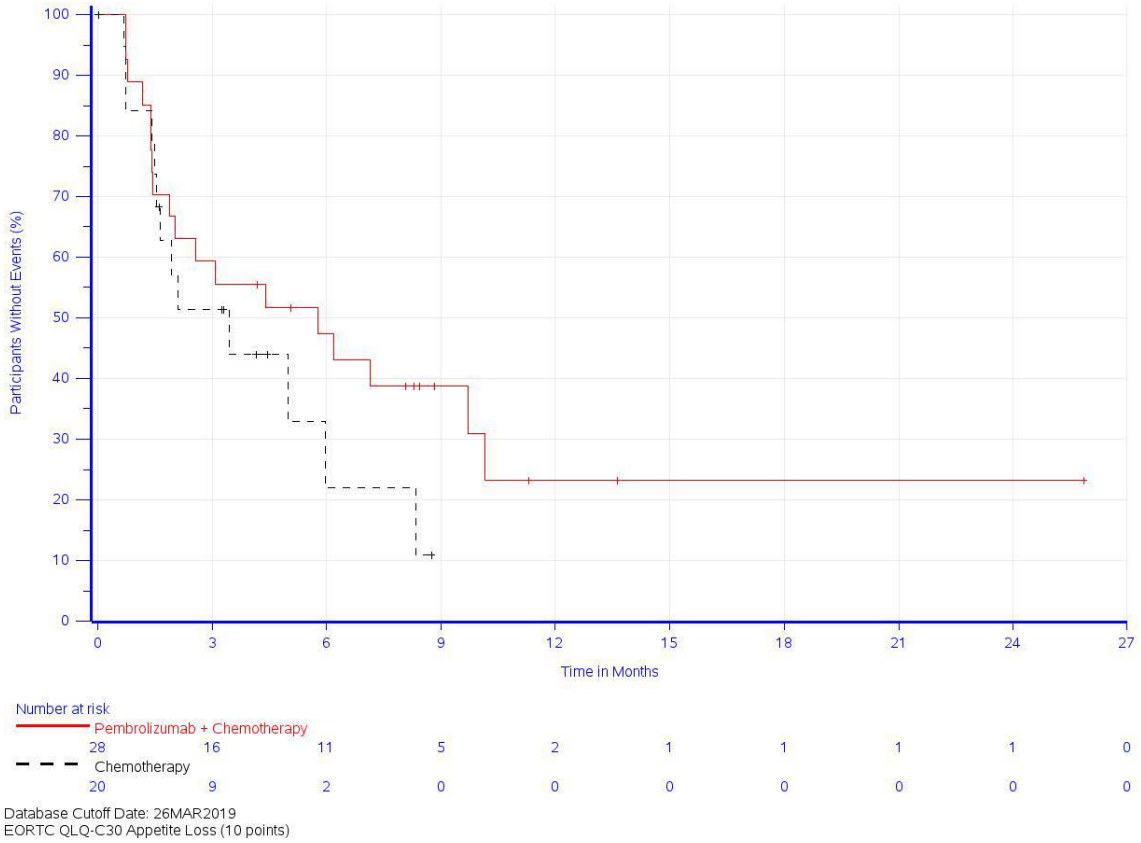

Figure 43: Kaplan-Meier curves for the outcome of appetite loss (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 062 study, subpopulation of patients with adenocarcinoma of the gastrooesophageal junction and CPS ≥ 10

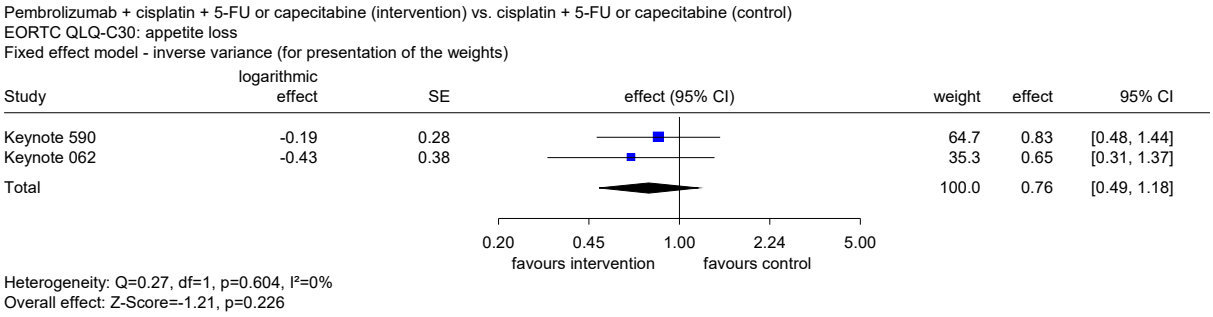

Figure 44: Metaanalysis with fixed effect for the outcome of appetite loss (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, effect measure of HR, KEYNOTE 590 and KEYNOTE 062 studies, subpopulations of patients with adenocarcinoma of the oesophagus or gastrooesophageal junction and CPS ≥ 10

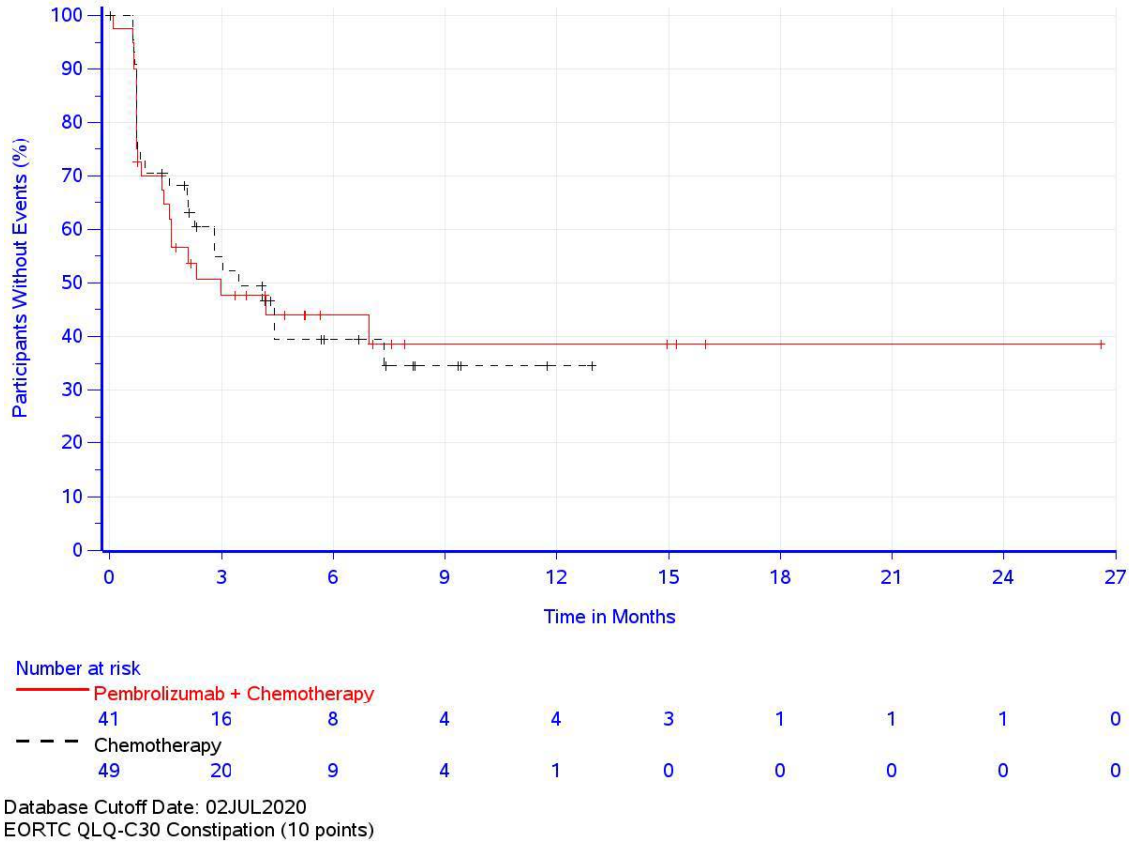

Figure 45: Kaplan-Meier curves for the outcome of constipation (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

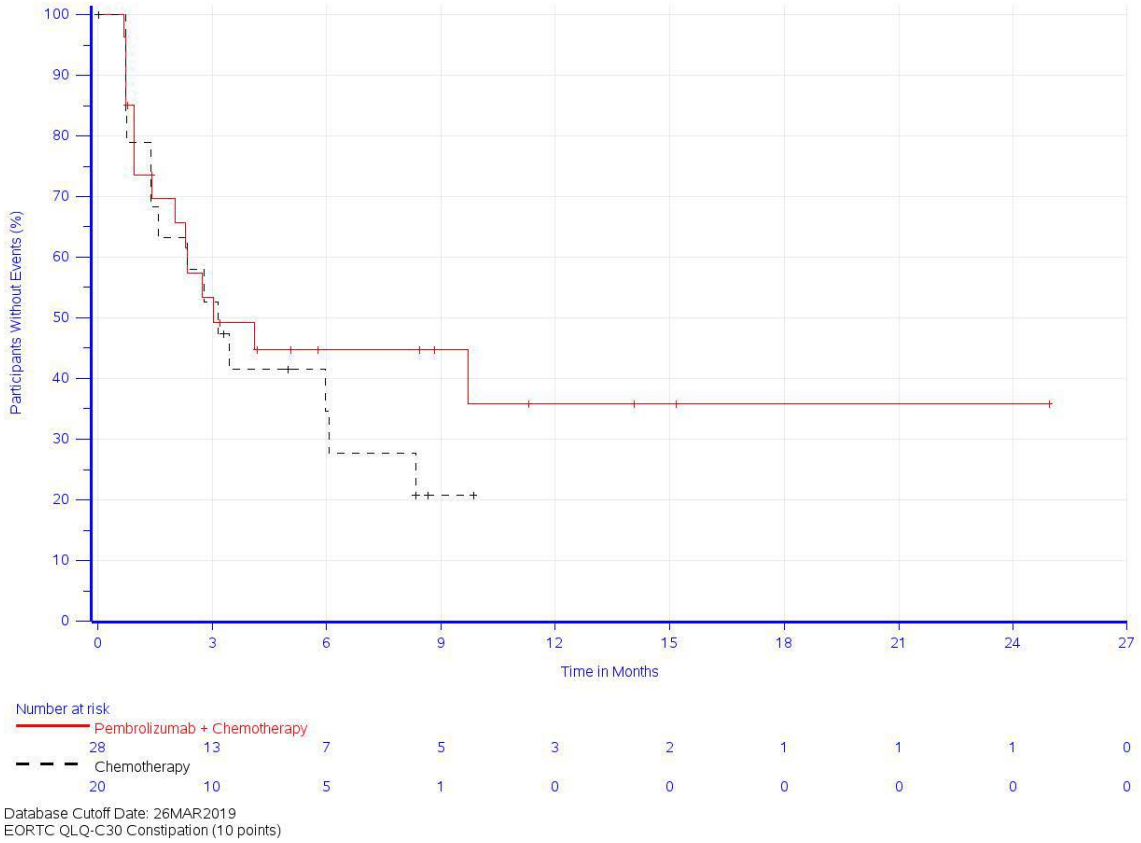

Figure 46: Kaplan-Meier curves for the outcome of constipation (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 062 study, subpopulation of patients with adenocarcinoma of the gastrooesophageal junction and CPS ≥ 10

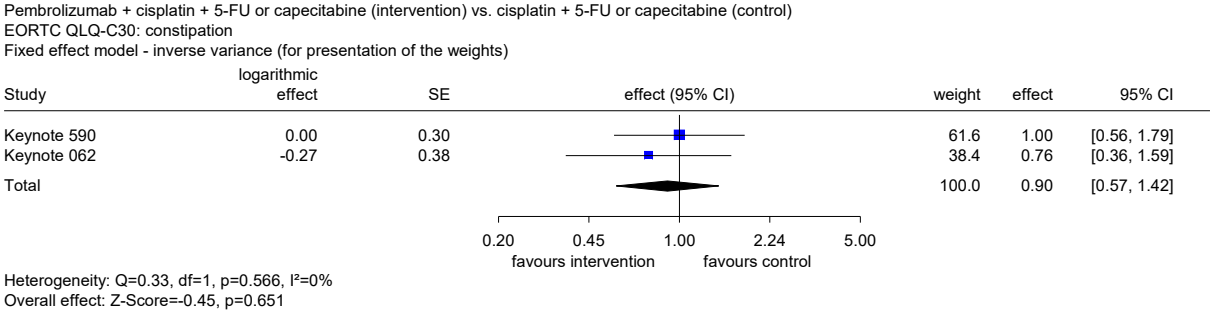

Figure 47: Metaanalysis with fixed effect for the outcome of constipation (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, effect measure of HR, KEYNOTE 590 and KEYNOTE 062 studies, subpopulations of patients with adenocarcinoma of the oesophagus or gastrooesophageal junction and CPS ≥ 10

