Pembrolizumab (gastric or gastro-oesophageal junction adenocarcinoma, HER2-positive)

Addendum to Project A24-01 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AEOSI	adverse events of special interest
CAPOX	capecitabine and oxaliplatin
CPS	combined positive score
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-OG22	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Oesophago-Gastric 25
EORTC QLQ-STO22	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Gastric Cancer 22
FP	5-fluorouracil + cisplatin
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GEJ	gastro-oesophageal junction
HER2	human epidermal growth factor receptor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PT	Preferred Term
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 8 May 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-01 (Pembrolizumab – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the KEYNOTE-811 study, taking into account the comparator therapies with oxaliplatin in the relevant patient population (programmed cell death ligand 1 [PD-L1] expressing tumours, combined positive score [CPS] ≥ 1), taking into account the information in the dossier [2].

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

2 Assessment

The company presented the KEYNOTE-811 study to assess the added benefit of pembrolizumab in combination with trastuzumab and a fluoropyrimidine and platinum-based chemotherapy compared to the appropriate comparator therapy (ACT) for first-line treatment of adult patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1).

As explained in dossier assessment A24-01 [1], the analyses for the subpopulation with PD-L1 expression ≥ 1% (CPS ≥ 1, hereinafter referred to as "PD-L1-positive population") of the KEYNOTE-811 study, which compared pembrolizumab in combination with trastuzumab and fluoropyrimidine and platinum-based chemotherapy with treatment with trastuzumab and fluoropyrimidine and platinum-based chemotherapy, presented by the company, were not used for the benefit assessment, as the ACT was not implemented. The comparator therapy used in the study included both regimens with the platinum component oxaliplatin and regimens with the component cisplatin. The ACT specified by the G-BA was treatment of physician's choice, selecting from

- trastuzumab in combination with capecitabine and cisplatin

or

- trastuzumab in combination with 5-fluorouracil and cisplatin (FP).

In compliance with the commission, the results of the KEYNOTE-811 study for the PD-L1-positive population are presented below, taking into account the comparator therapies with oxaliplatin (capecitabine and oxaliplatin [CAPOX]). This means that the entire PD-L1-positive population of the study's global cohort is included in the assessment.

2.1 Study characteristics

Detailed characteristics of the KEYNOTE-811 study can be found in dossier assessment A24-01 [1].

Analogous to the procedure in dossier assessment A24-01 [1], the most recent, third data cut-off from 29 March 2023 (planned interim analysis after at least 606 events in the outcome of progression-free survival [PFS]) is relevant for the present assessment.

In addition to the information provided in A24-01, it is noted that although the administration of combination chemotherapy with oxaliplatin, which is now also being considered, was off-label, it is in line with guideline recommendations, also regarding its dosage [3].

In this therapeutic indication, pembrolizumab is approved without restriction of the maximum treatment duration. In the KEYNOTE-811 study, however, treatment with pembrolizumab was limited to a maximum of 35 cycles (which corresponds to approx. 2 years). At the third data cut-off, at least 24 patients in the PD-L1-positive population in the intervention arm had reached the maximum duration of study medication. It is unclear for how many patients continued treatment with pembrolizumab after completion of the 35 cycles at the third data cut-off would have been indicated in compliance with the approval.

Planned duration of follow-up observation

Table 1 shows the planned duration of follow-up observation of the PD-L1-positive population for the individual outcomes.

Table 1: Planned duration of follow-up observation – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX

Study **Outcome category** **Outcome**	**Planned follow-up observation**
KEYNOTE-811	
Mortality	
Overall survival	Until death, withdrawal of consent, or end of study (whichever occurred first)
Morbidity	
Symptoms, health status (EORTC QLQ-C30, EORTC QLQ-STO22, EQ-5D VAS)	30 days after treatment discontinuation or end of treatment[a]
Health-related quality of life	
EORTC QLQ-C30	30 days after treatment discontinuation or end of treatment[a]
Side effects[b]	
AEs, severe AEs	Up to 30 days after treatment discontinuation or end of treatment
SAEs	Up to 90 days after treatment discontinuation or end of treatment or up to 30 days after treatment discontinuation or end of treatment when starting a new antineoplastic therapy, whichever occurred first

a. Patient-reported outcomes were recorded during treatment for a maximum of 1 year or until the end of treatment, whichever occurred first, and 30 days after the end of treatment. In deviation from the information provided by the company in Module 4 A, the questionnaires were only recorded every second cycle after week 12 (every 6 weeks).
b. In the second course phase, the observation of AEs in the intervention arm was resumed; it is unclear whether these surveys were included in the AE analyses presented. At the time of the third data cut-off, 8 (approx. 3%) of all patients with PD-L1 CPS ≥ 1 in the intervention arm were in the second course phase.

AE: adverse event; CPS: combined positive score; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-STO22: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Gastric Cancer 22; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

In the KEYNOTE-811 study, only overall survival was recorded until study end. The observation periods for the morbidity and health-related quality of life outcomes are systematically shortened because they were only recorded for up to 1 year or up to 30 days after the end of treatment (whichever occurred first). The observation durations for the side effects outcomes were recorded only for the period of treatment with the study medication (plus 30 or 90 days). However, drawing a reliable conclusion on the total study period or the time until patient death would require for the outcomes of the morbidity, health-related quality of life, and side effects categories to be recorded over the total period of time, as was the case for survival.

Characteristics of the PD-L1-positive population

Table 2 shows the characteristics of the PD-L1-positive population in the KEYNOTE-811 study.

Table 2: Characteristics of the PD-L1-positive study population as well as study/treatment discontinuation – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX (multipage table)

Study Characteristic Category	Pembrolizumab + trastuzumab + FP/CAPOX N = 298	Placebo + trastuzumab + FP/CAPOX N = 296
KEYNOTE-811		
Age [years], mean (SD)	61 (12)	61 (11)
Sex [F/M], %	19/81	20/80
Geographical region, n (%)		
Western Europe/Israel/North America/Australia	97 (33)	96 (32)
Asia	96 (32)	96 (32)
Rest of the world	105 (35)	104 (35)
Chemotherapy, n (%)		
CAPOX	251 (84)	253 (85)
FP	47 (16)	43 (15)
ECOG PS, n (%)		
0	127 (43)	122 (41)
1	171 (57)	174 (59)
Primary location, n (%)		
Gastro-oesophageal junction	97 (33)	99 (33)
Stomach	201 (67)	197 (67)
Disease status, n (%)		
Locally advanced	8 (3)	6 (2)
Metastatic	290 (97)	290 (98)

Table 2: Characteristics of the PD-L1-positive study population as well as study/treatment discontinuation – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX (multipage table)

Study Characteristic Category	**Pembrolizumab + trastuzumab + FP/CAPOX N = 298**	**Placebo + trastuzumab + FP/CAPOX N = 296**
HER2 status, n (%)		
IHC 1+	1 (< 1)	1 (< 1)
IHC 2+ ISH equivocal	0 (0)	1 (< 1)
IHC 2+ ISH negative	1 (< 1)	1 (< 1)
IHC 2+ ISH positive	51 (17)	68 (23)
IHC 3+	245 (82)	225 (76)
Prior gastrectomy/oesophagectomy, n (%)		
Yes	36 (12)	47 (16)
No	262 (88)	249 (84)
Treatment discontinuation, n (%)	ND[a]	ND[a]
Study discontinuation, n (%)	ND[a]	ND[a]

a. Information on treatment and study discontinuations at the third data cut-off is only available for the total population without restriction of the CPS. Data for the population with CPS ≥ 1 are available for the second data cut-off: Of these, 214 (72%) patients in the intervention arm vs. 245 (83%) patients in the comparator arm discontinued treatment. Common reasons for discontinuing treatment were disease progression (51% vs. 63% of patients), AEs (10% vs. 9%), and clinical progression (4% vs. 6%). In addition, 167 (56%) patients in the intervention arm vs. 184 (62%) patients in the comparator arm discontinued the study. The most common reason for study discontinuation was death (56% vs. 61%).

AE: adverse event; CAPOX: capecitabine + oxaliplatin; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; FP: 5-fluorouracil + cisplatin; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: in situ hybridization; M: male; n: number of patients in category; N: number of randomized patients with positive PD-L1 status (CPS ≥ 1); PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation

Both treatment arms are largely comparable in terms of the demographic and clinical characteristics of the PD-L1-positive population in the KEYNOTE-811 study.

The mean patient age was 61 years in both arms. At about 80%, most patients included in both arms were men. Around 33% of all patients came from Western Europe, Israel, North America or Australia. An Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1 was found in 57% and 59% of the patients; almost all patients had metastatic disease (97% versus 98%). In 67% of patients in both arms, the primary cancer location was the stomach.

Information on treatment and study discontinuations at the third data cut-off is not available for the PD-L1-positive subpopulation.

Information on the course of the study

Table 3 shows the median and mean treatment duration of the PD-L1-positive population and the median and mean observation period for the outcome of overall survival as well as the outcome categories of morbidity and side effects.

Table 3: Information on the course of the study – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab + trastuzumab + FP/CAPOX** **N[a] = 298**	**Placebo + trastuzumab + FP/CAPOX** **N[a] = 296**
KEYNOTE-811		
Treatment duration [months]		
Median [min; max]	10.2 [ND]	7.1 [ND]
Mean (SD)	ND	ND
Observation period [months][b]		
Overall survival		
Median [min; max]	16.9 [ND]	13.9 [ND]
Mean (SD)	ND	ND
Morbidity (EORTC QLQ-C30, EORTC QLQ-STO22, EQ-5D VAS)		
Median [min; max]	11.1 [ND]	7.8 [ND]
Mean (SD)	ND	ND
Health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	11.1 [ND]	7.8 [ND]
Mean (SD)	ND	ND
Side effects		
AEs and severe AEs (CTCAE ≥ 3)		
Median [min; max]	10.9 [ND]	8.0 [ND]
Mean (SD)	ND	ND
SAEs		
Median [min; max]	12.3 [ND]	9.9 [ND]
Mean (SD)	ND	ND

a. Number of randomized patients with positive PD-L1 status (CPS ≥ 1).
b. The company did not provide any information on the calculation method.

AE: adverse event; CAPOX: capecitabine + oxaliplatin; CPS: combined positive score; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-STO22: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Gastric Cancer Module; FP: 5-fluorouracil + cisplatin; max: maximum; min: minimum; N: number of patients; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale

The median treatment duration in the intervention arm (10.2 months) was longer than in the control arm (7.1 months). According to the study protocol, the observation periods for the outcomes in the morbidity and side effects categories were linked to the treatment duration and thus shortened. In the case of patient-reported outcomes, observation was additionally limited to a maximum of 12 months (+ 30 days) (see dossier assessment A24-01 [1]). For both outcome categories, this leads to different observation periods in both arms. For overall survival, the median observation period at the third data cut-off was 16.9 months in the intervention arm and 13.9 months in the control arm.

Information on subsequent therapies

The company presented data on the first subsequent therapy at drug level. Table 4 shows the subsequent therapies patients of the PD-L1-positive population received after termination of the study medication.

Table 4: Information on first subsequent therapy[a] (at least 2 patients in at least one treatment arm) – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX (multipage table)

Study	**Patients with subsequent therapy n (%)**	
Subsequent therapy **Category** **Drug class[b]** **Drug**	**Pembrolizumab + trastuzumab + FP/CAPOX** **N = 298**	**Placebo + trastuzumab + FP/CAPOX** **N = 296**
KEYNOTE-811		
Total with subsequent therapy	139 (46.6)[c]	162 (54.7)[c]
Radiotherapy	15 (5.0)	9 (3.0)
Systemic therapy	124 (41.6)	153 (51.7)
Taxanes	57 (19.1)	91 (30.7)
Paclitaxel	44 (14.8)	68 (23.0)
Nab-paclitaxel	5 (1.7)	8 (2.7)
Docetaxel	8 (2.7)	15 (5.1)
Platinum derivatives	17 (5.7)	21 (7.1)
Cisplatin	7 (2.4)	8 (2.7)
Oxaliplatin	8 (2.7)	11 (3.7)
Carboplatin	2 (0.7)	2 (0.7)
Topoisomerase inhibitors	24 (8.1)	18 (6.1)
Irinotecan	24 (8.1)	18 (6.1)
Pyrimidine analogues	40 (13.4)	38 (12.8)
5-fluorouracil	25 (8.4)[c]	19 (6.4)[c]
Capecitabine	8 (2.7)	12 (4.1)
Tegafur/gimeracil/oteracil	6 (2.0)	5 (1.7)
Tegafur	1 (0.3)	2 (0.7)

Table 4: Information on first subsequent therapy[a] (at least 2 patients in at least one treatment arm) – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX (multipage table)

Study	**Patients with subsequent therapy n (%)**	
Subsequent therapy **Category** **Drug class[b]** **Drug**	**Pembrolizumab + trastuzumab + FP/CAPOX** **N = 298**	**Placebo + trastuzumab + FP/CAPOX** **N = 296**
HER2-targeted therapies	34 (11.4)[c]	36 (12.2)[c]
Trastuzumab	26 (8.7)	21 (7.1)
Trastuzumab deruxtecan	7 (2.4)	5 (1.7)
Pyrotinib	0	5 (1.7)
PD-1/PD-L1 inhibitors	2 (0.7)	10 (3.4)
Pembrolizumab	0	4 (1.4)
Sintilimab	0	3 (1.0)
VEGF-targeted therapy	32 (10.7)[c]	43 (14.5)[c]
Ramucirumab	28 (9.4)	39 (13.2)
Study drugs	7 (2.4)	9 (3.0)

a. There is no information on therapies administered later than the first subsequent therapy.
b. If several systemic therapies of one drug class are administered, the patient is only counted once. If the therapy is carried out with drugs of different drug classes, the patient is counted several times.
c. Institute's calculation.

CAPOX: capecitabine + oxaliplatin; CPS: combined positive score; FP: 5-fluorouracil + cisplatin; HER2: human epidermal growth factor receptor 2; n: number of patients with subsequent therapy; N: number of randomized patients with positive PD-L1 status (CPS ≥ 1); PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor

Overall, 42% of the patients in the intervention arm and 52% of the patients in the comparator arm received subsequent systemic therapy. 5% and 3% of patients respectively received radiotherapy as their first subsequent therapy. 62 (21%) patients in the intervention arm and 36 (12%) patients in the comparator arm who were still under observation received no subsequent therapy. In addition, 33% of patients in both arms died without having received subsequent therapy.