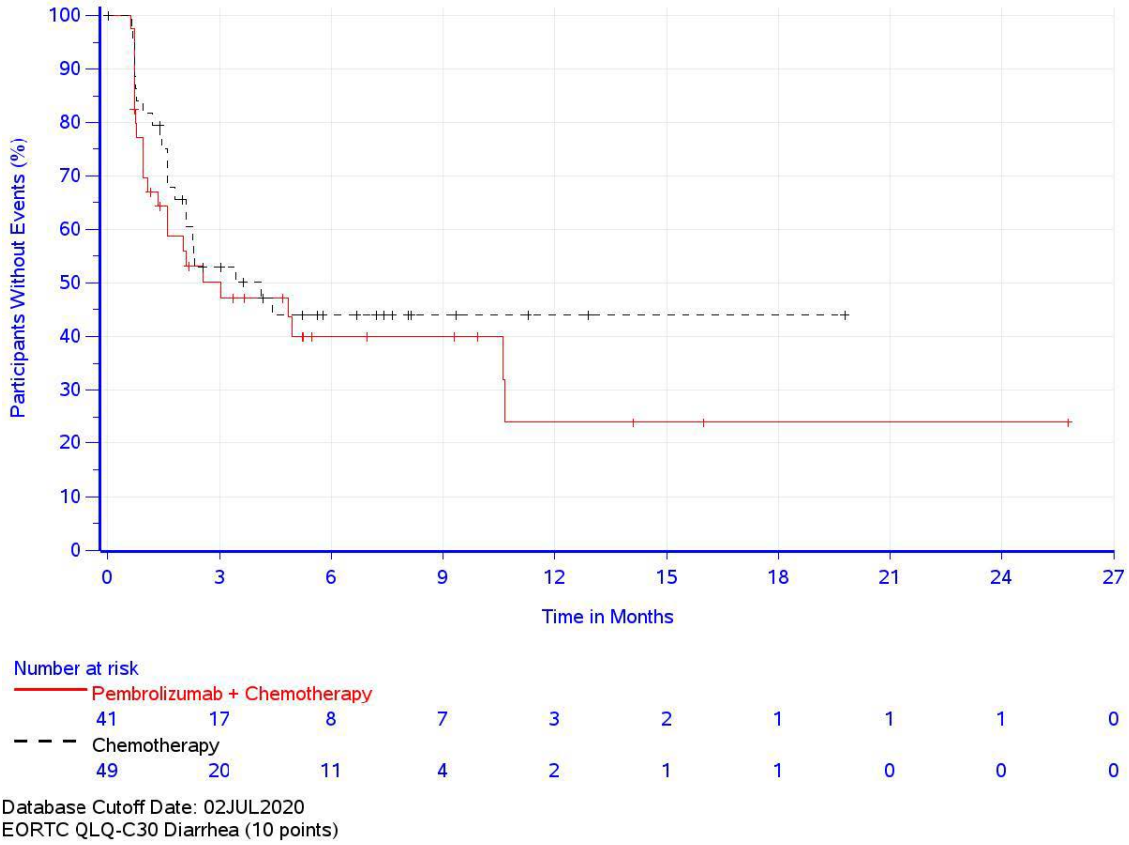

Figure 48: Kaplan-Meier curves for the outcome of diarrhoea (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

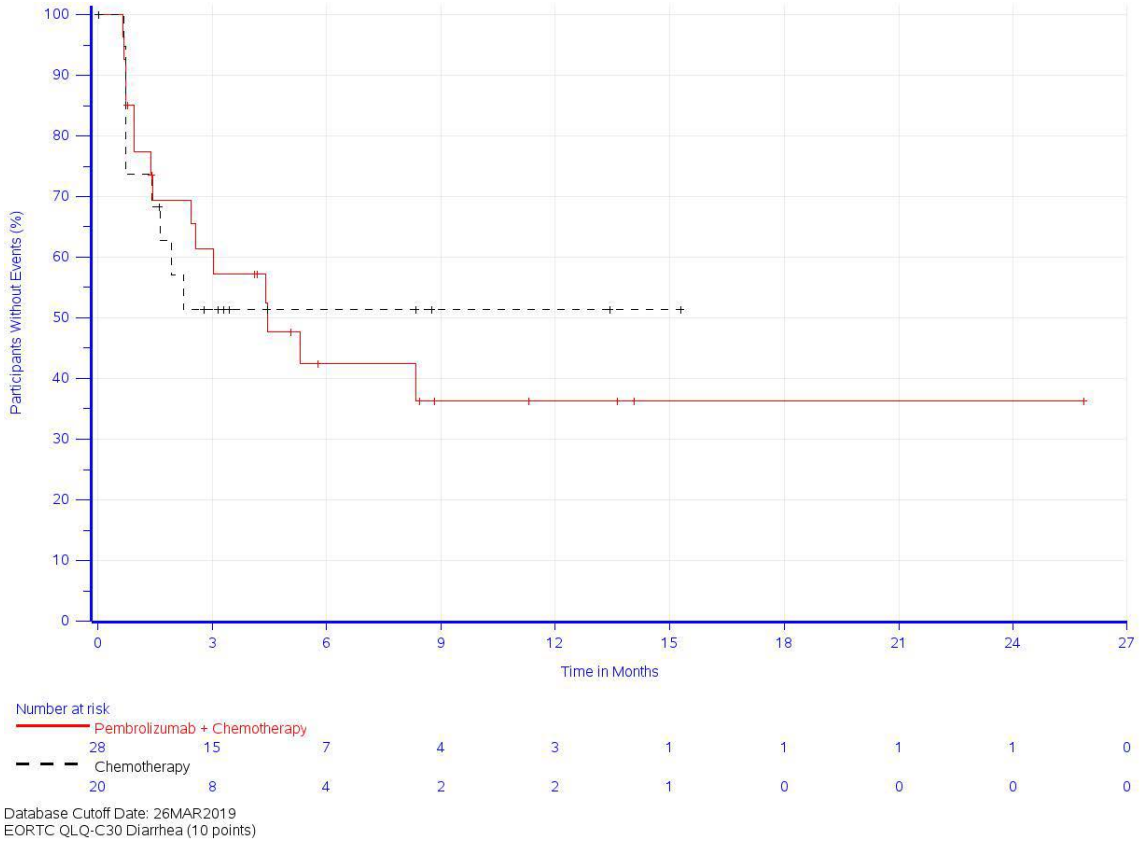

Figure 49: Kaplan-Meier curves for the outcome of diarrhoea (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 062 study, subpopulation of patients with adenocarcinoma of the gastrooesophageal junction and CPS ≥ 10

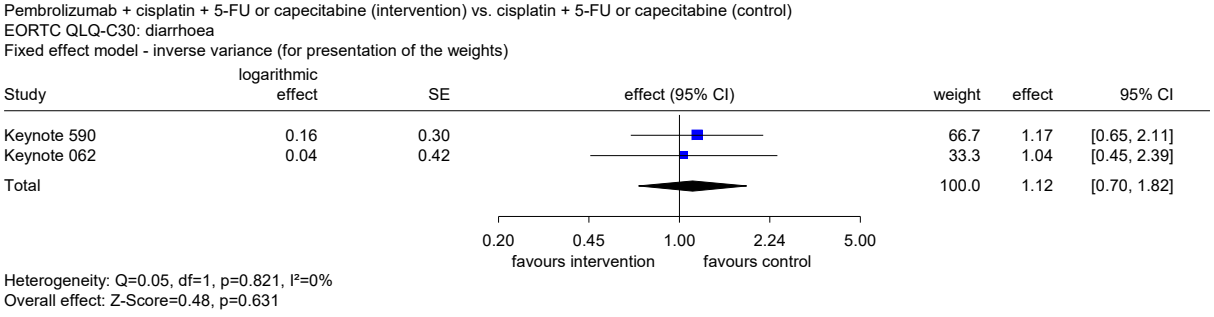

Figure 50: Metaanalysis with fixed effect for the outcome of diarrhoea (EORTC QLQ-C30 symptom scale), time to first deterioration by ≥ 10 points, effect measure of HR, KEYNOTE 590 and KEYNOTE 062 studies, subpopulations of patients with adenocarcinoma of the oesophagus or gastrooesophageal junction and CPS ≥ 10

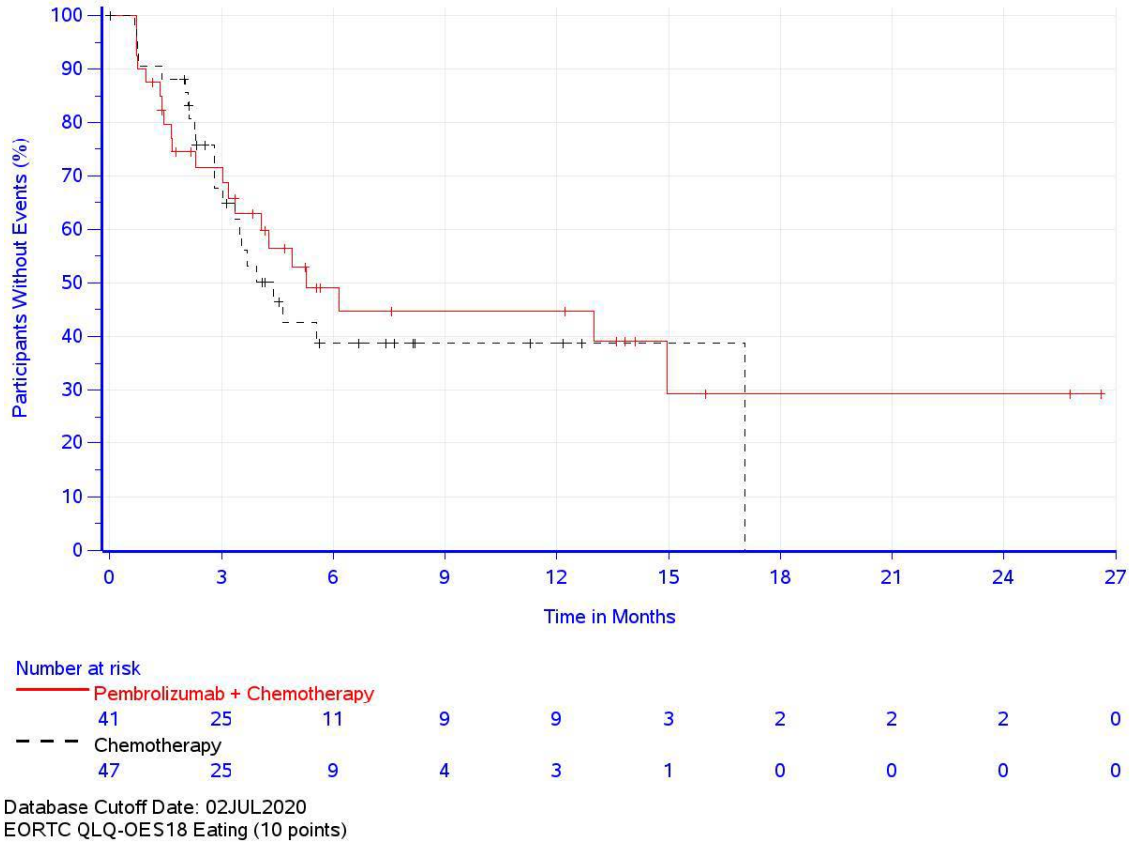

Figure 51: Kaplan-Meier curves for the outcome of eating (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

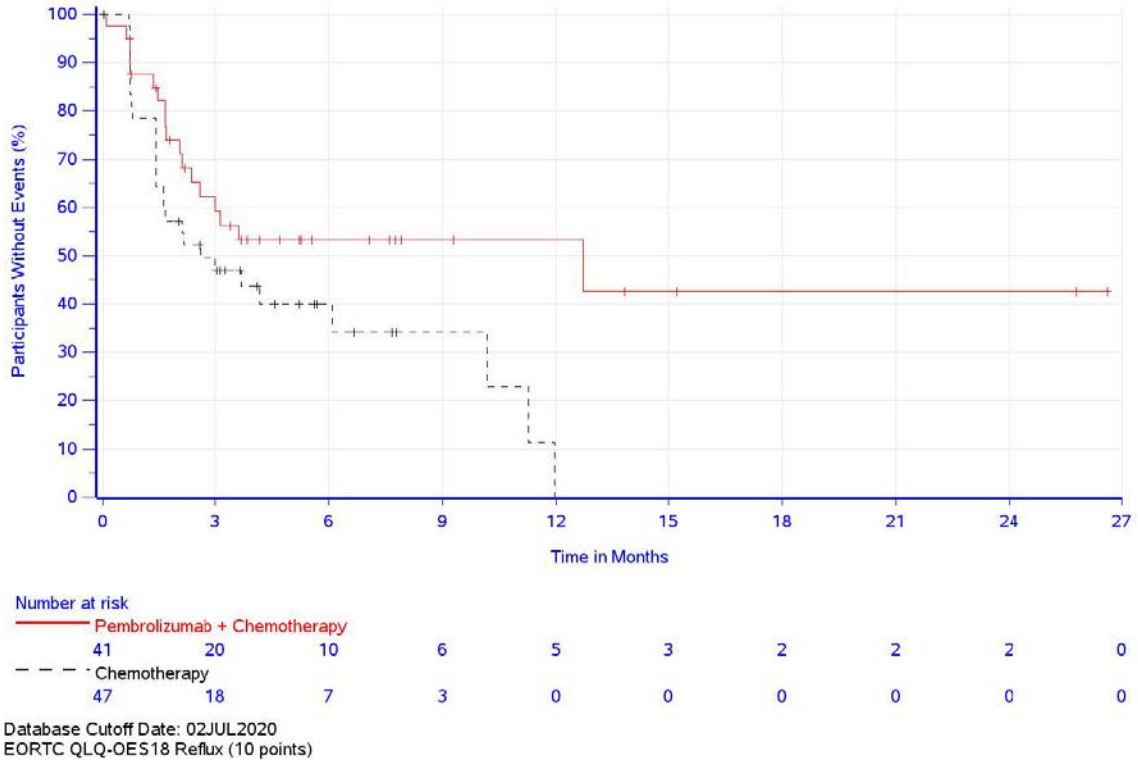

Figure 52: Kaplan-Meier curves for the outcome of reflux (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