The subsequent therapies used largely correspond to the treatment recommendations of the current guidelines. In particular, the S3 guidelines on the diagnosis and treatment of gastric cancer and of oesophageal squamous cell carcinoma and adenocarcinoma recommend irinotecan, paclitaxel, docetaxel, and ramucirumab alone or in combination with paclitaxel, regardless of HER2 status [4,5]. Of the PD-L1-positive patients in the study, 8.1% versus 6.1% received irinotecan, 19.1% versus 30.7% a taxane, and 9.4% versus 13.2% ramucirumab as first subsequent therapy. Only ramucirumab alone or in combination with paclitaxel is approved for second-line treatment. In addition, since December 2022, trastuzumab deruxtecan has

been approved as monotherapy in adults with advanced HER2-positive gastric or GEJ adenocarcinoma who have received one prior trastuzumab-based regimen [6]. In the PD-L1-positive population, the proportion of patients treated in the second line with trastuzumab deruxtecan is low (2.4% vs. 1.7%). However, there are currently no clear guideline recommendations for treatment with trastuzumab deruxtecan in the second line. While the German Society for Haematology and Medical Oncology exclusively recommends trastuzumab deruxtecan as second-line therapy for HER2-positive gastric or oesophageal cancer in patients treated with trastuzumab in the first line [7,8], other guidelines mention trastuzumab deruxtecan as one of several treatment options [3,9]. Since the relevance of trastuzumab deruxtecan in this therapeutic indication is still unclear, its limited use as a subsequent therapy is of no further consequence in the present assessment.

Risk of bias across outcomes (study level)

Table 5 shows the risk of bias across outcomes (risk of bias at study level).

Table 5: Risk of bias across outcomes (study level) – RCT, direct comparison: pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin vs. placebo + trastuzumab + 5-fluorouracil + cisplatin

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
KEYNOTE-811	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the KEYNOTE-811 study is rated as low.

2.2 Results

2.2.1 Presented outcomes

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

- Mortality
  - overall survival

- Morbidity
  - symptoms surveyed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) and the EORTC QLQ – Gastric Cancer 22 (EORTC QLQ-STO22)
  - health status, surveyed using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - surveyed using the EORTC QLQ-C30
- Side effects
  - serious adverse events (SAEs)
  - severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - cardiac disorders (System Organ Class [SOC], severe AEs)
  - immune-related SAEs and severe AEs
  - other specific AEs, if any

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

Table 6 shows the outcomes for which data were available in the included study.

Table 6: Matrix of outcomes – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX

Study	Outcomes										
	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-STO22)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs[a]	Severe AEs[a, b]	Discontinuation due to AEs[a, c]	Cardiac disorders (SOC, severe AEs[b])	Immune-related SAEs[d]	Immune-related severe AEs[b, d]	Further specific AEs[e]
KEYNOTE-811	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. The following progression events of the underlying disease according to MedDRA are not included: "neoplasm progression", "malignant neoplasm progression" and "disease progression".
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Discontinuation of ≥ 1 drug component.
d. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of AEs of special interest ("AEOSI, Version 23") was used.
e. The following events are considered (MedDRA coding): infections and infestations (SOC, AEs), renal and urinary disorders (SOC, AEs).

AE: adverse event; AEOSI: adverse event of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer-Core 30; EORTC QLQ-STO22: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Gastric Cancer 22; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes and analyses

Validity of the EORTC QLQ-STO22 for the considered patient population

The EORTC QLQ-STO22 is a gastric cancer-specific add-on module to the EORTC QLQ-C30. There is no specific EORTC questionnaire for patients with GEJ carcinoma. For patients with gastric, oesophageal or GEJ cancer, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Oesophago-Gastric 25 (QLQ-OG25) was developed. A comparison of the items of the QLQ-OG25 with the QLQ-STO22 shows that the 2 instruments are largely identical. Considering the extensive agreement between QLQ-STO22 and QLQ-OG25, QLQ-STO22 appears to be sufficiently valid for the considered patient population in the current situation, even though it was primarily developed only for gastric cancer.

Patient-reported outcomes, observation period

For the patient-reported outcomes, the company presented in its dossier analyses for the first deterioration by at least 10 points for the EORTC QLQ-C30 and the EORTC QLQ-STO22 and by at least 15 points for the EQ-5D VAS in the form of time-to-event analyses.

In the KEYNOTE-811 study, patient-reported outcomes were recorded during treatment for a maximum of 1 year or until the end of treatment, whichever occurred first, and 30 days after the end of treatment.

The observation period of the patient-reported outcomes was thus markedly shortened and differed between the treatment arms due to the link to the treatment duration; see Table 3. This affects the risk of bias of results (see Section 2.2.2).

Immune-related AEs

In Module 4 A of the dossier, the company presented analyses on AEs of special interest (AEOSI) predefined in the statistical analysis plan. This operationalization with the underlying PT collection is considered a sufficient approximation for the immune-related AEs. Both severe AEs (CTCAE grade ≥ 3) and SAEs were considered. For the PD-L1-positive population, no analysis at the level of PTs or superordinate categories is available for the most recent, third data cut-off.

2.2.2 Risk of bias

Table 7 describes the risk of bias for the results of the relevant outcomes for the PD-L1-positive population.

Table 7: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX

Study		Outcomes										
	Study level	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-STO22)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs[a]	Severe AEs[a, b]	Discontinuation due to AEs[a, c]	Cardiac disorders (SOC, severe AEs[b])	Immune-related SAEs[d]	Immune-related severe AEs[b, d]	Further specific AEs[e]
KEYNOTE-811	L	L	H[f]	H[f]	H[f]	H[f]	H[f]	L[g]	H[f]	H[f]	H[f]	H[f]

a. The following progression events of the underlying disease according to MedDRA are not included: "neoplasm progression", "malignant neoplasm progression" and "disease progression".
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Discontinuation of ≥ 1 drug component.
d. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of AEs of special interest ("AEOSI, Version 23") was used.
e. The following events are considered (MedDRA coding): infections and infestations (SOC, AEs), renal and urinary disorders (SOC, AEs).
f. Incomplete observations for potentially informative reasons with different lengths of follow-up observation.
g. Despite the low risk of bias, the certainty of results is presumably limited for the outcome of discontinuation due to AEs.

AE: adverse event; AEOSI: adverse event of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer-Core 30; EORTC QLQ-STO22: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Gastric Cancer 22; FP: 5-fluorouracil + cisplatin; H: high; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

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

The recording period under treatment was limited to a maximum of 1 year + 30 days for the results of the outcomes on symptoms, measured with the EORTC QLQ-C30 and the EORTC QLQ-STO22, the outcome of health status, measured with the EQ-5D VAS, and the outcomes on health-related quality of life, measured with the EORTC QLQ-C30. During this period, the observation was also linked to the discontinuation of treatment. The risk of bias is therefore assessed as high due to incomplete observations for potentially informative reasons with different lengths of follow-up observation. With the exception of the outcome of discontinuation due to AEs, the risk of bias of the results in the side effects category is also assessed as high, as the observation for all AEs was also linked to treatment discontinuation.

The certainty of results for the outcome of discontinuation due to AEs is limited despite a low risk of bias.

2.2.3 Results

Table 8 summarizes the results of the comparison of pembrolizumab + trastuzumab + FP/CAPOX with placebo + trastuzumab + FP/CAPOX in patients with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1). Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The Kaplan-Meier curves on time-to-event analyses are presented in Appendix A; no Kaplan-Meier curves are available for cardiac disorders (severe AEs, CTCAE ≥ 3). Tables on common AEs, SAEs, severe AEs (CTCAE ≥ 3), and discontinuations due to AEs are presented in Appendix B. There is no list of the immune-related AEs, immune-related SAEs, and immune-related severe AEs (CTCAE grade ≥ 3) according to SOC, PT, or collected by category.

Table 8: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX (multipage table)

Study Outcome category Outcome	Pembrolizumab + trastuzumab + FP/CAPOX		Placebo + trastuzumab + FP/CAPOX		Pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX
	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR [95%-CI]; p-value[b]
KEYNOTE-811					
Mortality					
Overall survival	298	20.0 [17.9; 22.7] 204 (68.5)	296	15.7 [13.5; 18.5] 218 (73.6)	0.77 [0.63; 0.93]; 0.007[c]
Morbidity					
Symptoms (EORTC QLQ-C30 – time to first deterioration[d])					
Fatigue	272	2.1 [1.5; 2.7] 191 (70.2)	274	2.8 [2.2; 4.3] 163 (59.5)	1.22 [0.99; 1.50]; 0.065
Nausea and vomiting	272	3.0 [2.1; 4.6] 154 (56.6)	274	2.9 [2.3; 4.6] 152 (55.5)	0.97 [0.77; 1.21]; 0.775
Pain	272	9.5 [6.7; NC] 123 (45.2)	274	8.5 [5.7; 15.6] 127 (46.4)	0.90 [0.70; 1.16]; 0.423
Dyspnoea	272	11.4 [8.9; NC] 113 (41.5)	274	11.5 [9.0; NC] 107 (39.1)	1.00 [0.77; 1.30]; > 0.999
Insomnia	272	11.4 [9.2; NC] 115 (42.3)	274	7.2 [5.6; NC] 125 (45.6)	0.78 [0.60; 1.01]; 0.055
Appetite loss	272	5.1 [2.9; 11.3] 142 (52.2)	274	6.0 [3.5; 11.7] 133 (48.5)	1.04 [0.82; 1.32]; 0.747
Constipation	272	NA 97 (35.7)	274	NA [9.9; NC] 96 (35.0)	0.93 [0.70; 1.23]; 0.617
Diarrhoea	272	2.8 [2.1; 4.1] 166 (61.0)	274	6.1 [3.0; 11.5] 132 (48.2)	1.30 [1.03; 1.63]; 0.026
Symptoms (EORTC QLQ-STO22 – time to first deterioration[d])					
Anxiety	271	5.0 [3.0; 8.7] 148 (54.6)	273	4.1 [2.4; 6.0] 151 (55.3)	0.85 [0.68; 1.07]; 0.165
Body image	271	8.3 [4.8; NC] 130 (48.0)	273	11.0 [6.5; NC] 116 (42.5)	1.10 [0.86; 1.42]; 0.449
Dry mouth	271	4.4 [3.3; 7.1] 147 (54.2)	273	6.5 [3.1; NC] 126 (46.2)	1.09 [0.86; 1.39]; 0.477
Dysphagia	271	9.9 [5.9; NC] 123 (45.4)	273	8.8 [5.6; NC] 119 (43.6)	0.98 [0.76; 1.27]; 0.902

Table 8: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX (multipage table)

Study **Outcome category** **Outcome**	**Pembrolizumab + trastuzumab + FP/CAPOX**		**Placebo + trastuzumab + FP/CAPOX**		**Pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX**
	N	**Median time to event in months [95% CI][a]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI][a]** **Patients with event n (%)**	**HR [95%-CI]; p-value[b]**
Eating restrictions	271	NC [10.5; NC] 110 (40.6)	273	9.9 [6.3; NC] 117 (42.9)	0.87 [0.67; 1.13]; 0.281
Alopecia	No suitable data[e]				
Pain	271	NA [11.2; NC] 97 (35.8)	273	NC [13.7; NC] 96 (35.2)	0.89 [0.67; 1.18]; 0.410
Reflux	271	4.6 [2.6; 9.0] 147 (54.2)	273	6.8 [4.3; 11.3] 134 (49.1)	1.13 [0.90; 1.44]; 0.297
Dysgeusia	271	2.8 [2.3; 4.6] 158 (58.3)	273	5.6 [2.9; 8.9] 138 (50.5)	1.15 [0.92; 1.45]; 0.226
Health status (EQ-5D VAS – time to first deterioration[f])	275	16.0 [10.6; NC] 114 (41.5)	275	12.7 [8.3; NC] 114 (41.5)	0.84 [0.65; 1.10]; 0.205
Health-related quality of life					
EORTC QLQ-C30 – time to first deterioration[g]					
Global health status	272	5.4 [2.6; 7.0] 148 (54.4)	274	4.7 [3.1; 7.1] 144 (52.6)	0.99 [0.78; 1.25]; 0.927
Physical functioning	272	4.3 [3.2; 5.7] 162 (59.6)	274	5.2 [3.5; 7.4] 143 (52.2)	1.08 [0.86; 1.36]; 0.491
Role functioning	272	3.1 [2.3; 4.6] 174 (64.0)	274	4.4 [3.0; 6.0] 149 (54.4)	1.18 [0.95; 1.47]; 0.141
Emotional functioning	272	11.7 [9.8; NC] 110 (40.4)]	274	8.3 [6.0; 11.5] 127 (46.4)	0.75 [0.58; 0.97]; 0.031
Cognitive functioning	272	5.8 [4.1; 8.4] 151 (55.5)	274	6.3 [4.0; 7.4] 140 (51.1)	1.04 [0.82; 1.30]; 0.770
Social functioning	272	3.0 [2.1; 4.2] 172 (63.2)	274	5.5 [3.9; 7.1] 149 (54.4)	1.26 [1.01; 1.57]; 0.040

Table 8: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX (multipage table)

Study **Outcome category** **Outcome**	**Pembrolizumab + trastuzumab + FP/CAPOX**		**Placebo + trastuzumab + FP/CAPOX**		**Pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX**
	N	**Median time to event in months [95% CI][a]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI][a]** **Patients with event n (%)**	**HR [95%-CI]; p-value[b]**
Side effects					
AEs[h] (supplementary information)	298	0.1 [0.1; 0.1] 296 (99.3)	295	0.1 [0.1; 0.2] 295 (100.0)	–
SAEs[h]	298	17.5 [11.2; 32.7] 143 (48.0)	295	13.8 [7.6; NC] 141 (47.8)	0.91 [0.72; 1.15]; 0.430
Severe AEs[h, i]	298	3.3 [2.6; 4.2] 220 (73.8)	295	3.5 [2.8; 4.4] 194 (65.8)	1.11 [0.91; 1.35]; 0.292
Discontinuation due to AEs[h]	298	17.1 [11.0; 27.1] 127 (42.6)	295	26.9 [15.9; NC] 108 (36.6)	1.06 [0.82; 1.37]; 0.652
Cardiac disorders (SOC, severe AEs[i])	298	NA 10 (3.4)	295	NA 8 (2.7)	1.12 [0.44; 2.84]; 0.811
Immune-related AEs[j] (supplementary information)	ND				
Immune-related SAEs[j]	298	NA 33 (11.1)	295	NA 14 (4.7)	2.19 [1.17; 4.10]; 0.014
Immune-related severe AEs[i, j]	298	NA 33 (11.1)	295	NA 10 (3.4)	3.00 [1.48; 6.09]; 0.002
Infections and infestations (SOC, AE)	298	14.9 [10.7; 19.5] 139 (46.6)	295	26.0 [19.6; 37.0] 79 (26.8)	1.74 [1.32; 2.30]; < 0.001
Renal and urinary disorders (SOC, AE)	298	NA 38 (12.8)	295	NA 14 (4.7)	2.48 [1.34; 4.59]; 0.004

Table 8: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX (multipage table)

Study Outcome category Outcome	Pembrolizumab + trastuzumab + FP/CAPOX		Placebo + trastuzumab + FP/CAPOX		Pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX
	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR [95%-CI]; p-value[b]

a. Kaplan-Meier estimate, Institute's conversion from weeks to months for operationalizations in the side effects category.
b. HR, CI and p-value: Cox proportional hazards model with Wald CI and 2-sided Wald test, stratified by region (Western Europe/Israel/North America/Australia vs. Asia vs. rest of the world) and chemotherapy (FP vs. CAPOX), not differentiated by chemotherapy due to too small strata within Asia. According to the information provided by the company in Module 4 A, stratification is implemented by including the stratification variables as covariables in the model. An unstratified model is used for the outcome category of side effects.
c. In contrast to the information in Module 4 A, the CSR and the original publication [10] do not provide the stratified but the unstratified HR for the PD-L1-positive population at the third data cut-off. This is 0.81 [0.67, 0.98]; 0.0142 (HR, 95% CI and one-sided p-value).
d. A score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: up to 100).
e. Only 11 vs. 21 patients were included in the analysis.
f. A score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
g. A score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
h. The following progression events of the underlying disease according to MedDRA are not included: "neoplasm progression", "malignant neoplasm progression" and "disease progression".
i. Operationalized as CTCAE grade ≥ 3.
j. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of AEs of special interest ("AEOSI, Version 23") was used.

AE: adverse event; AEOSI: adverse event of special interest; CAPOX: capecitabine + oxaliplatin; CI: confidence interval; CSR: clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-STO22: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Gastric Cancer 22; FP: 5-fluorouracil + cisplatin; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found between treatment groups in favour of pembrolizumab + trastuzumab + FP/CAPOX in comparison with placebo + trastuzumab + FP/CAPOX.

Morbidity

Symptoms

Data on symptoms outcomes were recorded using the instruments EORTC QLQ-C30 and the EORTC QLQ-STO22.

Diarrhoea

For the outcome of diarrhoea (EORTC QLQ-C30, time to first deterioration), a statistically significant difference was found between treatment groups to the disadvantage of pembrolizumab + trastuzumab + FP/CAPOX in comparison with placebo + trastuzumab + FP/CAPOX.

Fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, anxiety, body image, dry mouth, dysphagia, eating restrictions, pain, reflux, and dysgeusia

No statistically significant difference between treatment groups was found for any of the outcomes of fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, anxiety, body image, dry mouth, dysphagia, eating restrictions, pain, reflux, and dysgeusia.

Alopecia

No suitable data are available for the outcome of alopecia.

Health status (EQ-5D VAS)

No statistically significant difference between treatment groups was shown for the outcome of health status recorded with the EQ-5D VAS.

Health-related quality of life

Data on health-related quality of life outcomes were recorded using the EORTC QLQ-C30 instrument.

Emotional functioning

For the outcome of emotional functioning (EORTC QLQ-C30, time to first deterioration), a statistically significant difference was found between treatment groups in favour of pembrolizumab + trastuzumab + FP/CAPOX in comparison with placebo + trastuzumab + FP/CAPOX.

Social functioning

For the outcome of social functioning (EORTC QLQ-C30, time to first deterioration), a statistically significant difference was found between treatment groups to the disadvantage of pembrolizumab + trastuzumab + FP/CAPOX in comparison with placebo + trastuzumab + FP/CAPOX.

Cognitive functioning

For the outcome of cognitive functioning (EORTC QLQ-C30, time to first deterioration), no statistically significant difference between treatment groups was found for the PD-L1-positive population. However, there was an effect modification by the characteristic of age. For patients ≥ 65 years of age, a statistically significant difference was found between treatment groups to the disadvantage of pembrolizumab + trastuzumab + FP/CAPOX. However, no statistically significant difference between treatment groups was found for patients < 65 years.

Global health status, physical functioning, and role functioning

No statistically significant difference between treatment groups was found for the outcomes of global health status, physical functioning, and role functioning.

Side effects

Severe AEs

No statistically significant difference between treatment groups was found for the outcome of severe AEs in the entire PD-L1-positive population. However, there was an effect modification by the characteristic of age. For patients < 65 years of age, a statistically significant difference was found between treatment groups to the disadvantage of pembrolizumab + trastuzumab + FP/CAPOX. However, no statistically significant difference between treatment groups was found for patients ≥ 65 years.

Discontinuation due to AEs

No statistically significant difference between treatment groups was found for the outcome of discontinuation due to AEs in the entire PD-L1-positive population.

SAEs

No statistically significant difference between treatment groups was found for the outcome of SAEs.

Specific AEs

Cardiac disorders (severe AEs)

No statistically significant difference between treatment groups was found for the outcome of cardiac disorders (severe AEs).

Immune-related SAEs and immune-related severe AEs

For the outcome of immune-related SAEs and immune-related severe AEs, a statistically significant difference was found between treatment groups to the disadvantage of pembrolizumab + trastuzumab + FP/CAPOX in comparison with placebo + trastuzumab + FP/CAPOX.

Infections and infestations (AEs), renal and urinary disorders (AEs)

For the outcomes of infections and infestations (AEs) and renal and urinary disorders (AEs), a statistically significant difference was found between treatment groups to the disadvantage of pembrolizumab + trastuzumab + FP/CAPOX in comparison with placebo + trastuzumab + FP/CAPOX.

2.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered for the present benefit assessment:

- sex (male versus female)
- age (< 65 years versus ≥ 65 years)
- chemotherapy (FP versus CAPOX)

Subgroup analyses of the 3 characteristics mentioned were planned a priori. For the outcomes "immune-related SAEs" and "immune-related severe AEs", subgroup analyses are completely missing.

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

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

The results are presented in Table 9. Kaplan-Meier curves on the subgroup results can be found in Appendix A.

Table 9: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX

Study Outcome Characteristic Subgroup	Pembrolizumab + trastuzumab + FP/CAPOX		Placebo + trastuzumab + FP/CAPOX		Pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX	
	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR [95% CI][b]	p-value[b]
KEYNOTE-811						
Morbidity						
Health-related quality of life						
EORTC QLQ-C30, cognitive functioning – time to first deterioration[c]						
Age						
< 65 years	160	6.2 [4.1; NC] 81 (50.6)	155	4.4 [2.5; 7.0] 90 (58.1)	0.80 [0.59; 1.08]	0.147
≥ 65 years	112	4.2 [2.7; 7.3] 70 (62.5)	119	7.6 [4.7; NC] 50 (42.0)	1.56 [1.08; 2.24]	0.017
Total					Interaction[d]:	0.005
Side effects						
Severe AEs[e]						
Age						
< 65 years	174	3.1 [2.2; 4.2] 135 (77.6)	164	4.4 [2.9; 8.9] 99 (60.4)	1.36 [1.05; 1.76]	0.020
≥ 65 years	124	3.3 [2.2; 5.3] 85 (68.5)	131	2.8 [2.0; 3.7] 95 (72.5)	0.86 [0.64; 1.15]	0.308
Total					Interaction[d]:	0.019

a. Kaplan-Meier estimate, Institute's conversion from weeks to months unless already provided in months.
b. HR, CI and p-value: Cox proportional hazards model with Wald CI and 2-sided Wald test or score test, for 0 events in one arm, unstratified.
c. A score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
d. Likelihood ratio test; Cox proportional hazards regression model with treatment, subgroup characteristic, and interaction term between treatment and subgroup characteristic.
e. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CAPOX: capecitabine + oxaliplatin; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-STO22: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Gastric Cancer 22; FP: 5-fluorouracil + cisplatin; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; VAS: visual analogue scale

Health-related quality of life

Cognitive functioning (EORTC QLQ-C30)

For the outcome of cognitive functioning (measured with the EORTC QLQ-C30 instrument), there was an effect modification by the characteristic of age. For patients ≥ 65 years of age, a statistically significant difference was found between treatment groups to the disadvantage of pembrolizumab + trastuzumab + FP/CAPOX. However, no statistically significant difference between treatment groups was found for patients < 65 years.

Side effects

Severe AEs

There was an effect modification by the characteristic of age for the outcome of severe AEs. For patients < 65 years of age, a statistically significant difference was found between treatment groups to the disadvantage of pembrolizumab + trastuzumab + FP/CAPOX. However, no statistically significant difference between treatment groups was found for patients ≥ 65 years.

2.2.5 Summary of the results

Overall, at the third data cut-off on 23 March 2023, an advantage of pembrolizumab in combination with trastuzumab and FP/CAPOX in comparison with placebo in combination with trastuzumab and FP/CAPOX was shown for the following outcomes:

- overall survival
- health-related quality of life (EORTC QLQ-C30, emotional functioning)

Disadvantages were shown for the following outcomes:

- symptoms (EORTC QLQ-C30, diarrhoea)
- health-related quality of life (EORTC QLQ-C30, social functioning)
- health-related quality of life (EORTC QLQ-C30, cognitive functioning) in patients ≥ 65 years of age
- severe AEs in patients < 65 years of age
- immune-related SAEs
- immune-related severe AEs
- infections and infestations (SOC, AE)
- renal and urinary disorders (SOC, AE)

2.3 Summary

The conclusion on the added benefit of pembrolizumab in combination with trastuzumab and fluoropyrimidine and platinum-based chemotherapy compared with the ACT specified by the G-BA does not change in comparison with dossier assessment A24-01 [1].

Table 10 below shows the result of the benefit assessment of pembrolizumab, taking into account dossier assessment A24-01 and the present addendum.

Table 10: Pembrolizumab in combination with trastuzumab and fluoropyrimidine and platinum-based chemotherapy – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1); first-line treatment[b]	▪ Trastuzumab in combination with capecitabine and cisplatin or ▪ trastuzumab in combination with 5-fluorouracil and cisplatin	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. b. It is assumed that radiotherapy with curative intent is not indicated for the patients in the present therapeutic indication. ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; PD-L1: programmed cell death ligand 1		

The G-BA decides on the added benefit.

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Appendix A Kaplan-Meier curves on the observed outcomes (PD-L1-positive population)

A.1 All-cause mortality

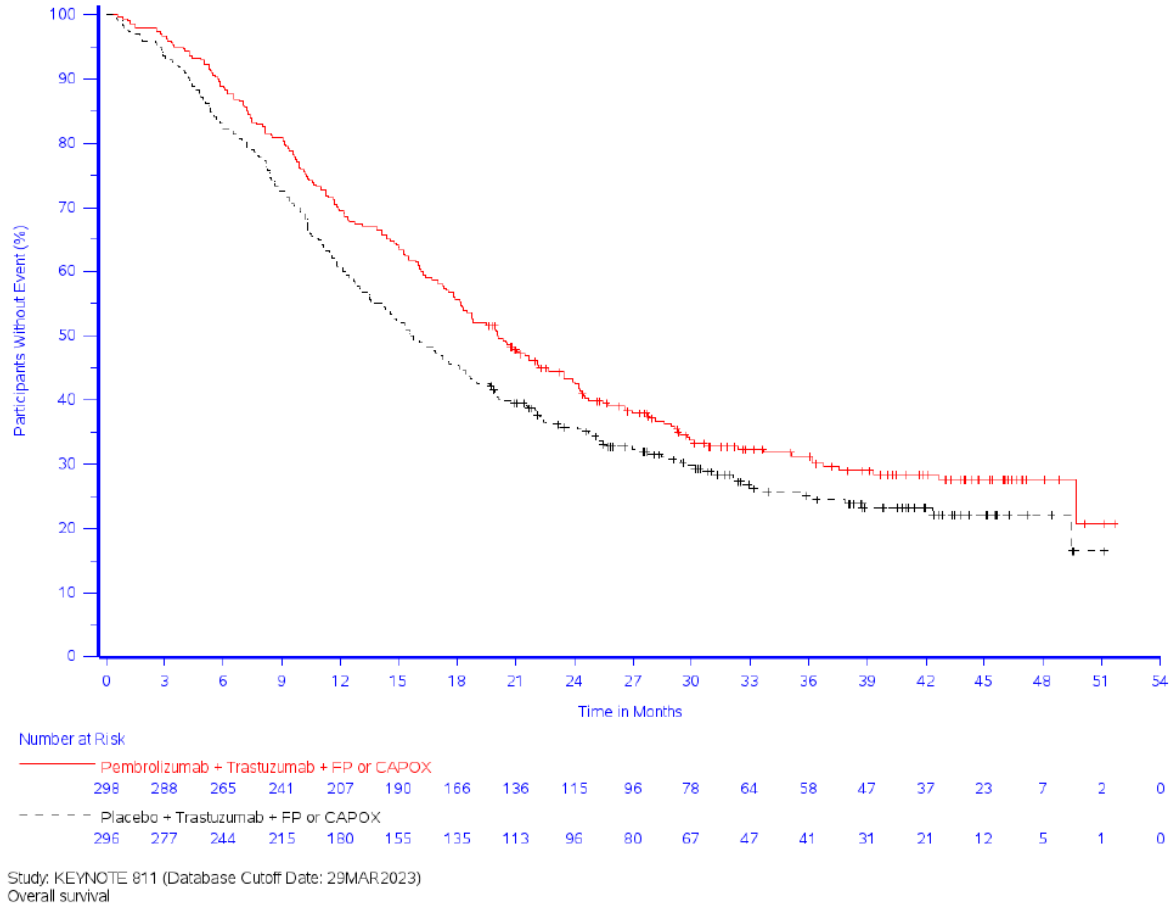

Figure 1: Kaplan-Meier curves for the outcome of overall survival (KEYNOTE 811 study, PD-L1-positive population)