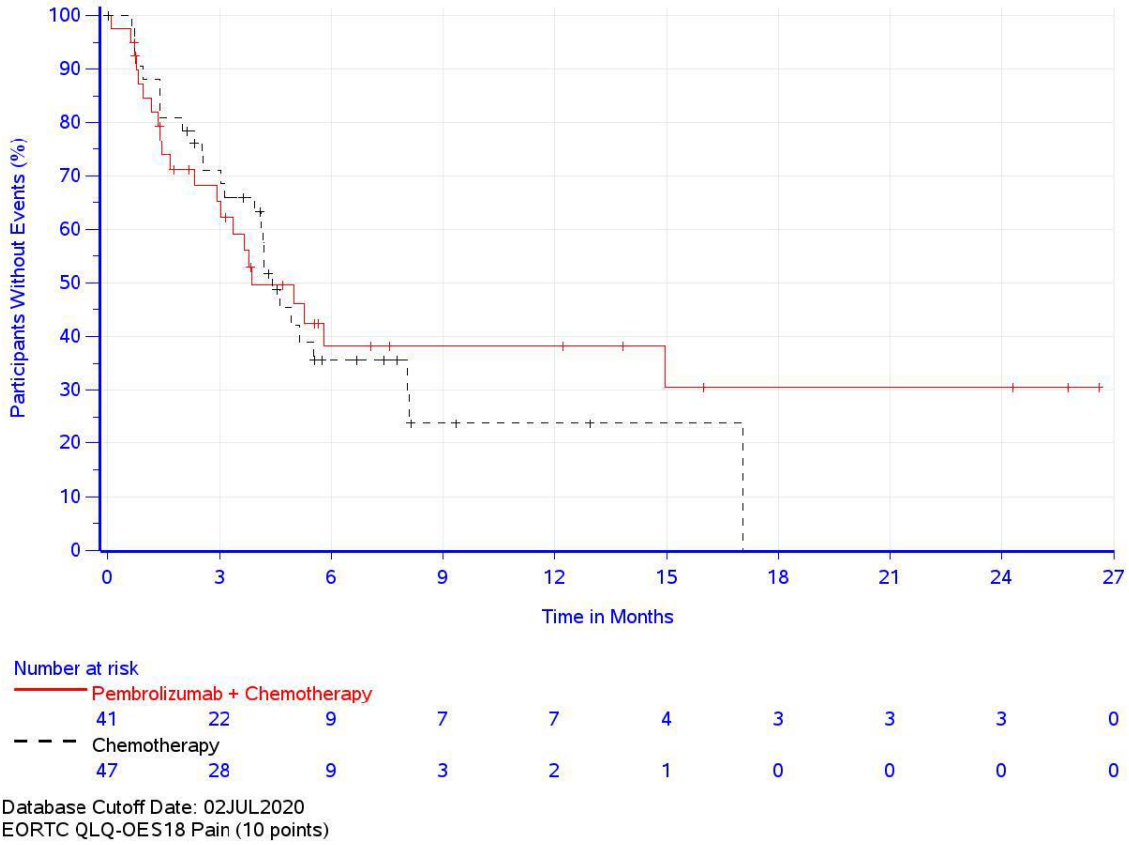

Figure 53: Kaplan-Meier curves for the outcome of pain (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

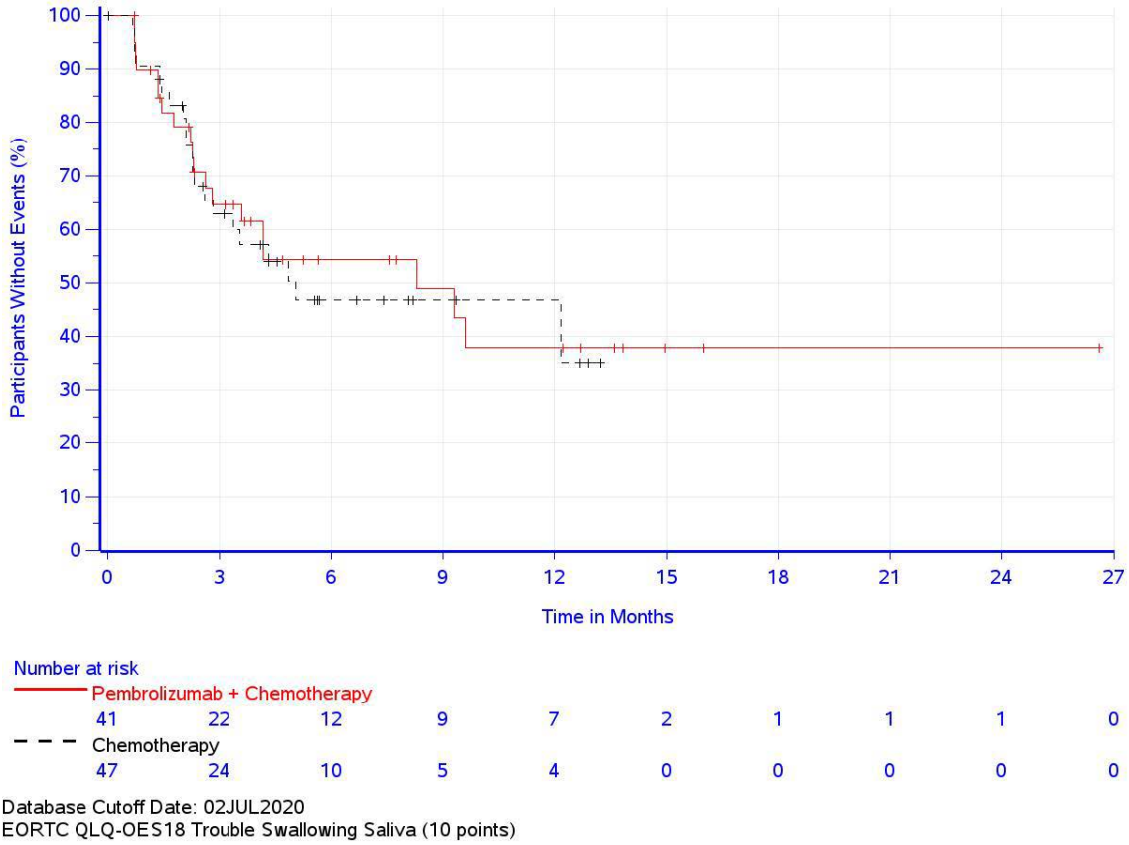

Figure 54: Kaplan-Meier curves for the outcome of swallowing saliva (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

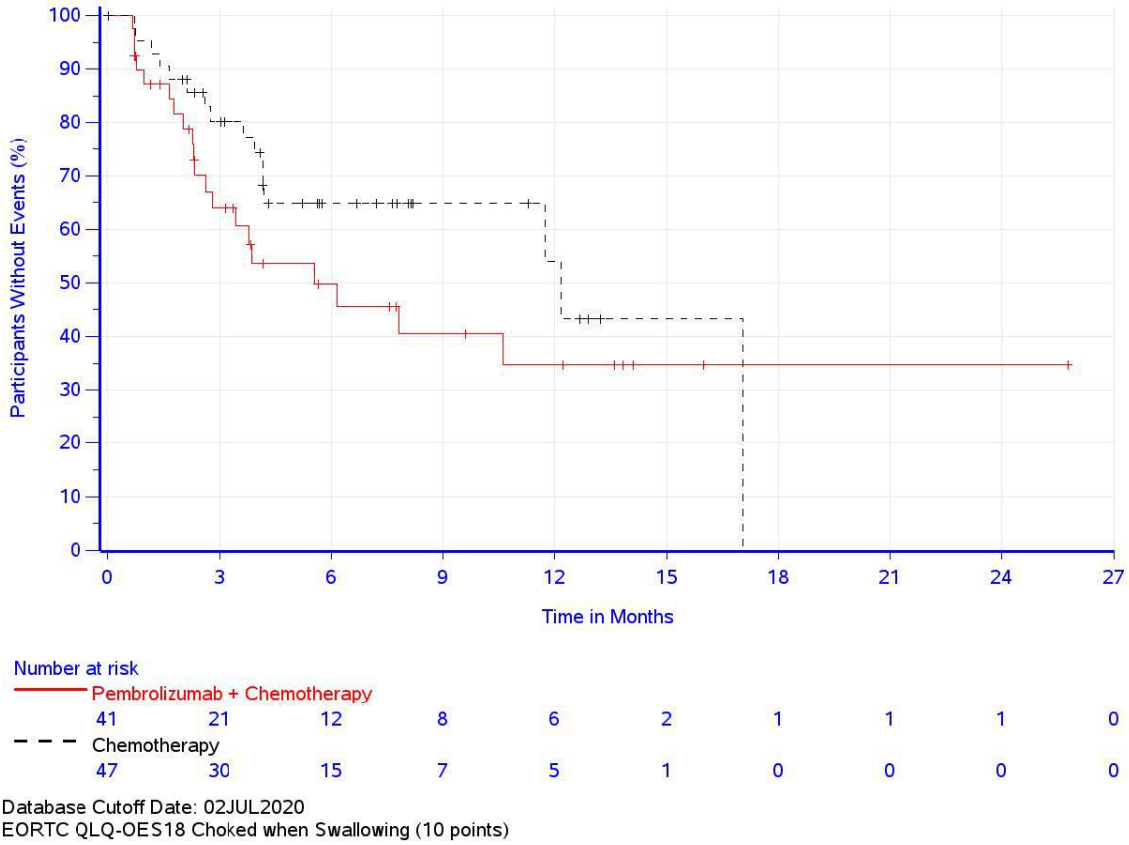

Figure 55: Kaplan-Meier curves for the outcome of choking (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

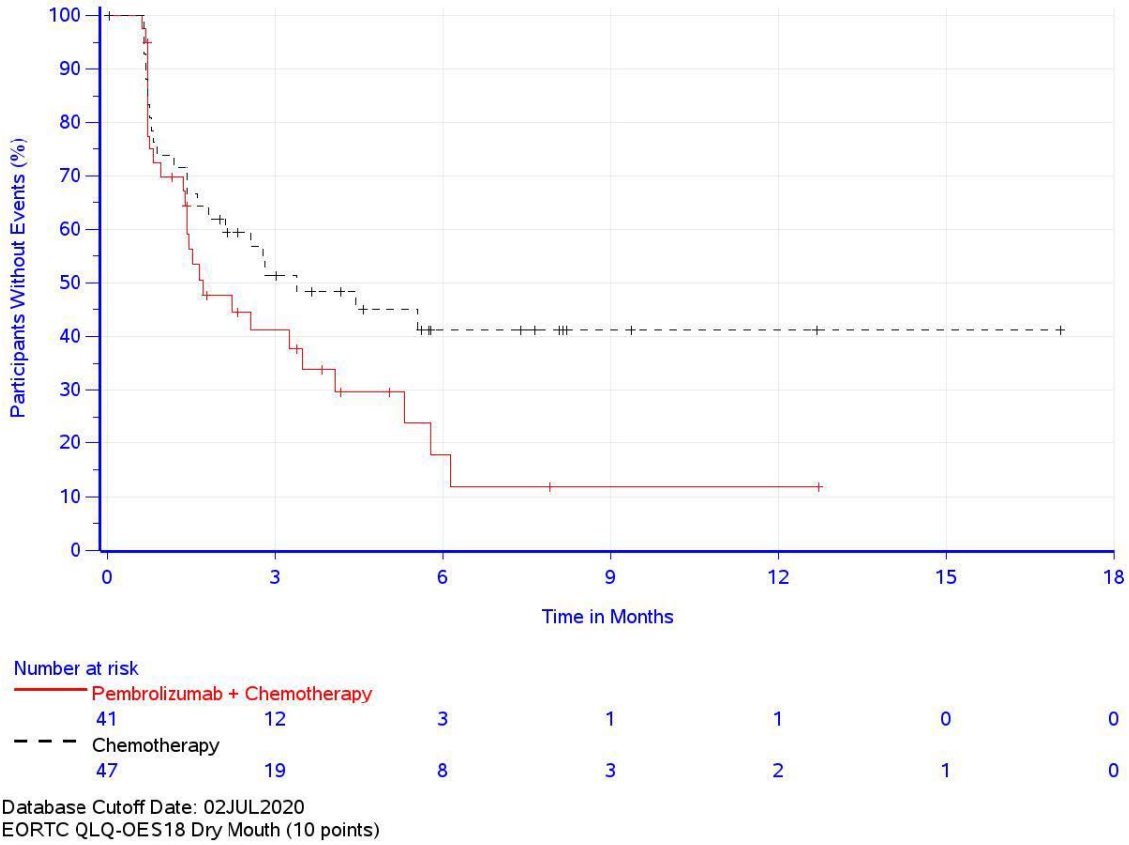

Figure 56: Kaplan-Meier curves for the outcome of dry mouth (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

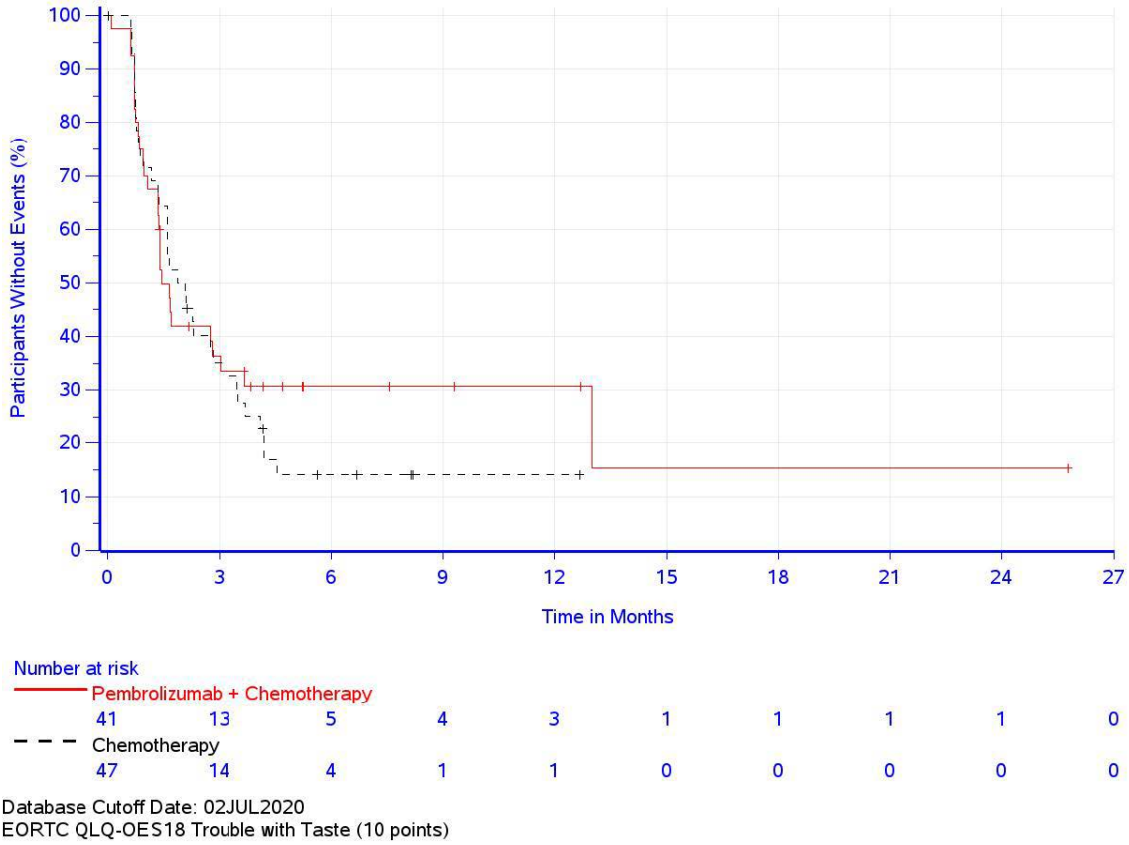

Figure 57: Kaplan-Meier curves for the outcome of taste (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

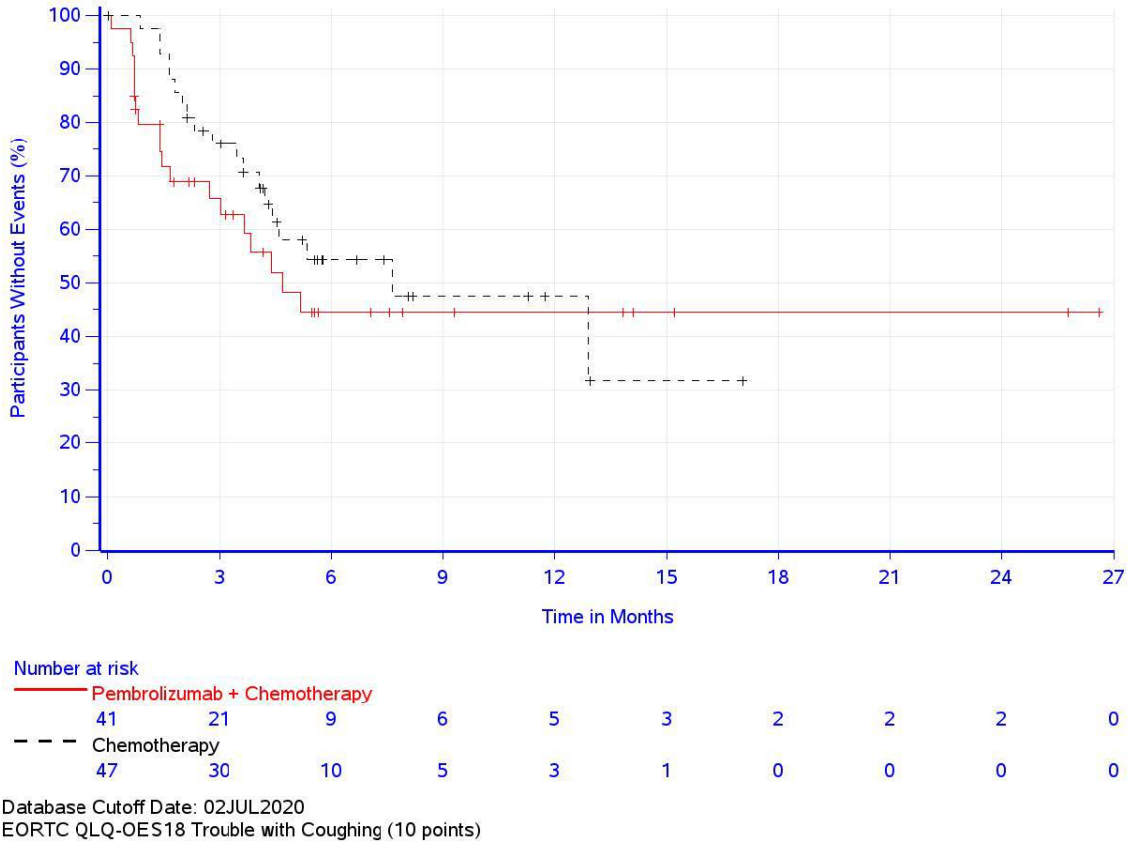

Figure 58: Kaplan-Meier curves for the outcome of cough (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

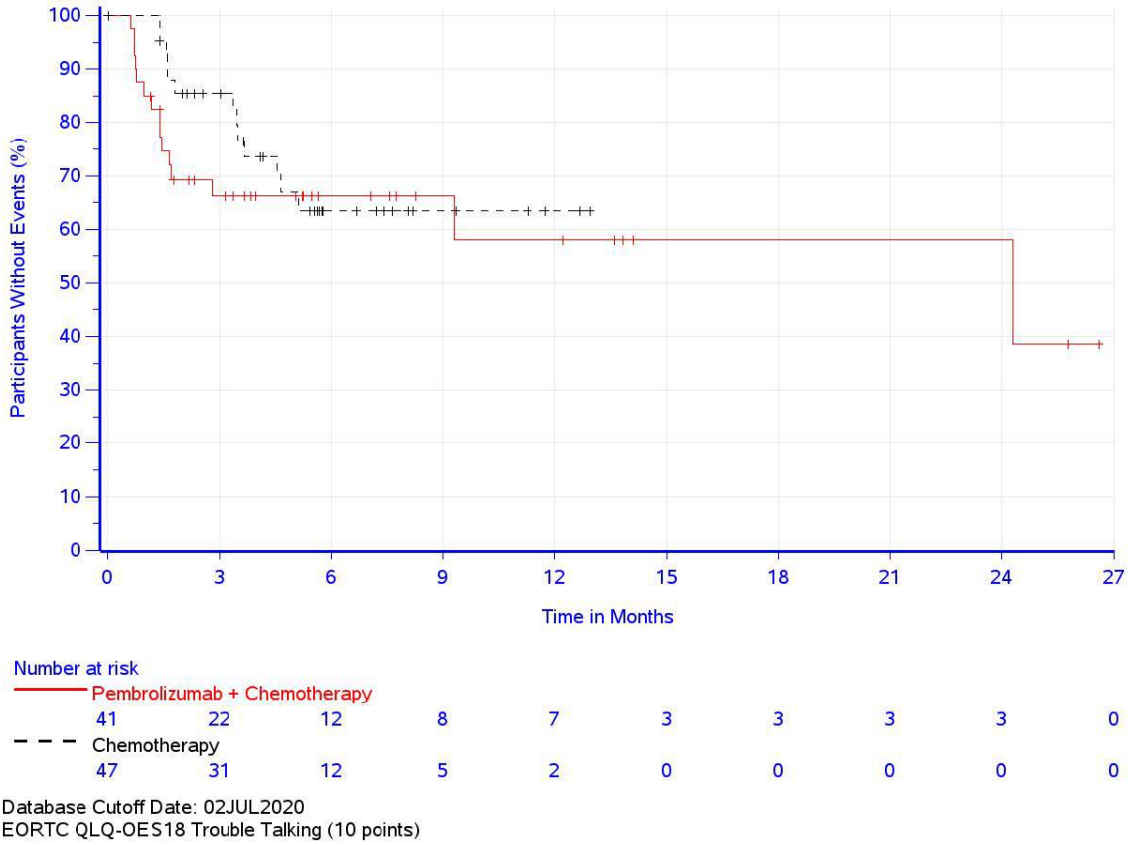

Figure 59: Kaplan-Meier curves for the outcome of speech (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

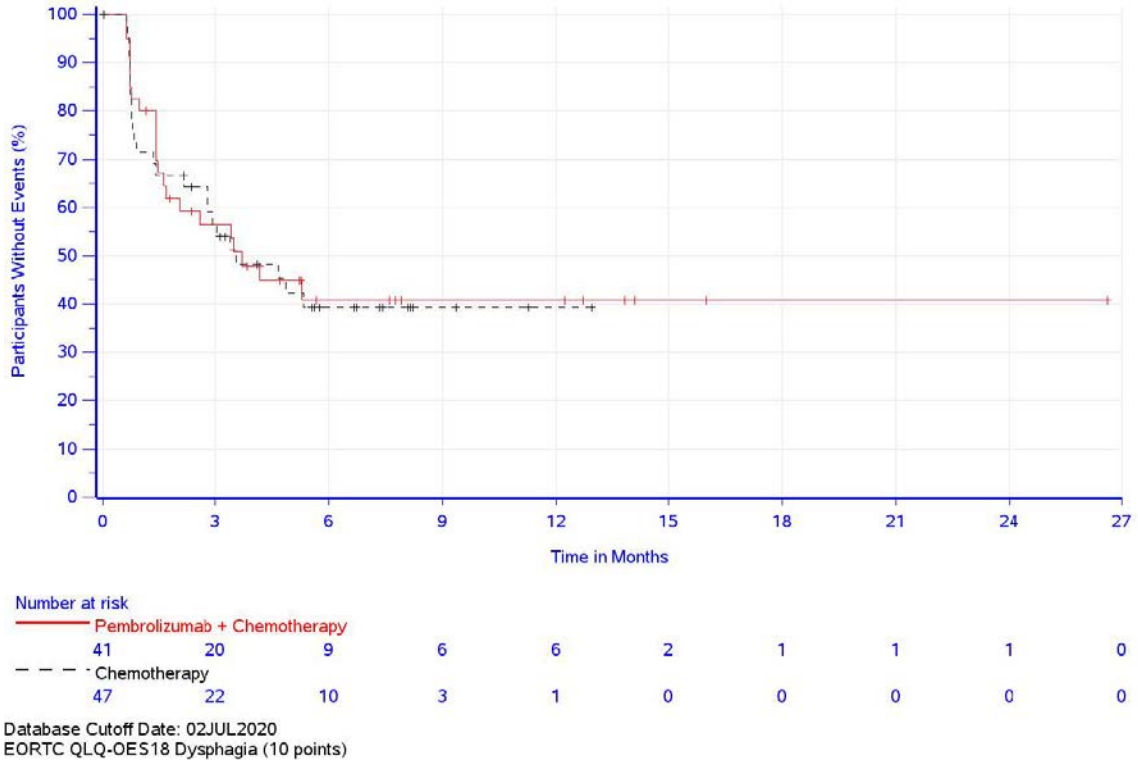

Figure 60: Kaplan-Meier curves for the outcome of dysphagia (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

B.2.2 Health-related quality of life

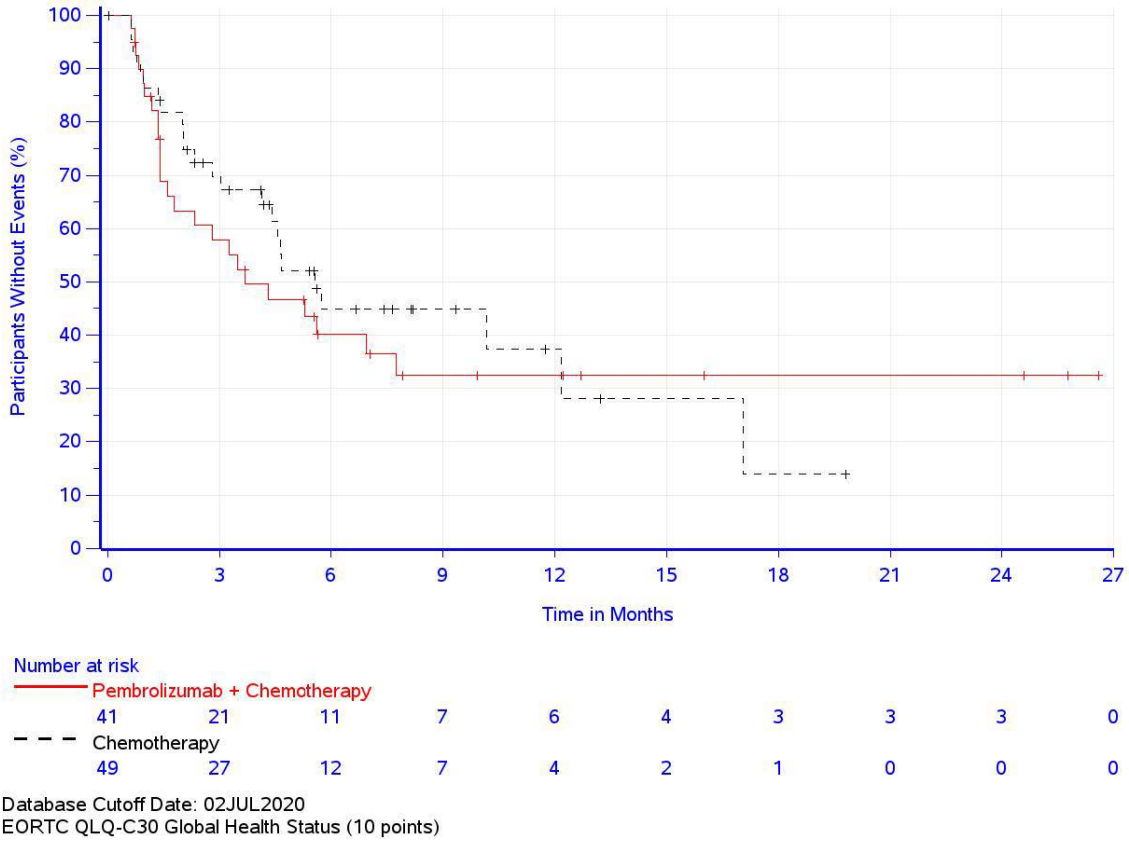

Figure 61: Kaplan-Meier curves for the outcome of global health status (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