A.2 Morbidity

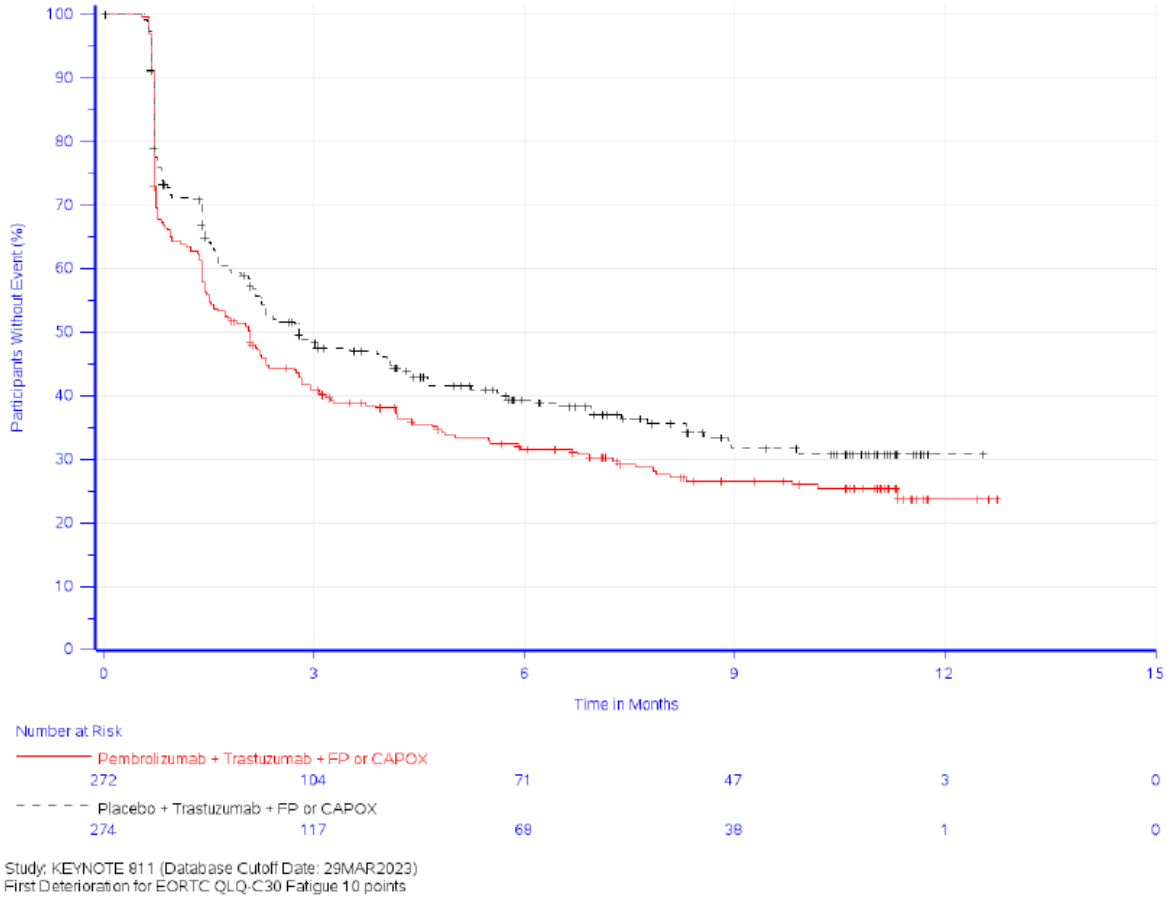

Figure 2: Kaplan-Meier curves for the outcome of fatigue (EORTC QLQ-C30, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

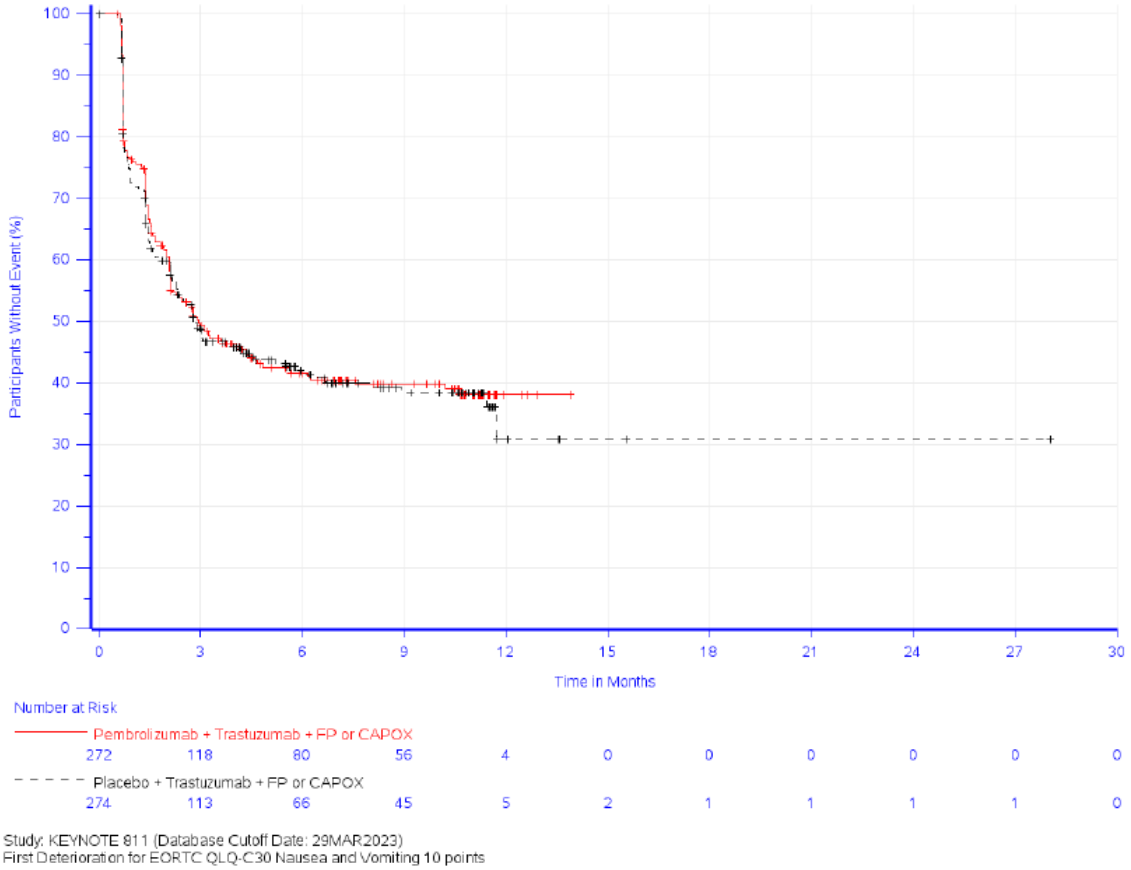

Figure 3: Kaplan-Meier curves for the outcome of nausea and vomiting (EORTC QLQ-C30, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

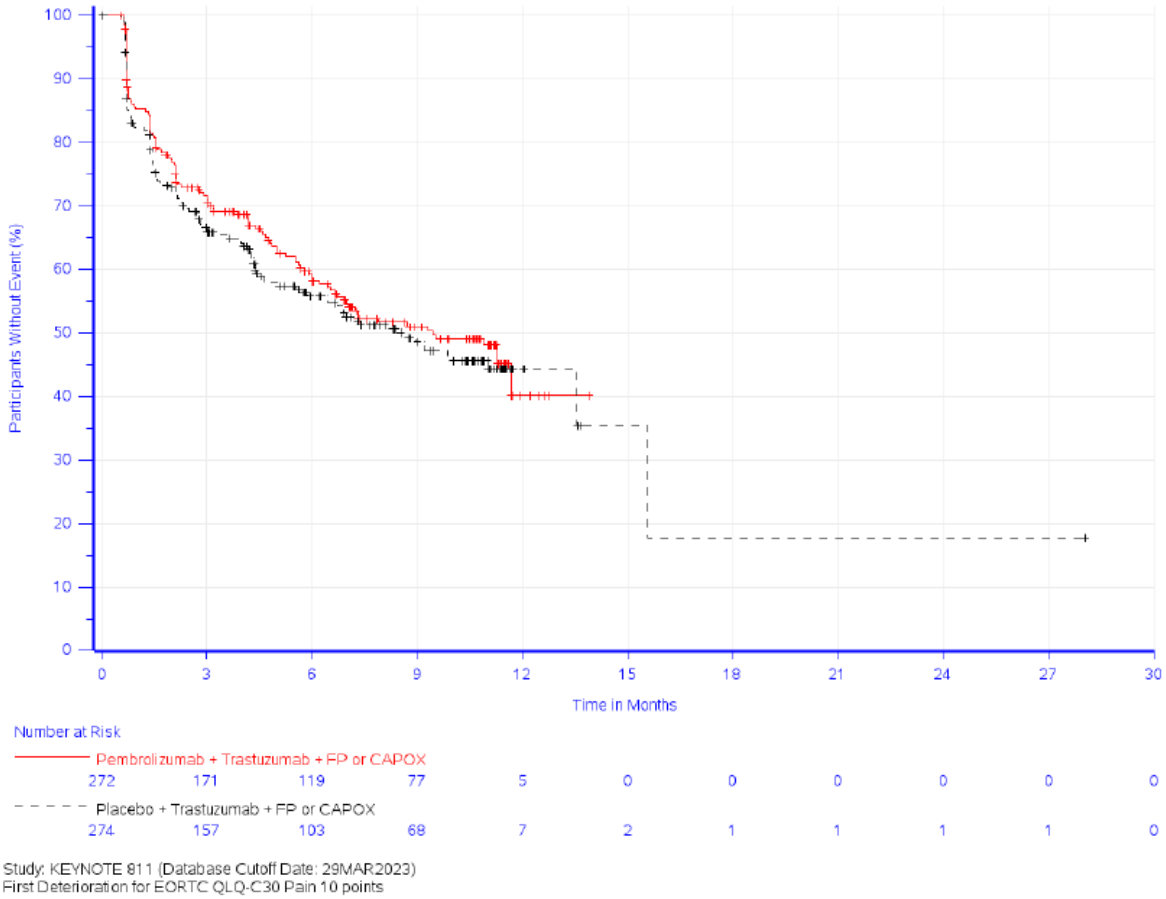

Figure 4: Kaplan-Meier curves for the outcome of pain (EORTC QLQ-C30, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

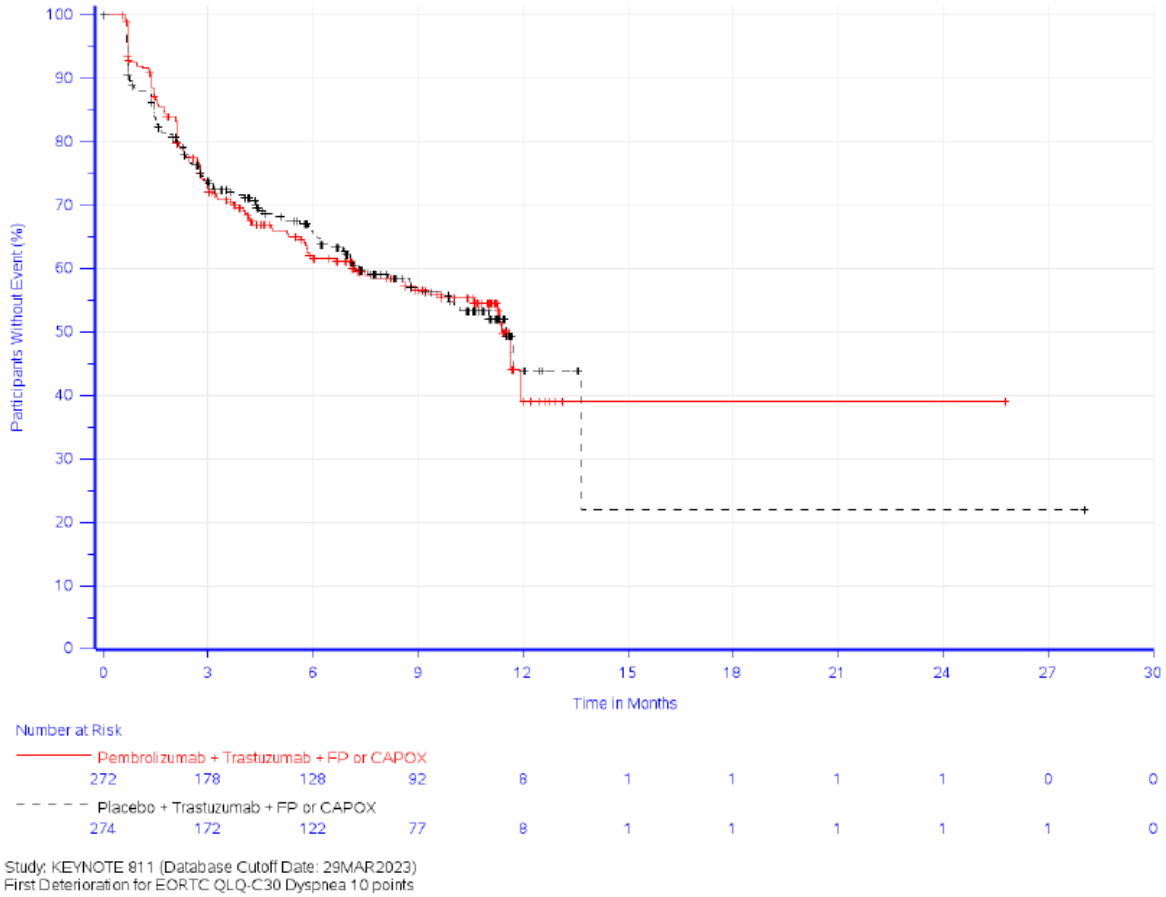

Figure 5: Kaplan-Meier curves for the outcome of dyspnoea (EORTC QLQ-C30, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

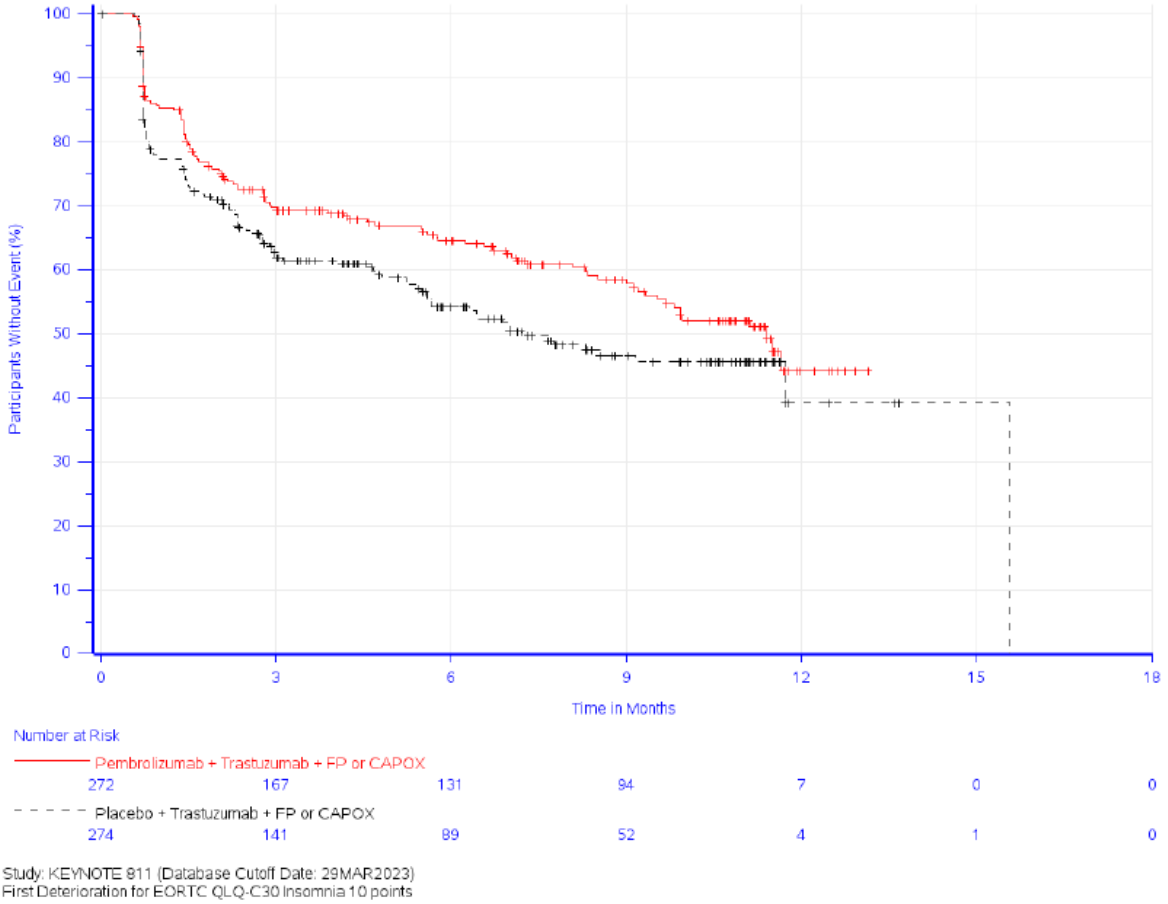

Figure 6: Kaplan-Meier curves for the outcome of insomnia (EORTC QLQ-C30, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

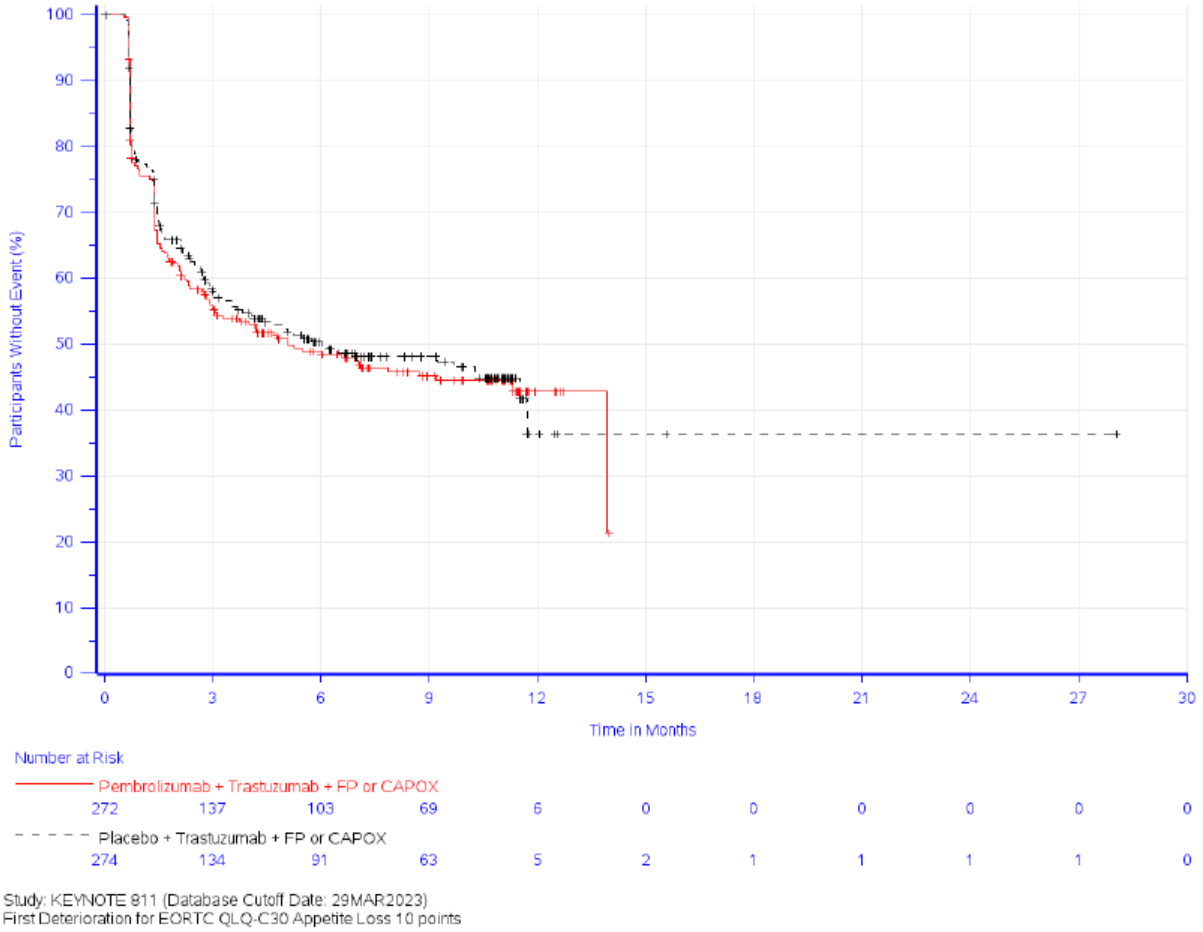

Figure 7: Kaplan-Meier curves for the outcome of appetite loss (EORTC QLQ-C30, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

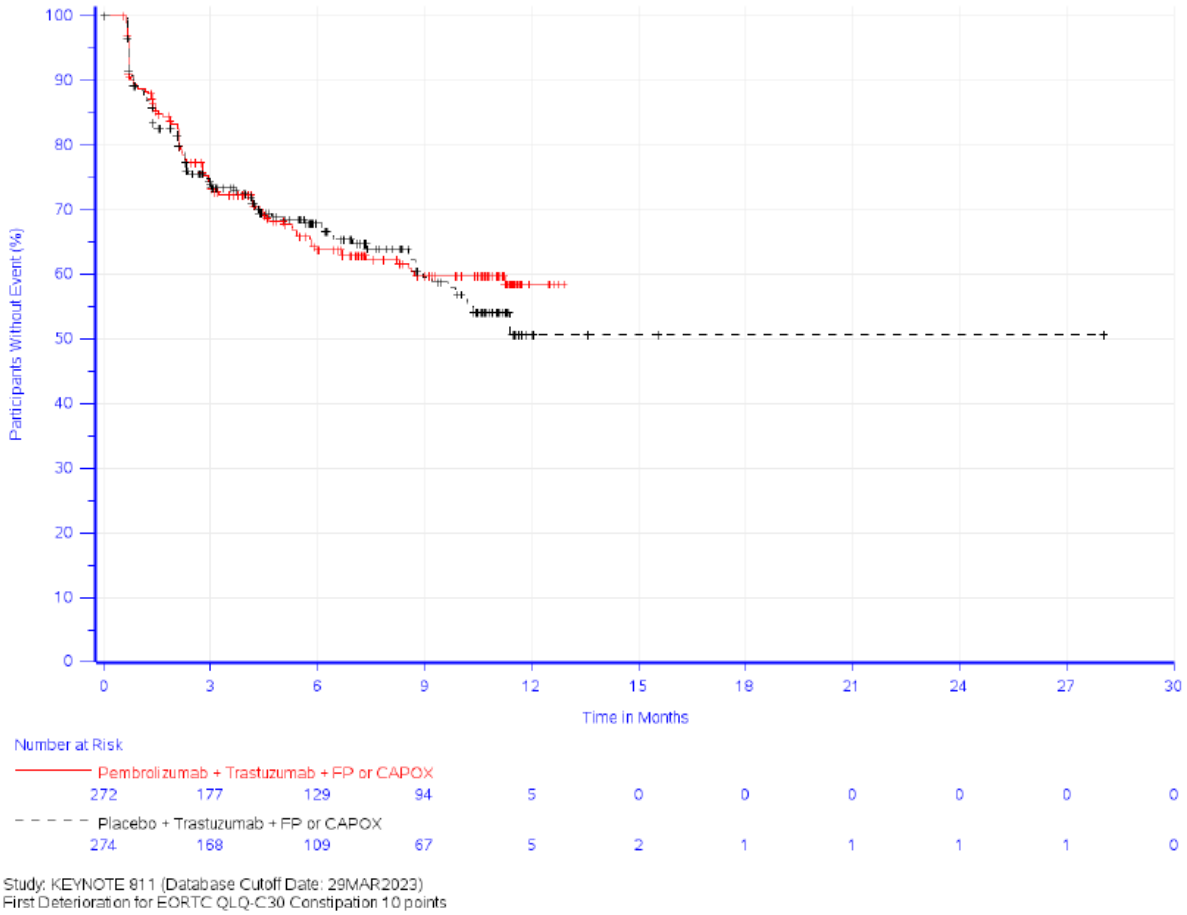

Figure 8: Kaplan-Meier curves for the outcome of constipation (EORTC QLQ-C30, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

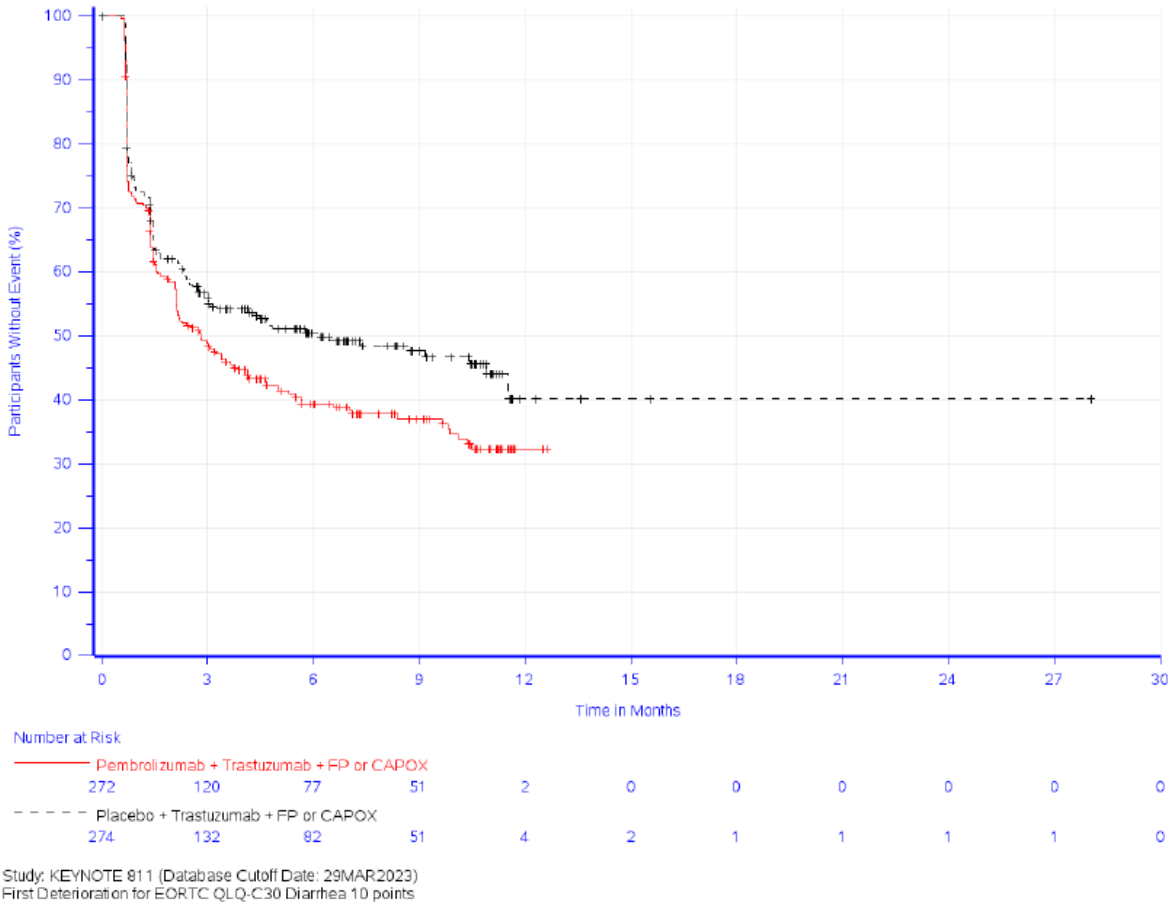

Figure 9: Kaplan-Meier curves for the outcome of diarrhoea (EORTC QLQ-C30, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