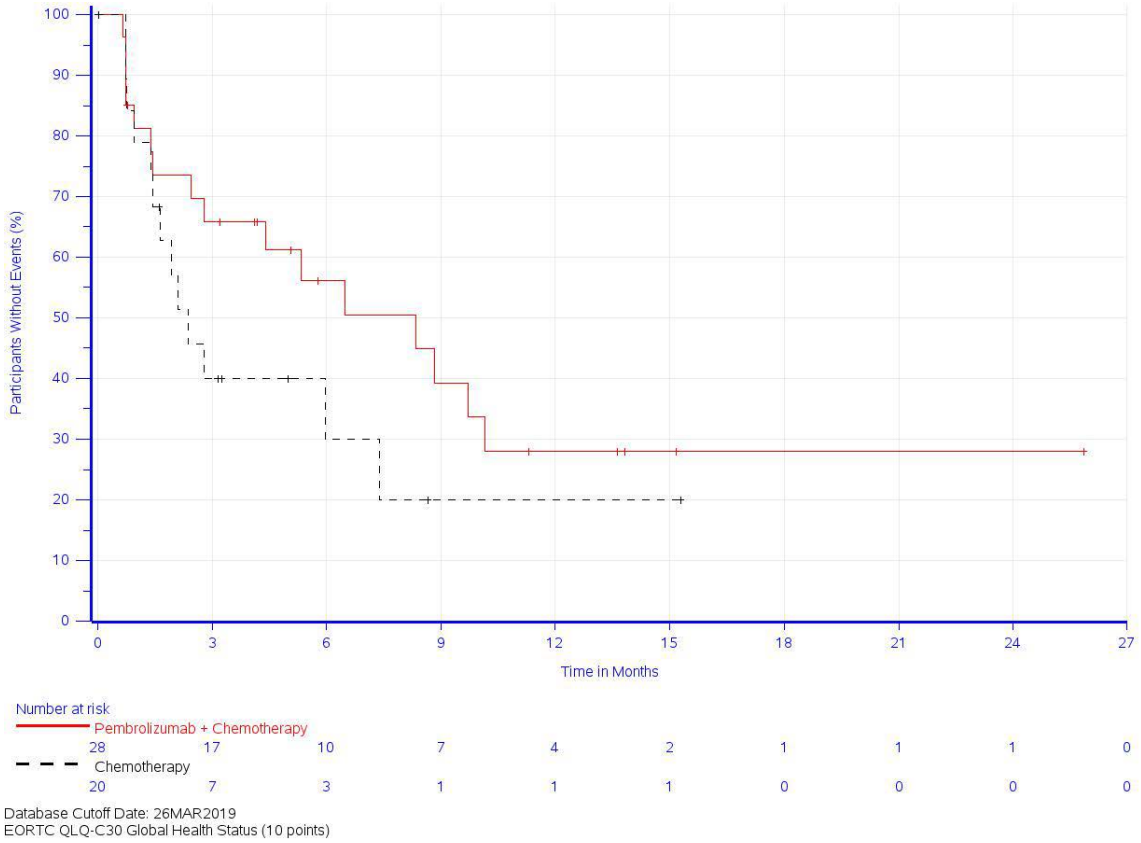

Figure 62: Kaplan-Meier curves for the outcome of global health status (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, KEYNOTE 062 study, subpopulation of patients with adenocarcinoma of the gastrooesophageal junction and CPS ≥ 10

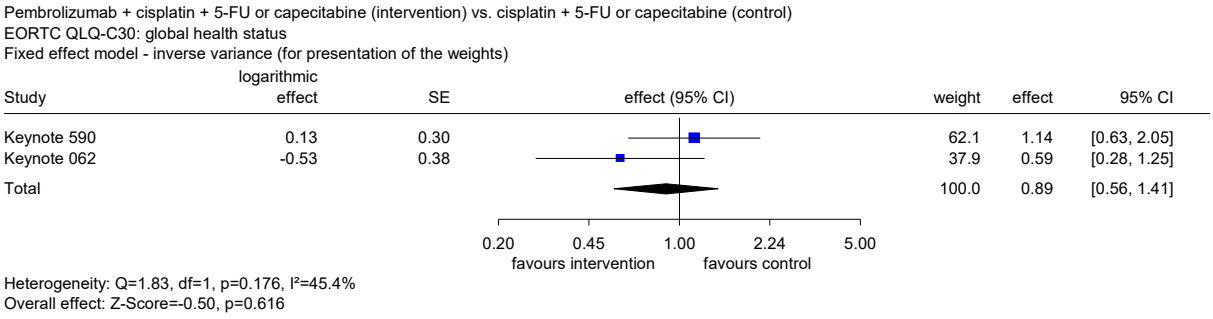

Figure 63: Metaanalysis with fixed effect for the outcome of global health status (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, effect measure of HR, KEYNOTE 590 and KEYNOTE 062 studies, subpopulations of patients with adenocarcinoma of the oesophagus or gastrooesophageal junction and CPS ≥ 10

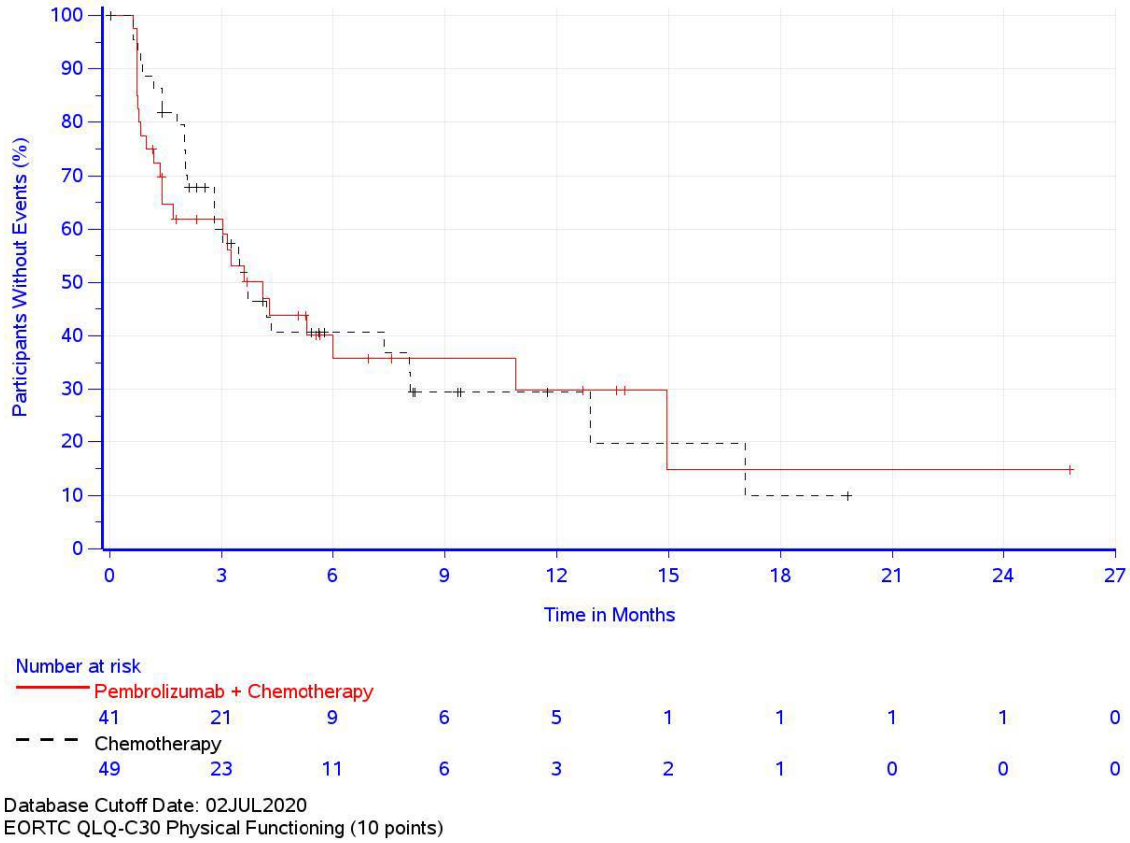

Figure 64: Kaplan-Meier curves for the outcome of physical functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

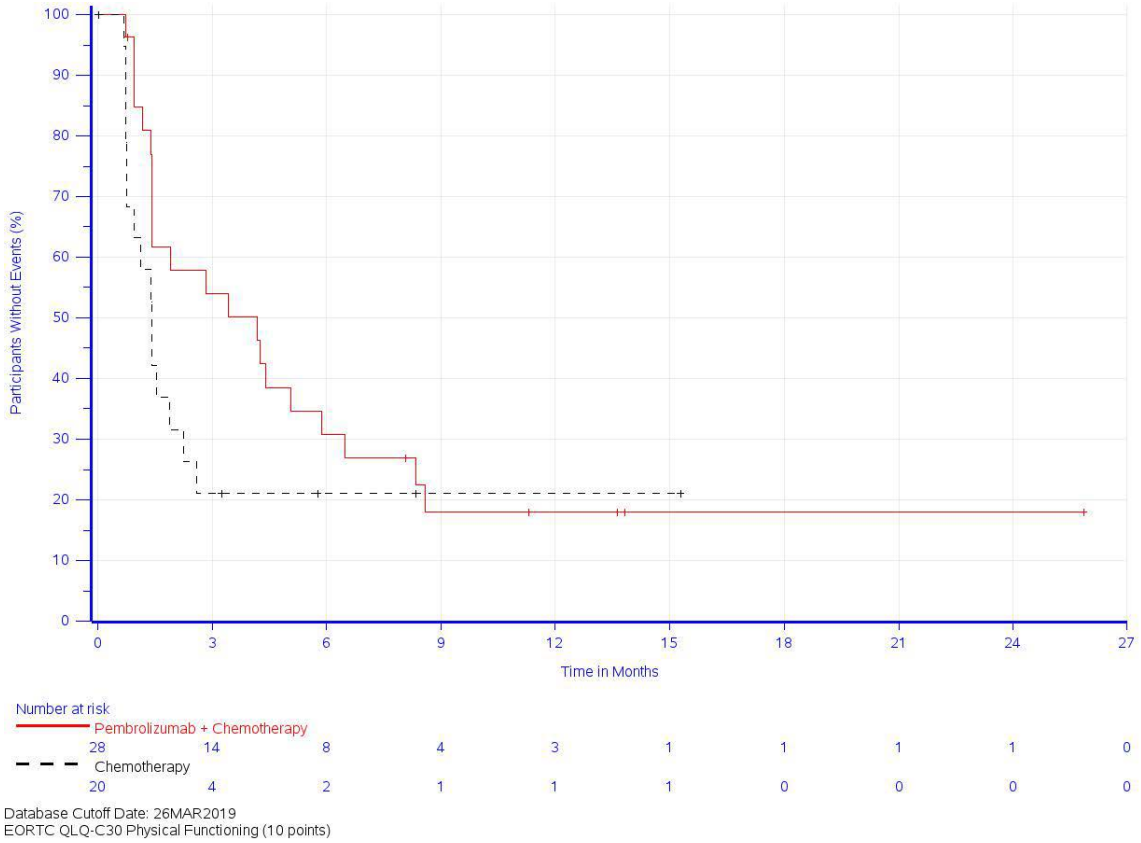

Figure 65: Kaplan-Meier curves for the outcome of physical functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, KEYNOTE 062 study, subpopulation of patients with adenocarcinoma of the gastrooesophageal junction and CPS ≥ 10

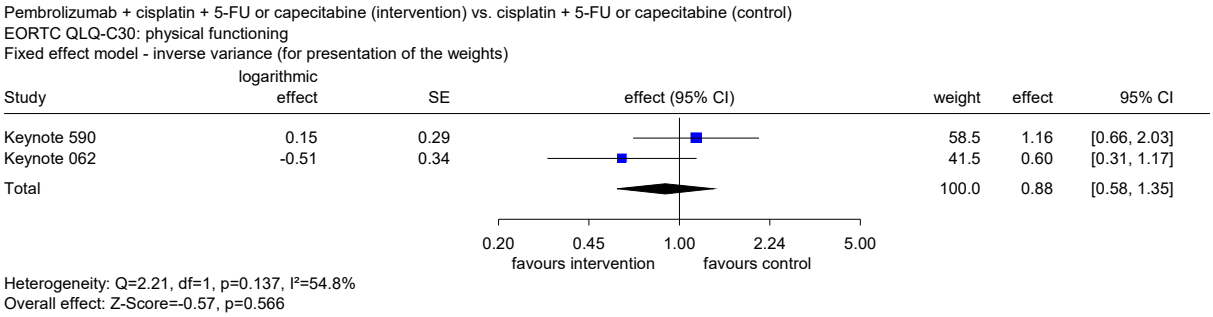

Figure 66: Metaanalysis with fixed effect for the outcome of physical functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, effect measure of HR, KEYNOTE 590 and KEYNOTE 062 studies, subpopulations of patients with adenocarcinoma of the oesophagus or gastrooesophageal junction and CPS ≥ 10

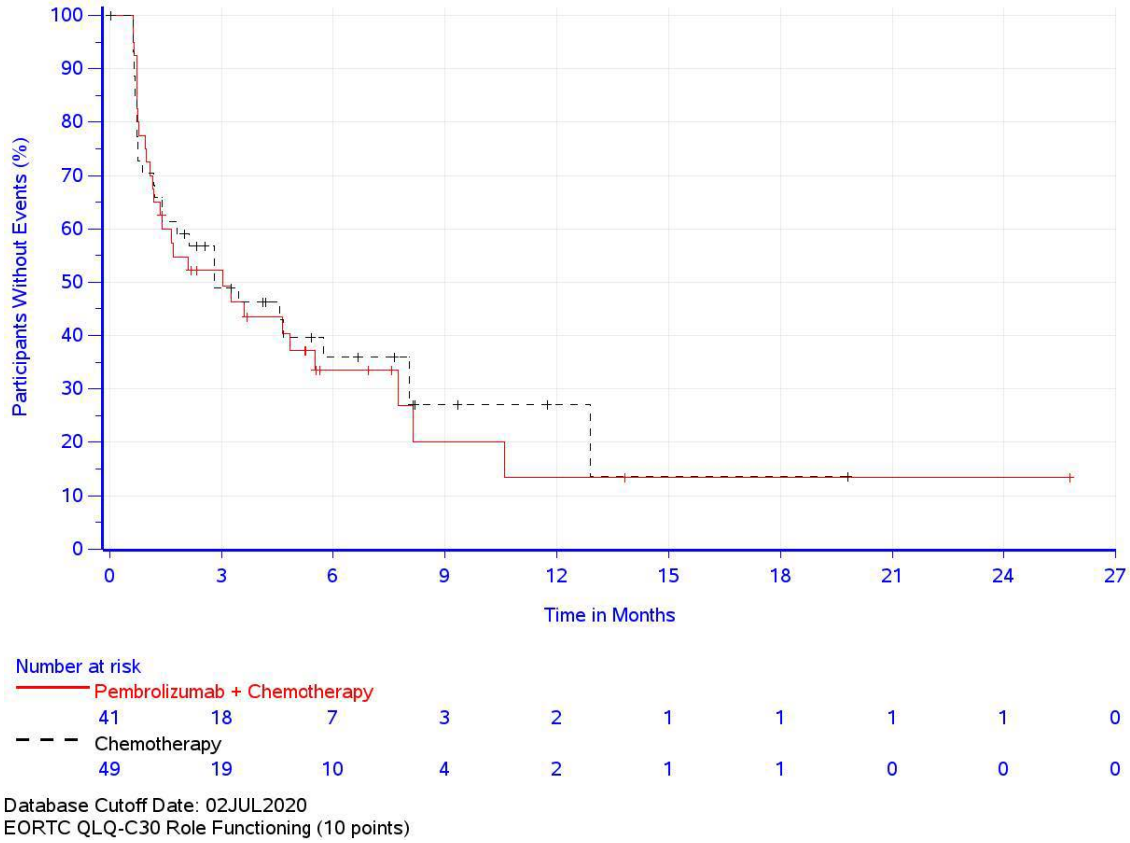

Figure 67: Kaplan-Meier curves for the outcome of role functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