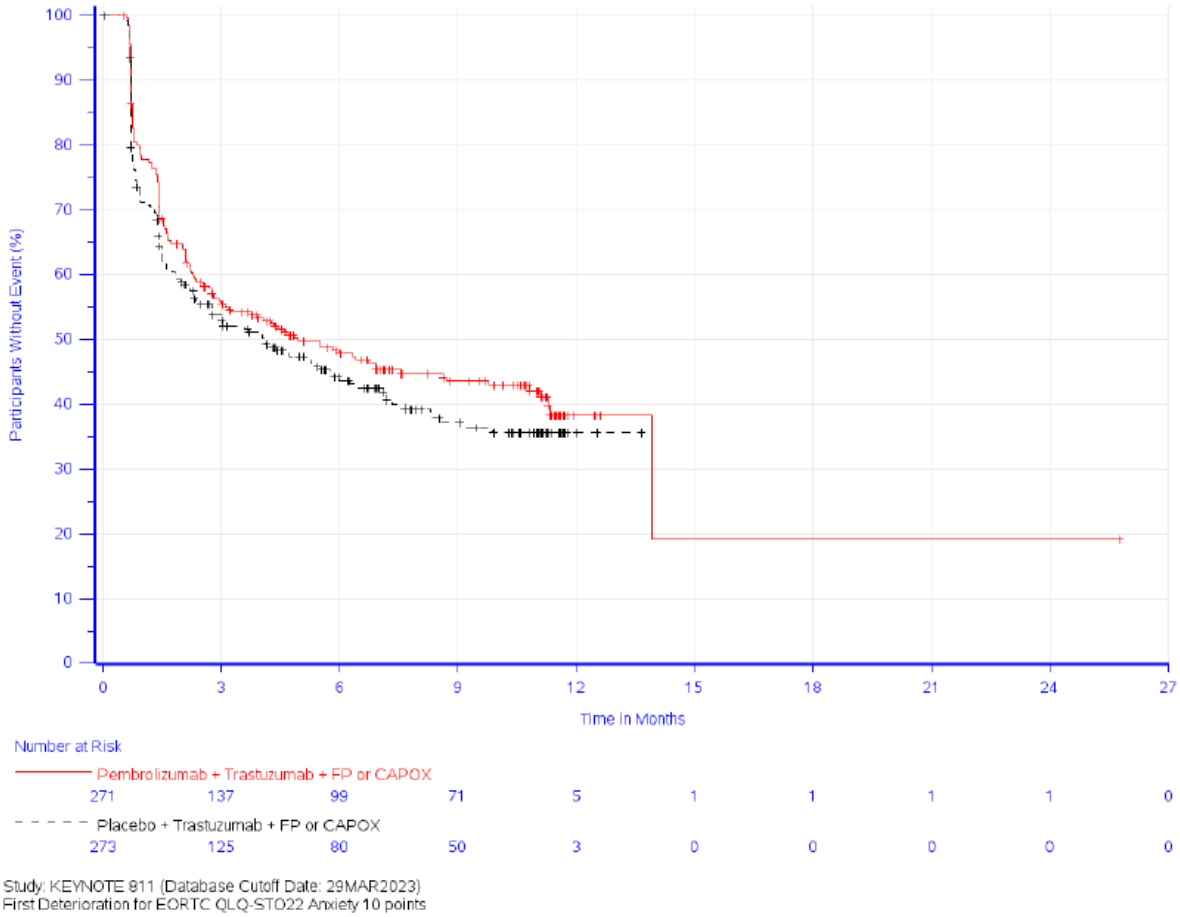

Figure 10: Kaplan-Meier curves for the outcome of anxiety (EORTC QLQ-STO22, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

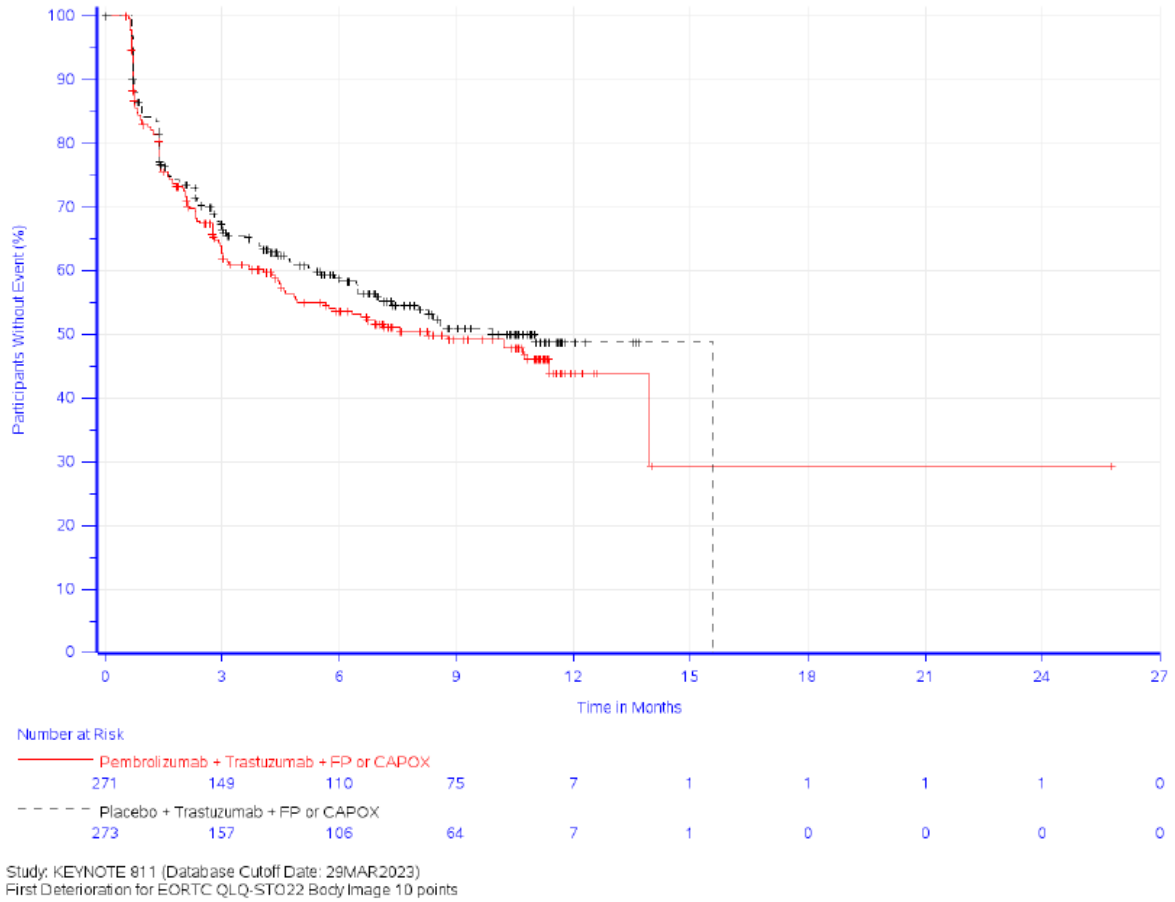

Figure 11: Kaplan-Meier curves for the outcome of body image (EORTC QLQ-STO22, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

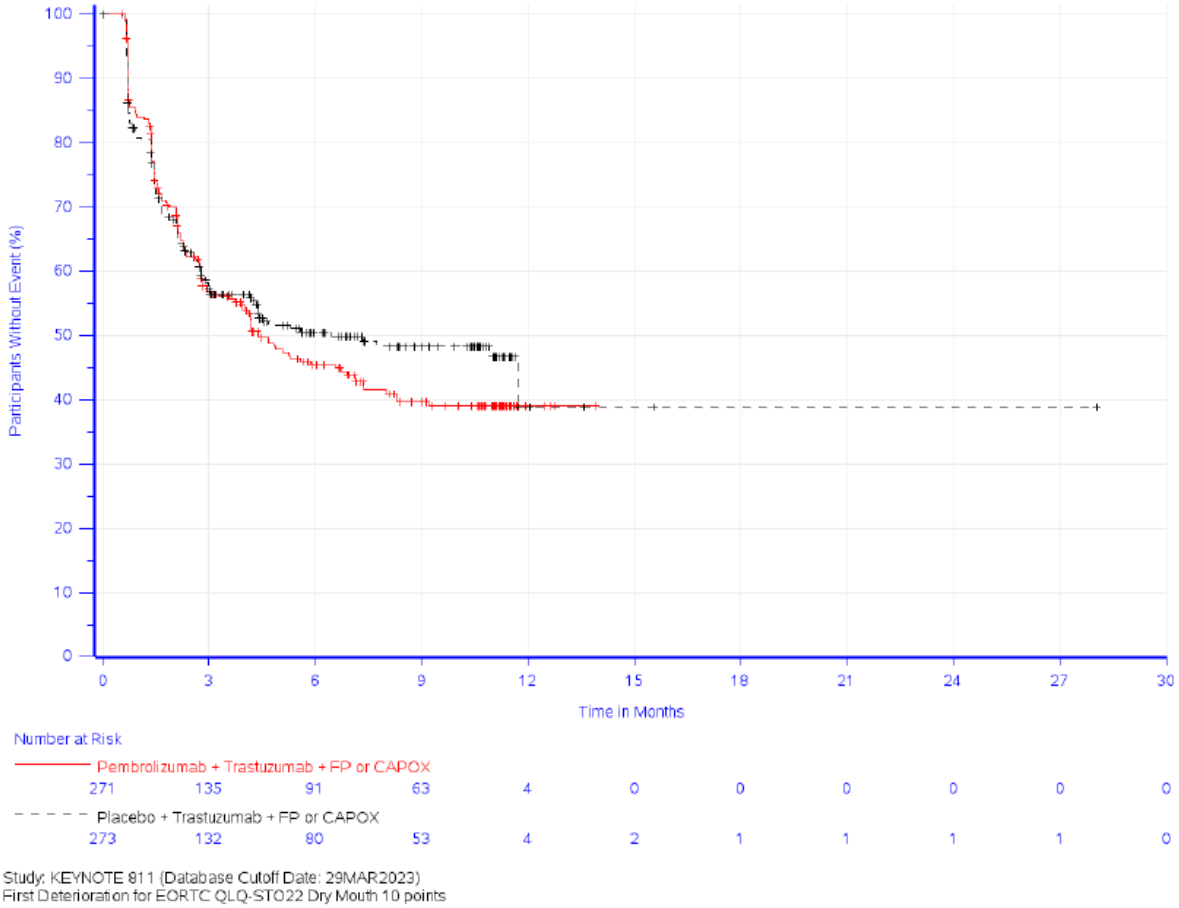

Figure 12: Kaplan-Meier curves for the outcome of dry mouth (EORTC QLQ-STO22, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

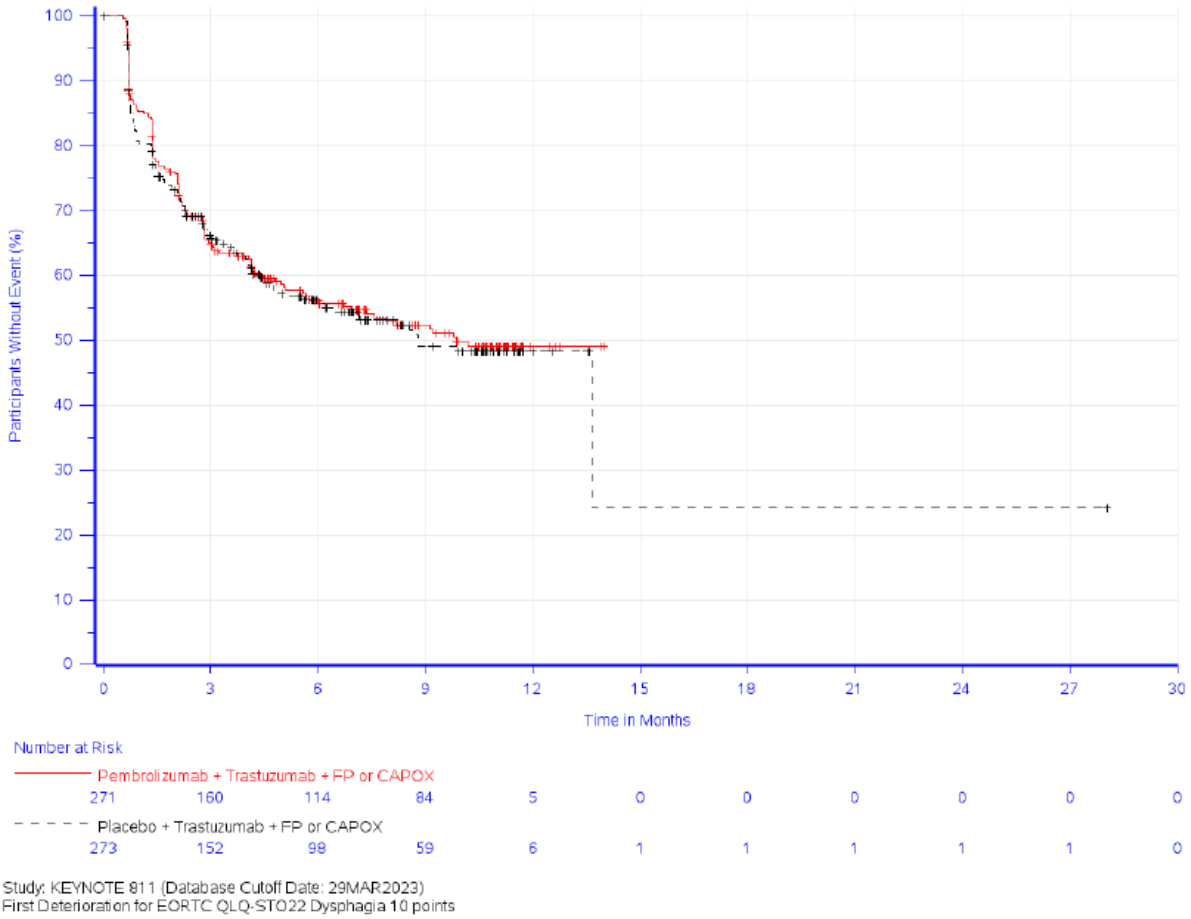

Figure 13: Kaplan-Meier curves for the outcome of dysphagia (EORTC QLQ-STO22, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

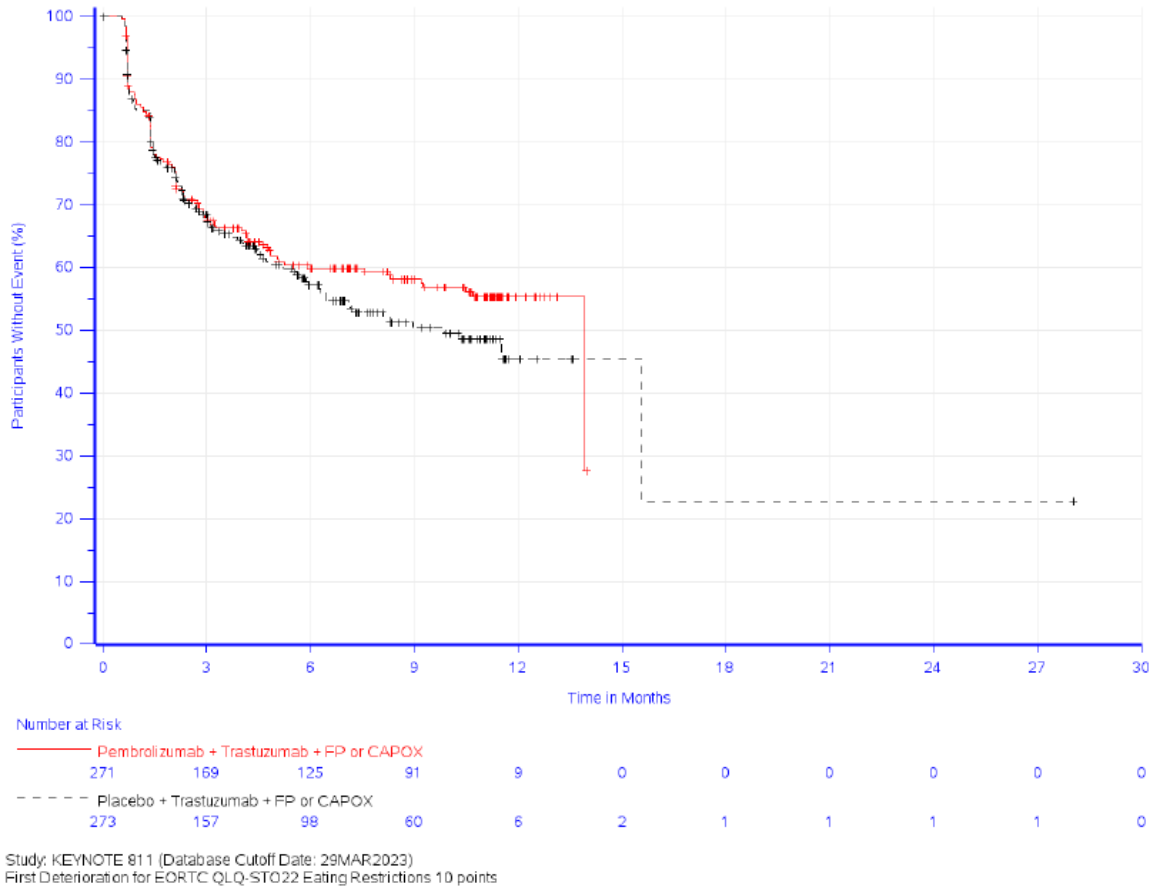

Figure 14: Kaplan-Meier curves for the outcome of eating restrictions (EORTC QLQ-STO22, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

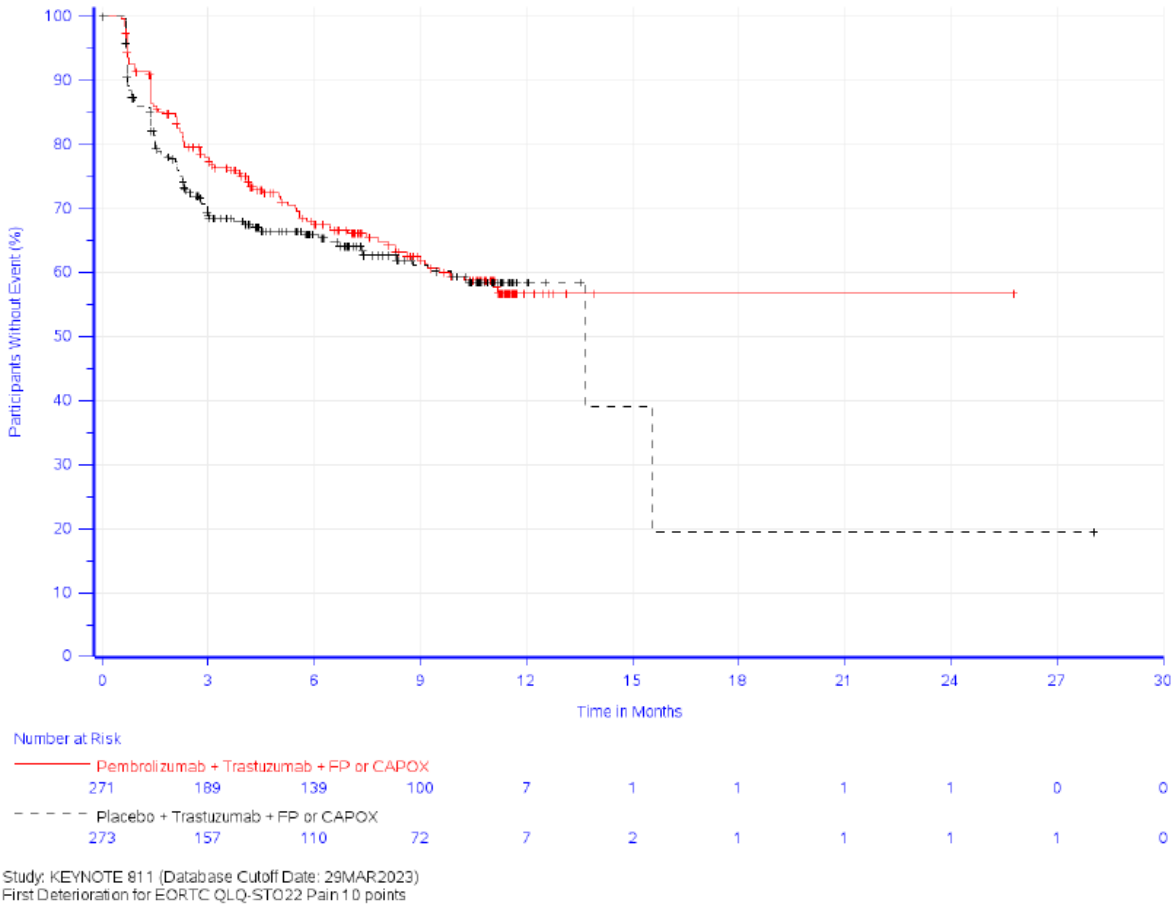

Figure 15: Kaplan-Meier curves for the outcome of pain (EORTC QLQ-STO22, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

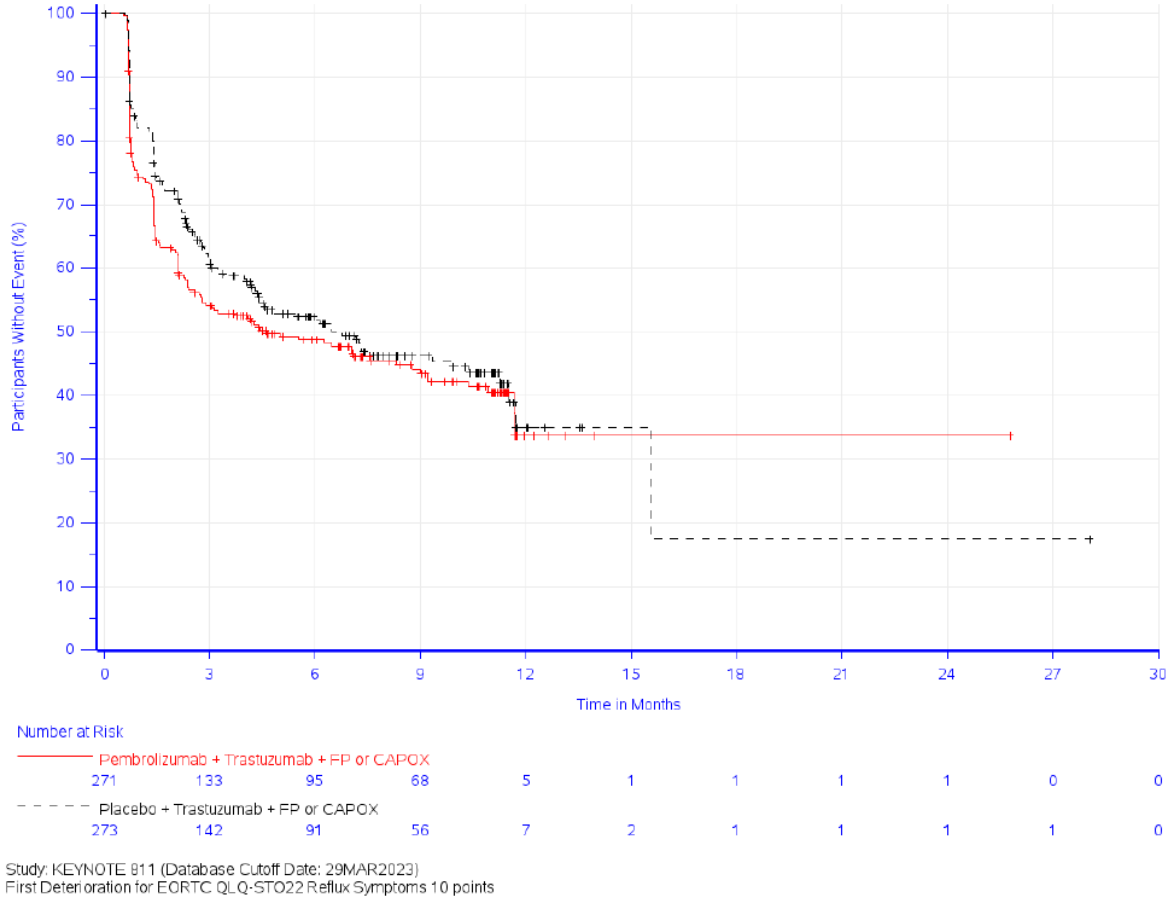

Figure 16: Kaplan-Meier curves for the outcome of reflux (EORTC QLQ-STO22, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

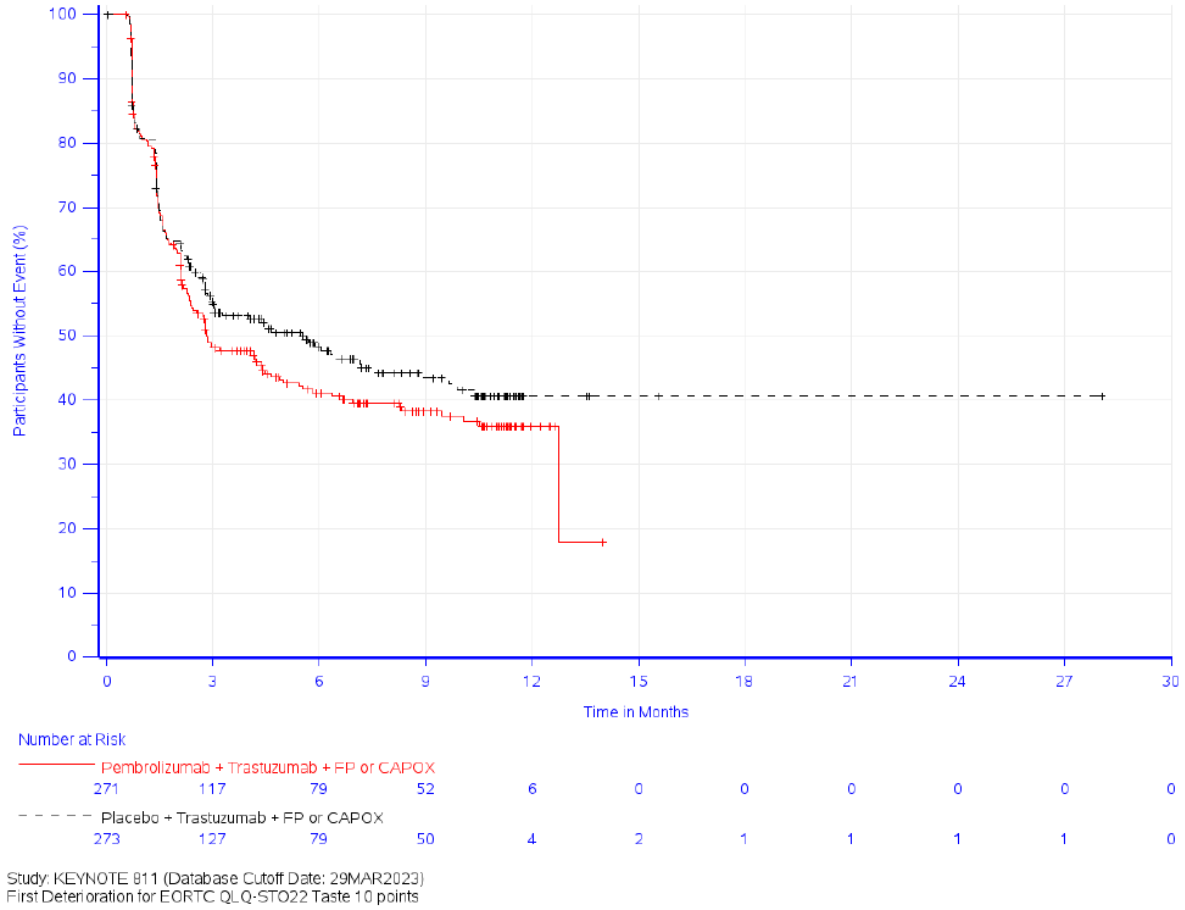

Figure 17: Kaplan-Meier curves for the outcome of dysgeusia (EORTC QLQ-STO22, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

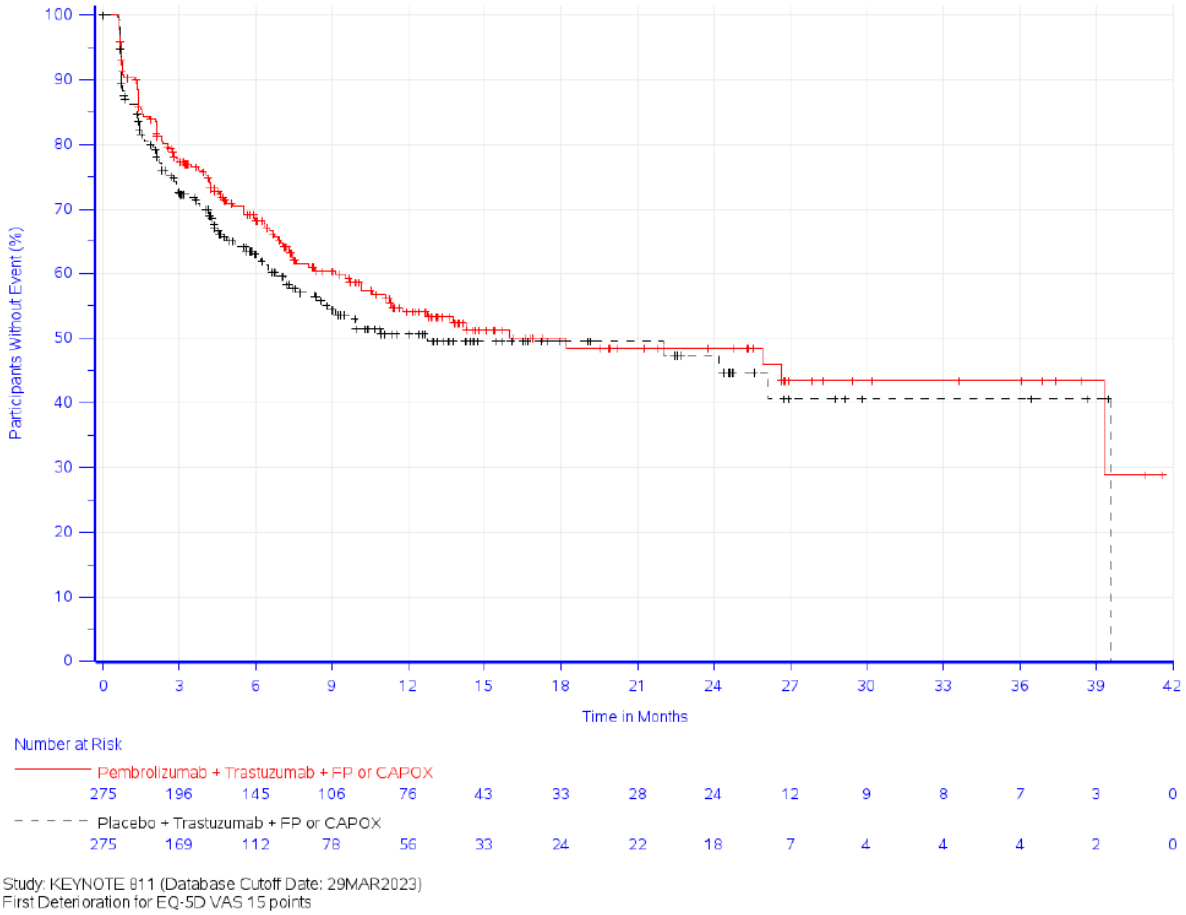

Figure 18: Kaplan-Meier curves for the outcome of health status (EQ-5D VAS, time to first deterioration by ≥ 15 points, KEYNOTE-811 study, PD-L1-positive population)