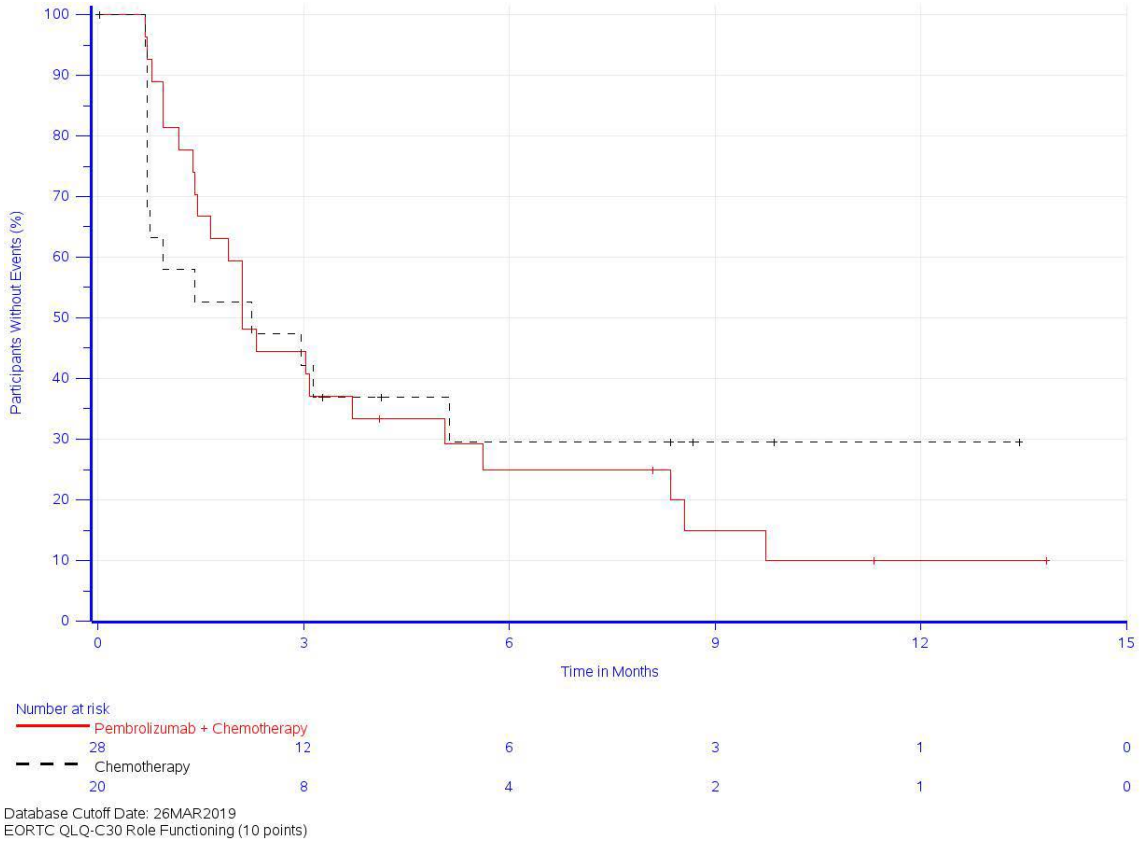

Figure 68: Kaplan-Meier curves for the outcome of role functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, KEYNOTE 062 study, subpopulation of patients with adenocarcinoma of the gastrooesophageal junction and CPS ≥ 10

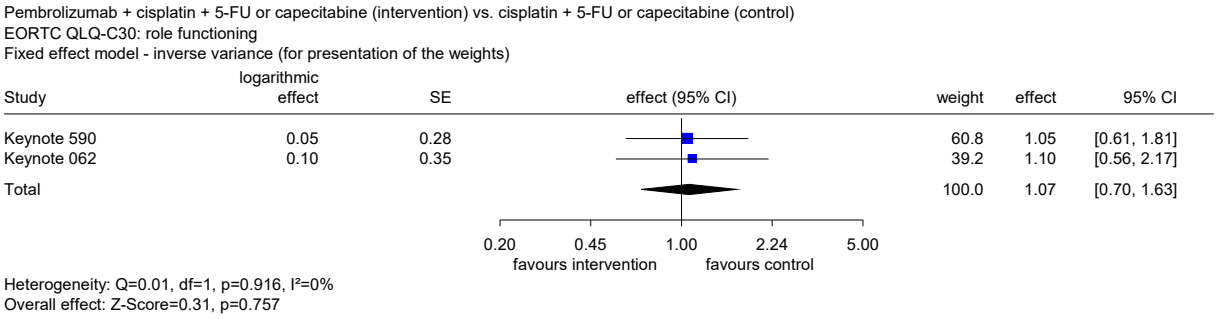

Figure 69: Metaanalysis with fixed effect for the outcome of role functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, effect measure of HR, KEYNOTE 590 and KEYNOTE 062 studies, subpopulations of patients with adenocarcinoma of the oesophagus or gastrooesophageal junction and CPS ≥ 10

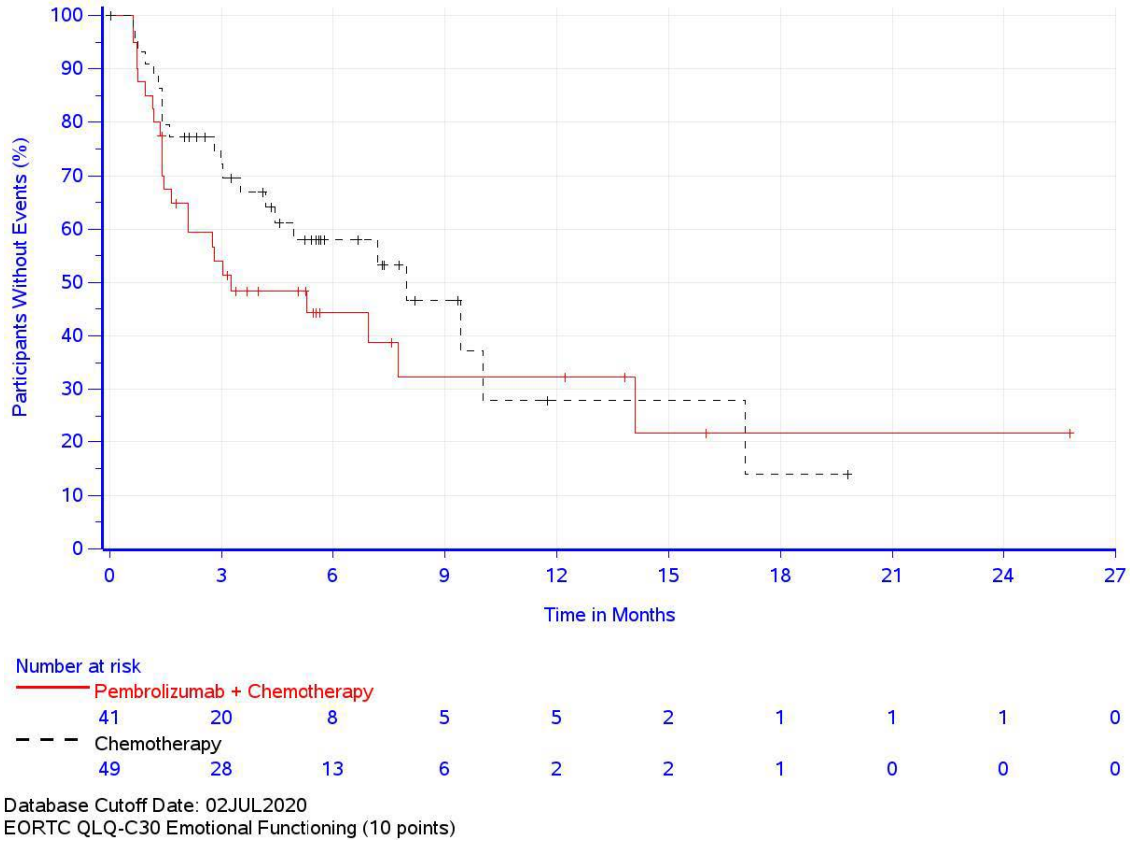

Figure 70: Kaplan-Meier curves for the outcome of emotional functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

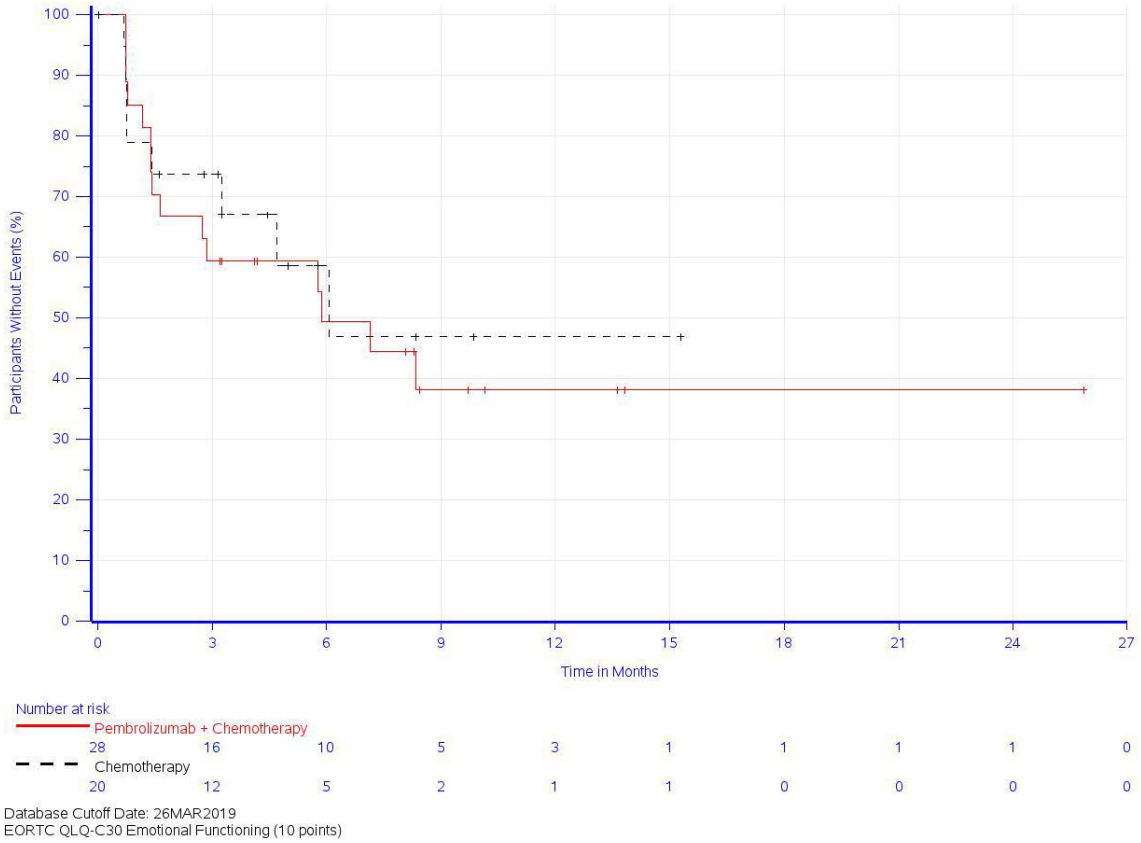

Figure 71: Kaplan-Meier curves for the outcome of emotional functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, KEYNOTE 062 study, subpopulation of patients with adenocarcinoma of the gastrooesophageal junction and CPS ≥ 10

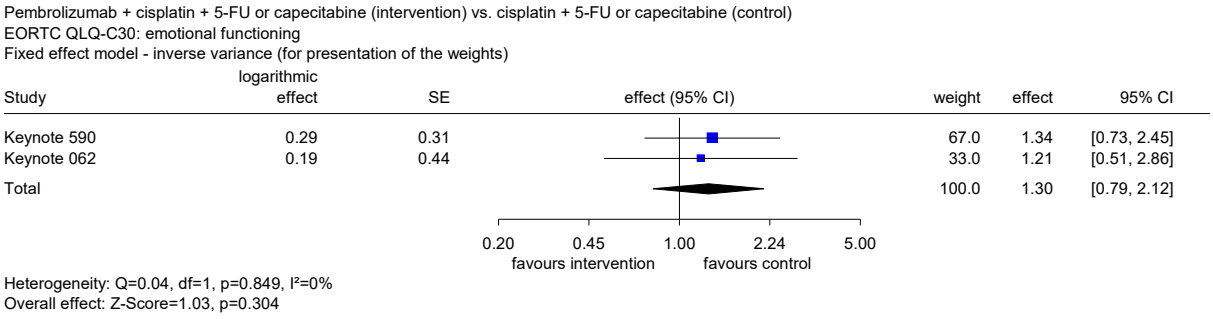

Figure 72: Metaanalysis with fixed effect for the outcome of emotional functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, effect measure of HR, KEYNOTE 590 and KEYNOTE 062 studies, subpopulations of patients with adenocarcinoma of the oesophagus or gastrooesophageal junction and CPS ≥ 10

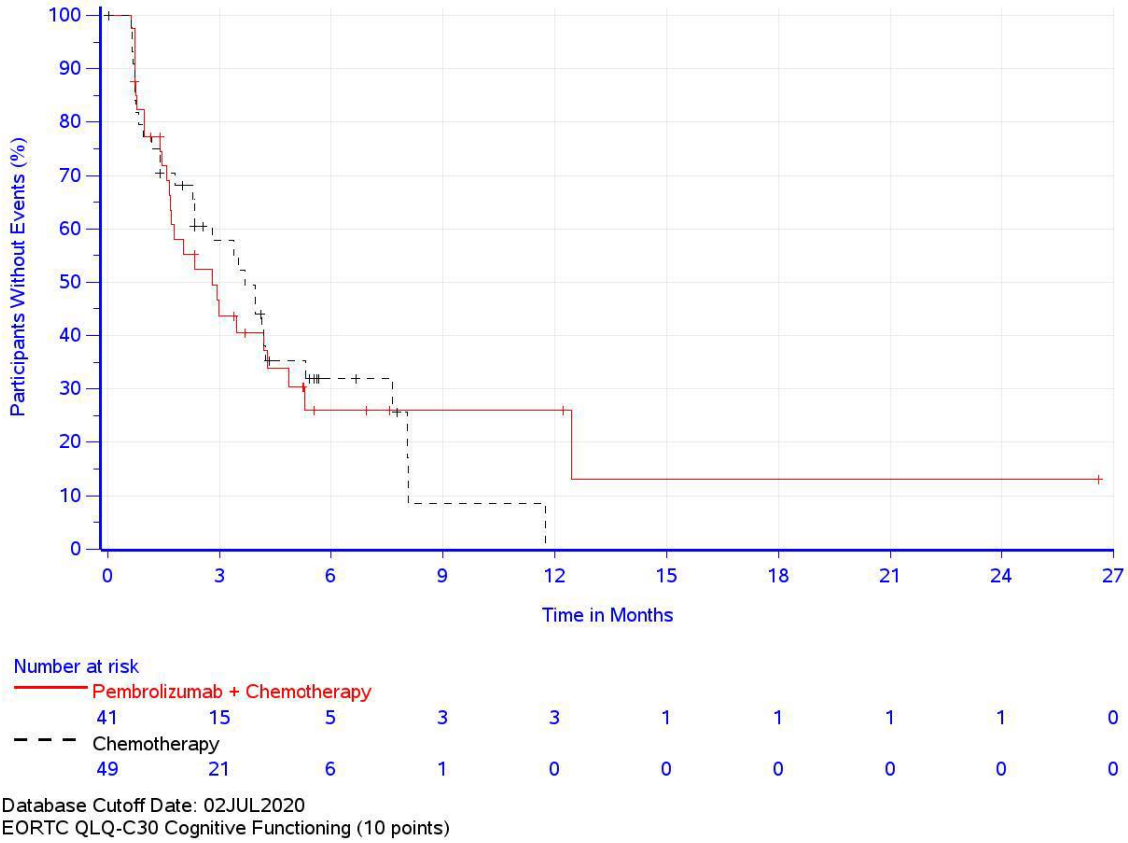

Figure 73: Kaplan-Meier curves for the outcome of cognitive functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

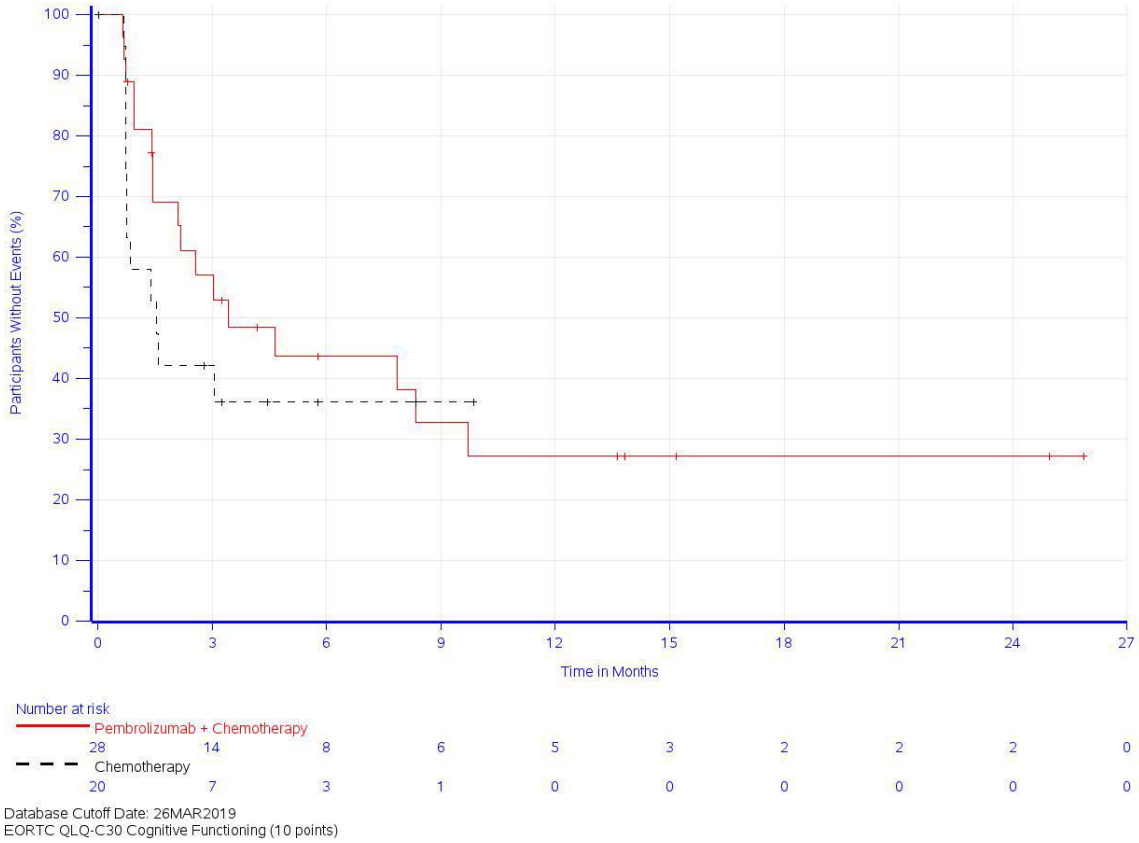

Figure 74: Kaplan-Meier curves for the outcome of cognitive functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, KEYNOTE 062 study, subpopulation of patients with adenocarcinoma of the gastrooesophageal junction and CPS ≥ 10

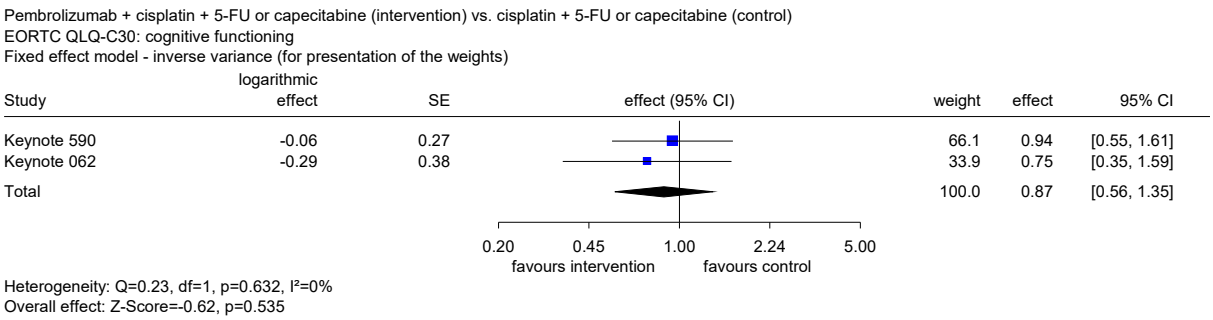

Figure 75: Metaanalysis with fixed effect for the outcome of cognitive functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, effect measure of HR, KEYNOTE 590 and KEYNOTE 062 studies, subpopulations of patients with adenocarcinoma of the oesophagus or gastrooesophageal junction and CPS ≥ 10

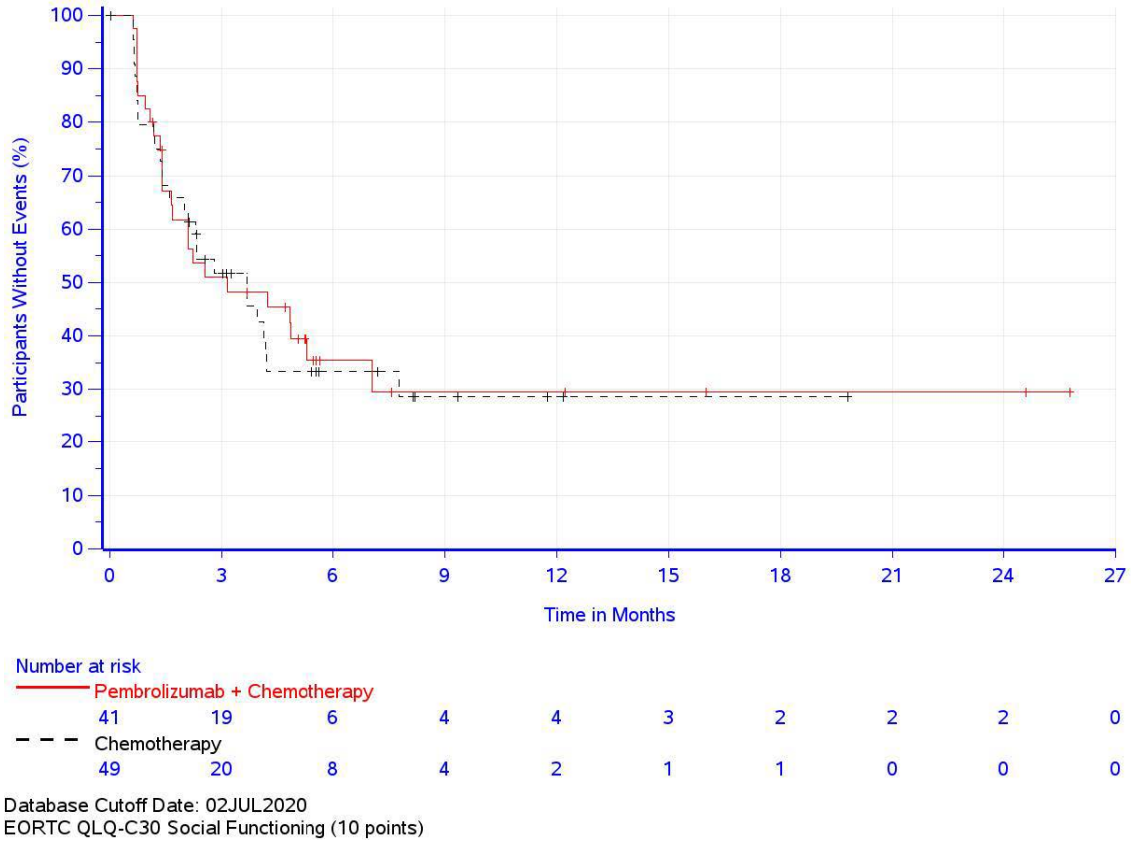

Figure 76: Kaplan-Meier curves for the outcome of social functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

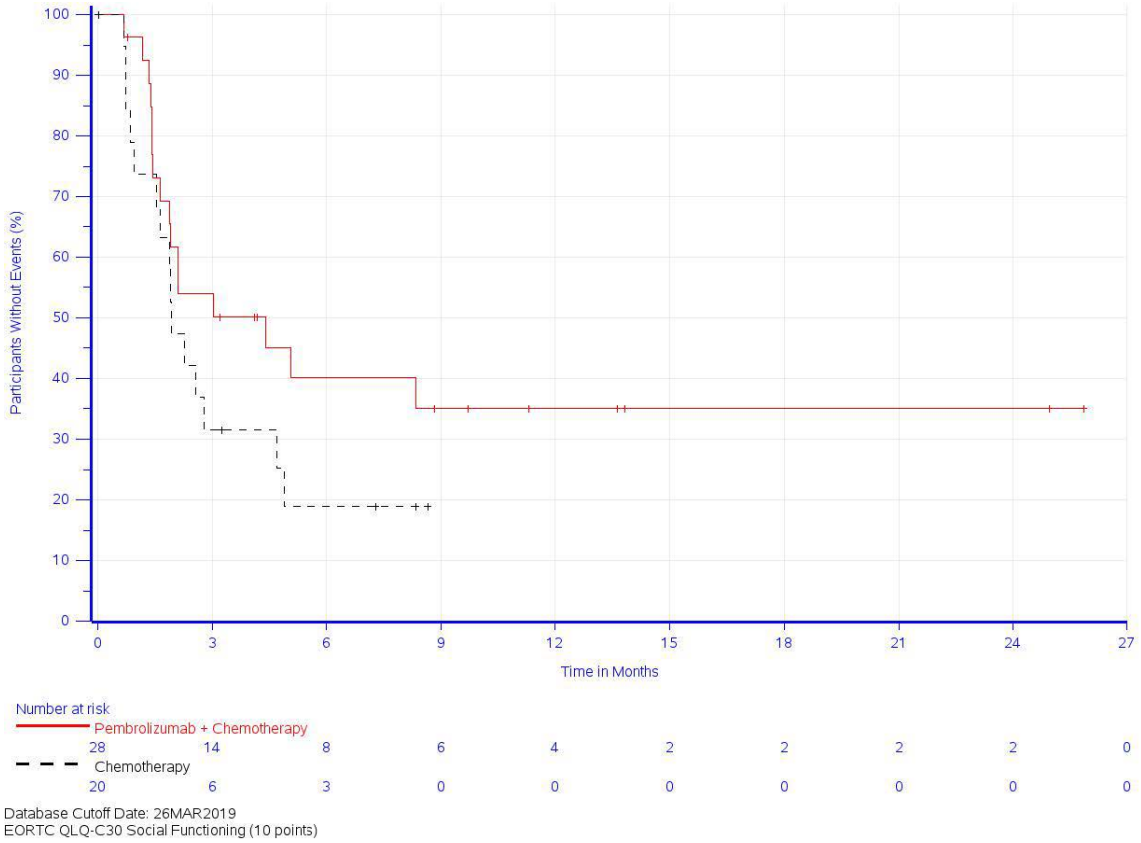

Figure 77: Kaplan-Meier curves for the outcome of social functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, KEYNOTE 062 study, subpopulation of patients with adenocarcinoma of the gastrooesophageal junction and CPS ≥ 10

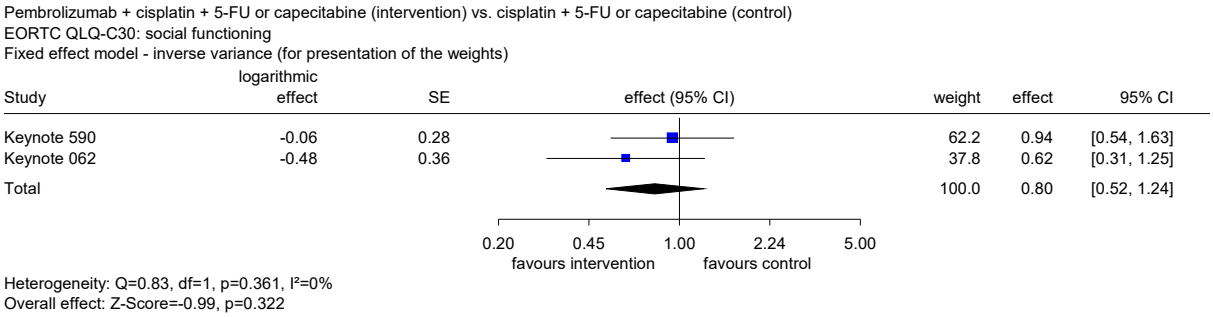

Figure 78 Metaanalysis with fixed effect for the outcome of social functioning (EORTC QLQ-C30 functional scale), time to first deterioration by ≥ 10 points, effect measure of HR, KEYNOTE 590 and KEYNOTE 062 studies, subpopulations of patients with adenocarcinoma of the oesophagus or gastrooesophageal junction and CPS ≥ 10

B.2.3 Discontinuation due to AEs

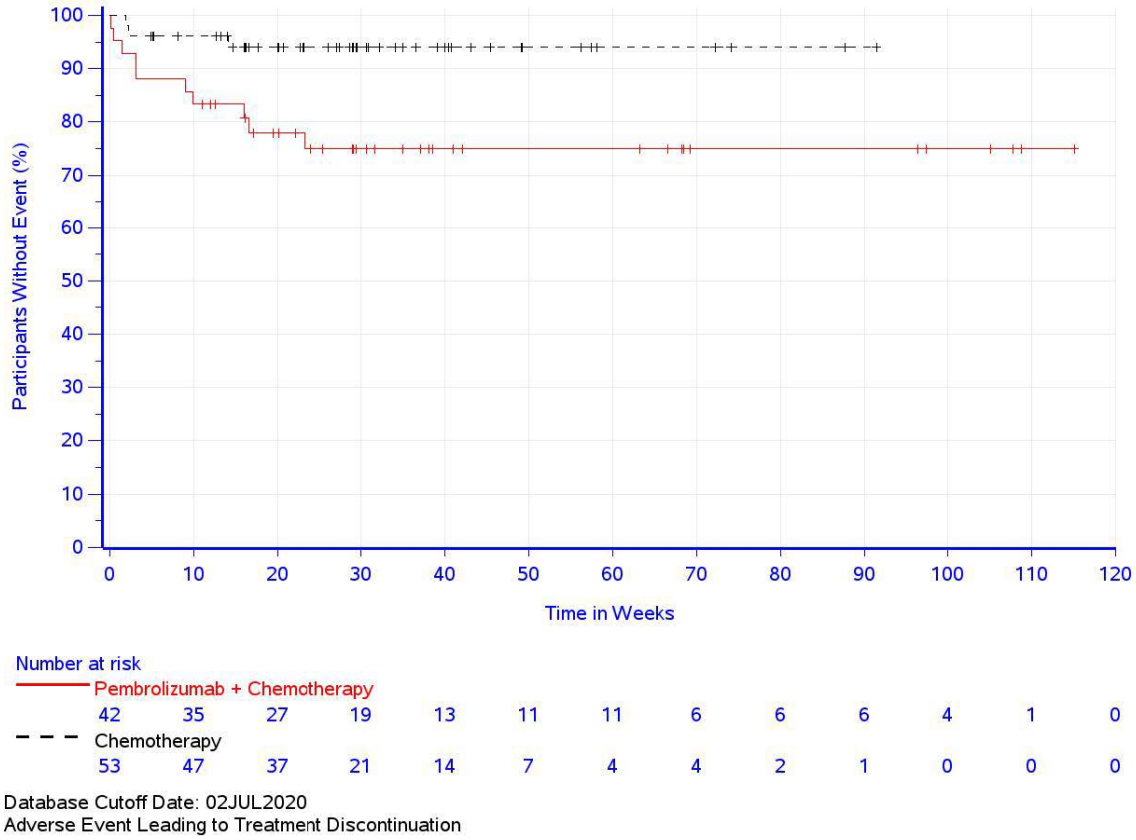

Figure 79: Kaplan-Meier curves for the outcome of discontinuation due to AEs, KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or gastrooesophageal junction and CPS ≥ 10

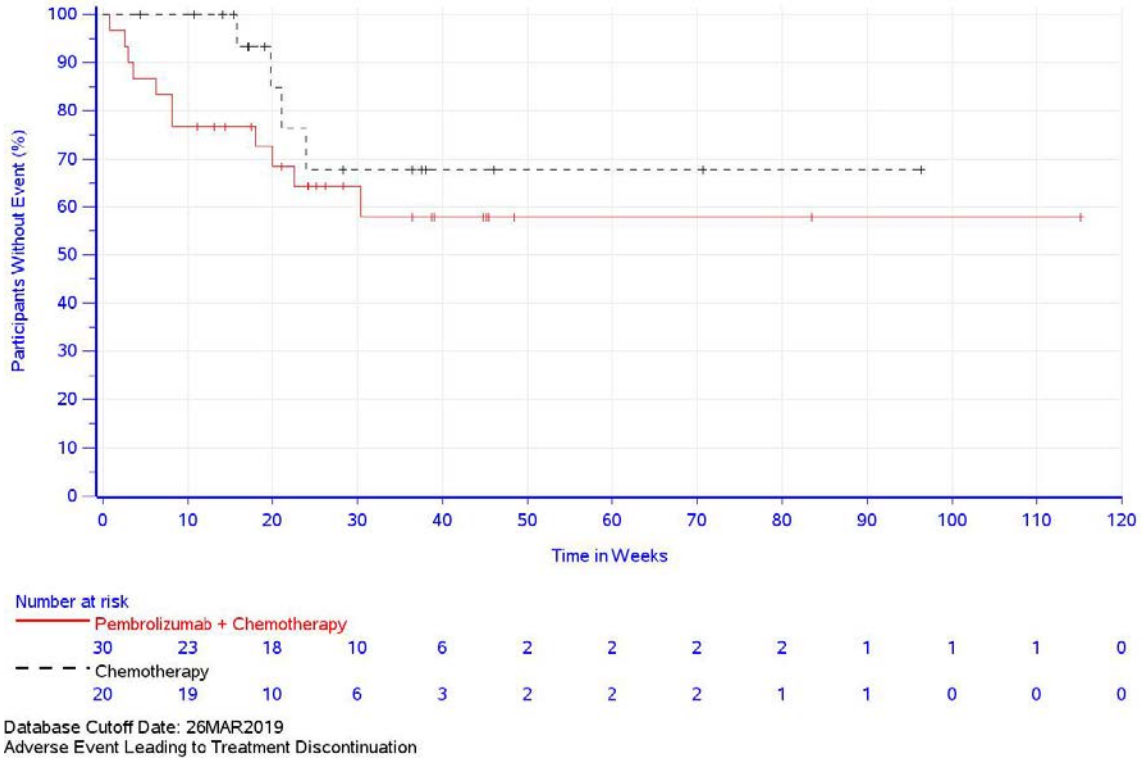

Figure 80: Kaplan-Meier curves for the outcome of discontinuation due to AEs, KEYNOTE 062 study, subpopulation of patients with adenocarcinoma of the gastrooesophageal junction and CPS ≥ 10

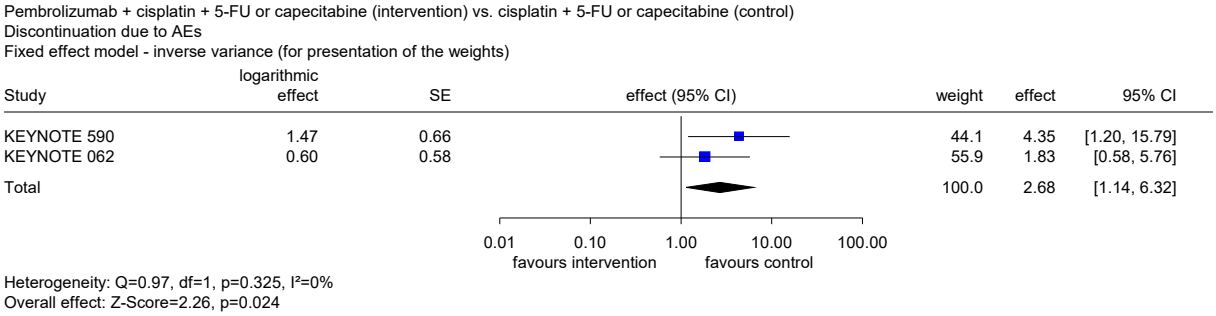

Figure 81: Metaanalysis with fixed effect for the outcome of discontinuation due to AEs, effect measure of HR, KEYNOTE 590 and KEYNOTE 062 studies, subpopulations of patients with adenocarcinoma of the oesophagus or gastrooesophageal junction and CPS ≥ 10

B.2.4 Subgroup analyses

Sex (female versus male)

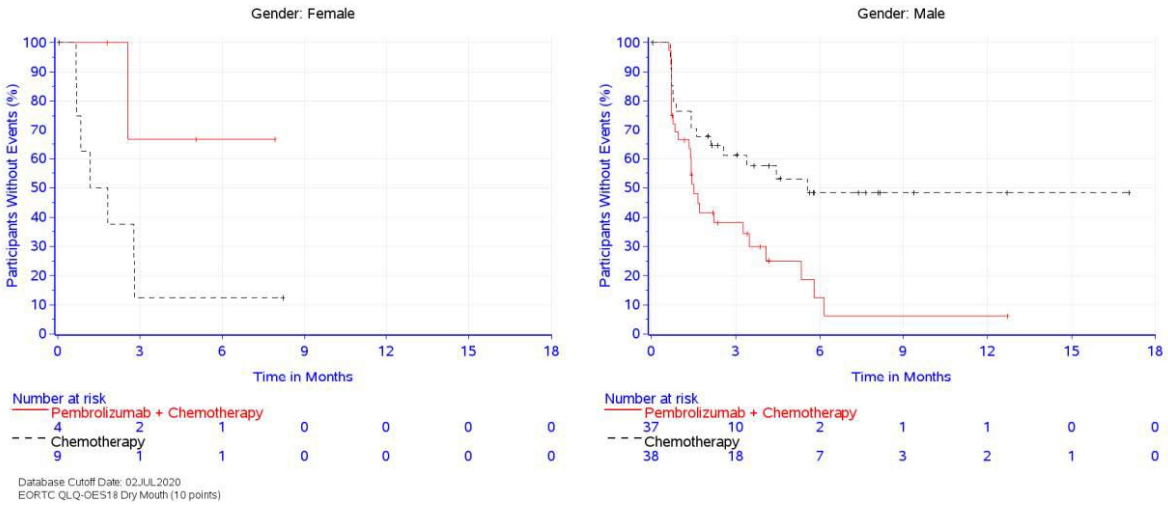

Figure 82: Kaplan-Meier curves for the outcome of dry mouth (EORTC QLQ-OES18 symptom scale), time to first deterioration by ≥ 10 points, subgroup analysis by sex (female versus male), KEYNOTE 590 study, subpopulation of patients with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

Appendix C Supplementary presentation of responder analyses of EQ-5D VAS (research question B1: subpopulation with adenocarcinoma of the oesophagus or gastrooesophageal junction and CPS ≥ 10, KEYNOTE 590 and KEYNOTE 062 studies)

Table 13: Results (morbidity, time to event, supplementary presentation) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine versus placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastrooesophageal junction and CPS ≥ 10

Study Outcome category Outcome	Pembrolizumab + cisplatin + 5-FU/capecitabine		Placebo + cisplatin + 5-FU/capecitabine		Pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine
	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
Morbidity					
EQ-5D VAS[a]					
Deterioration by 7 points					
KEYNOTE 590	41	4.8 [3.2; 9.3] 24 (58.5)	49	4.5 [2.8; 8.1] 27 (55.1)	0.83 [0.47; 1.48]; 0.529[b]
KEYNOTE 062	29	2.3 [1.0; 8.3] 21 (72.4)	20	2.8 [0.8; 6.1] 14 (70.0)	1.02 [0.51; 2.00]; 0.966[c]
Total[d]					0.90 [0.58; 1.40]; 0.652
Deterioration by 10 points					
KEYNOTE 590	41	7.8 [3.6; 13.8] 22 (53.7)	49	4.9 [3.0; 8.1] 27 (55.1)	0.78 [0.43; 1.41]; 0.410[b]
KEYNOTE 062	29	2.4 [1.4; 8.3] 21 (72.4)	20	3.0 [1.9; NC] 11 (55.0)	1.38 [0.66; 2.87]; 0.387[c]
Total[d]					0.98 [0.62; 1.55]; 0.922

a. Time to first deterioration; a score decrease by 7 or 10 points from baseline is defined as a deterioration (scale range 0 to 100).
b. HR and CI from Cox proportional hazards model, stratified by region (Asia vs. rest of the world) and ECOG (0 vs. 1) with associated p-value from 2-sided Wald test.
c. HR and CI from Cox proportional hazards model, nonstratified with associated p-value from 2-sided Wald test.
d. IQWiG calculation; metaanalysis with fixed effect (method with inverse variance).

5-FU: 5 fluorouracil; CI: confidence interval; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; VAS: visual analogue scale