A.3 Health-related quality of life

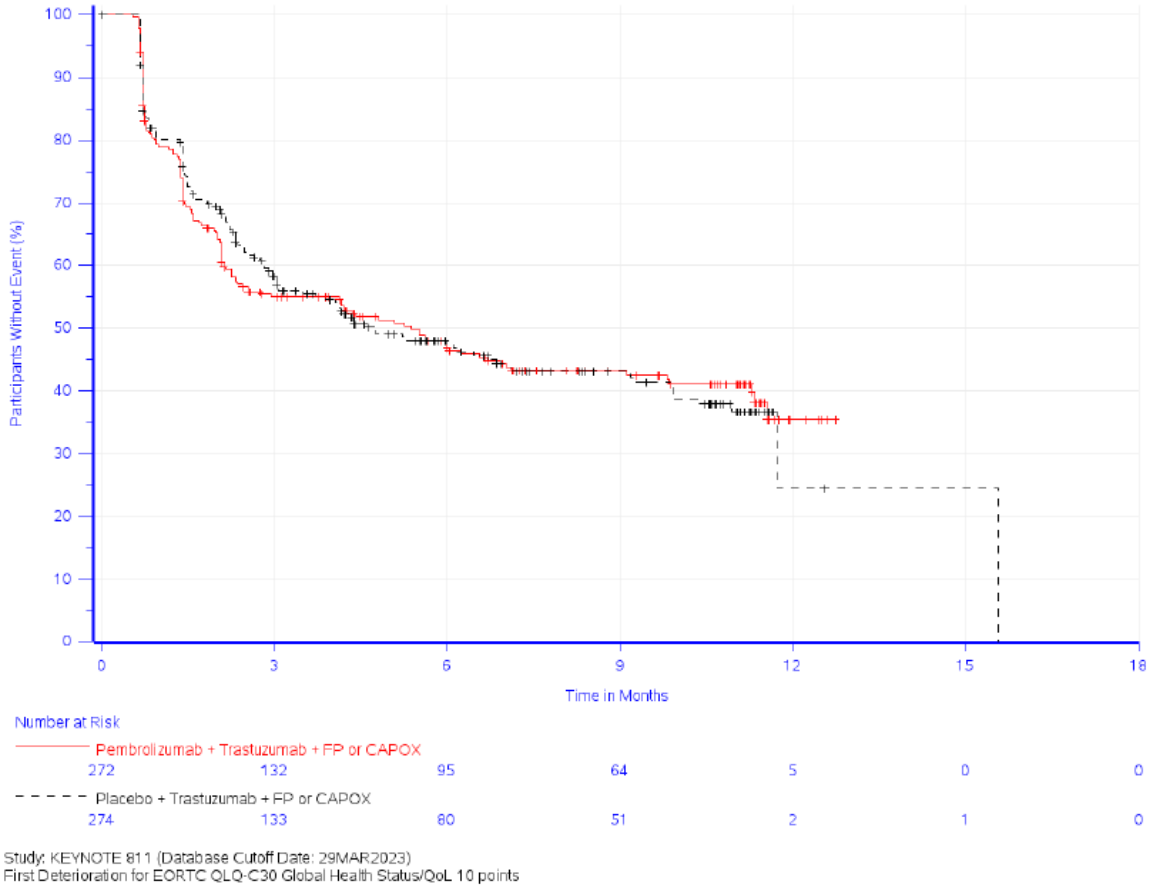

Figure 19: Kaplan-Meier curves for the outcome of global health status (EORTC QLQ-C30, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

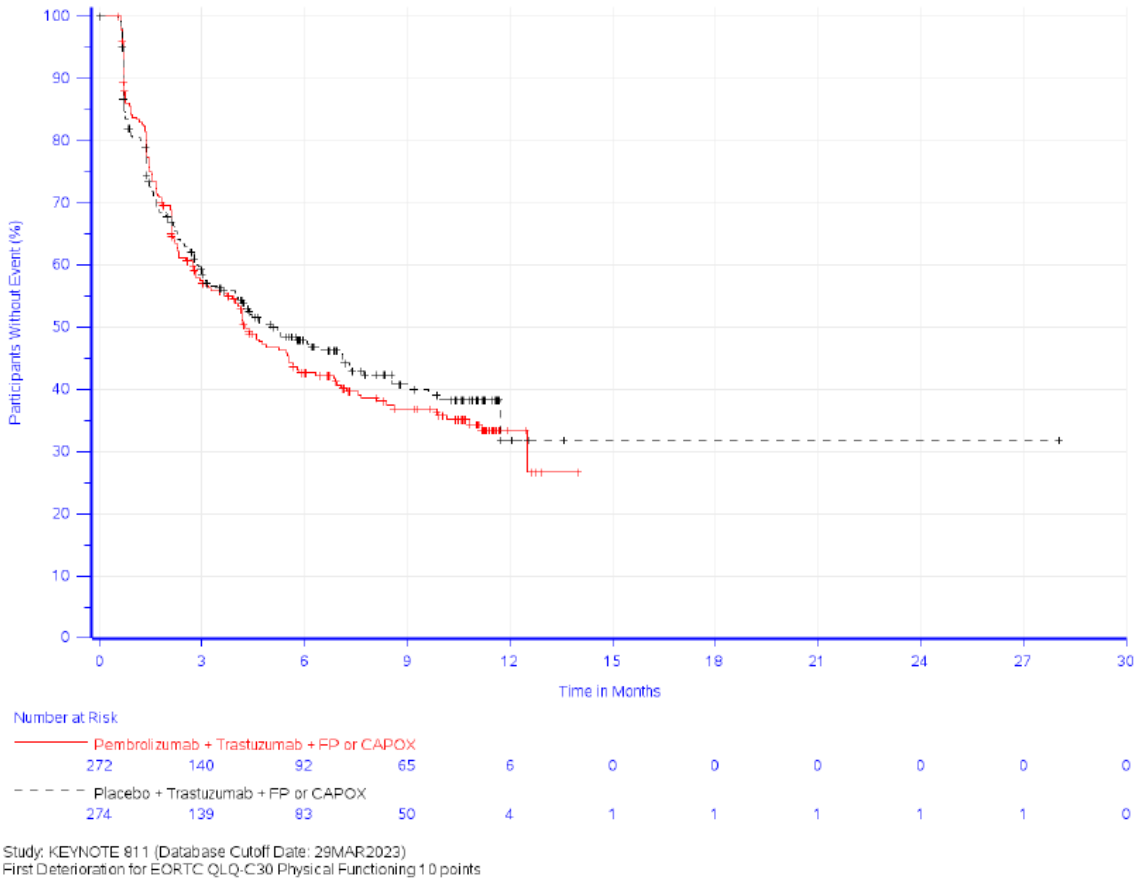

Figure 20: Kaplan-Meier curves for the outcome of physical functioning (EORTC QLQ-C30, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

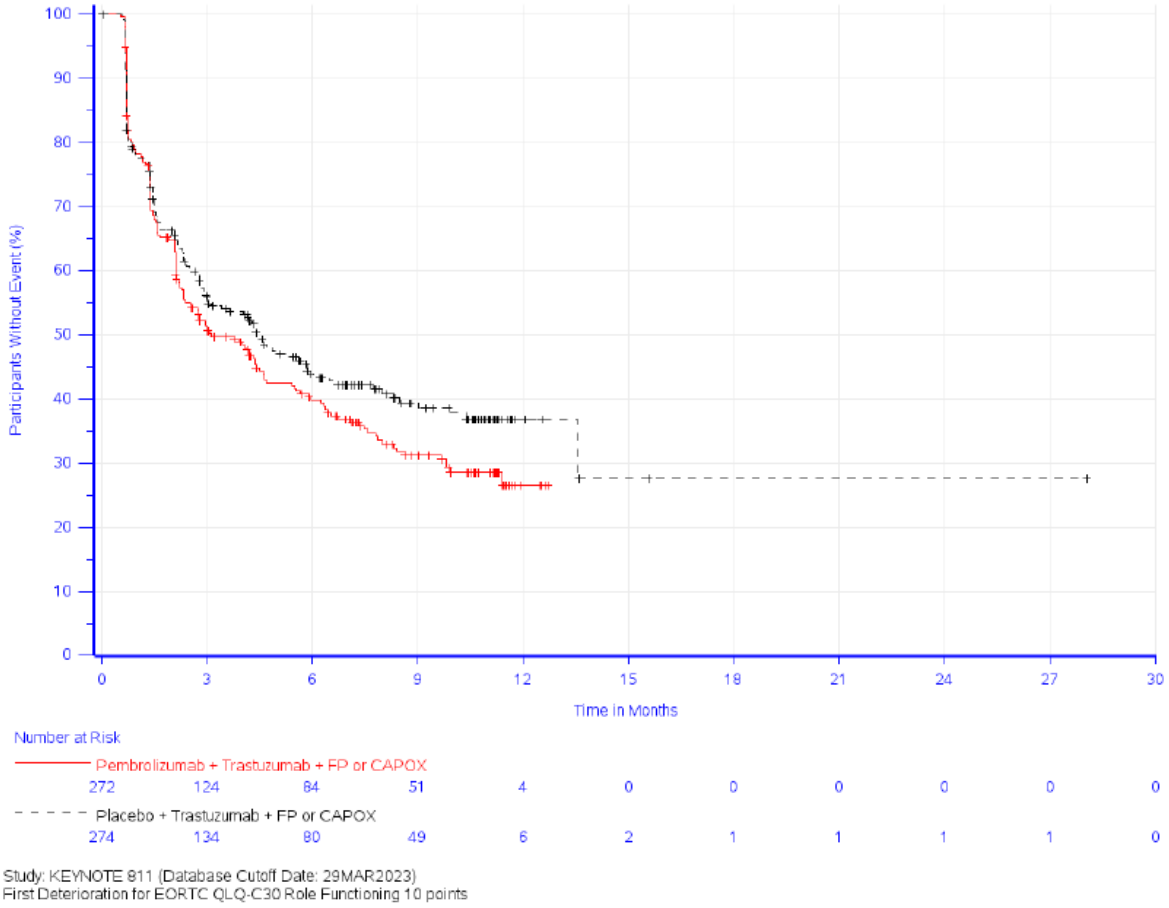

Figure 21: Kaplan-Meier curves for the outcome of role functioning (EORTC QLQ-C30, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

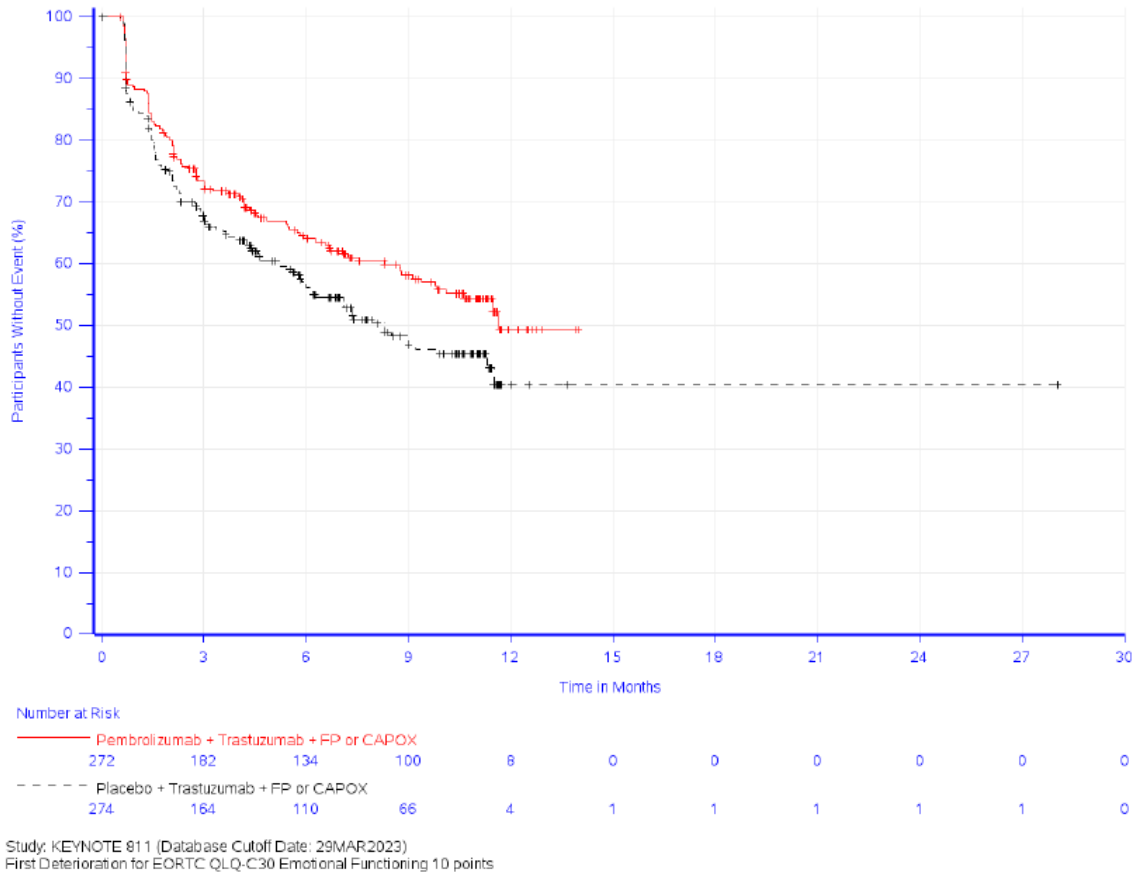

Figure 22: Kaplan-Meier curves for the outcome of emotional functioning (EORTC QLQ-C30, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

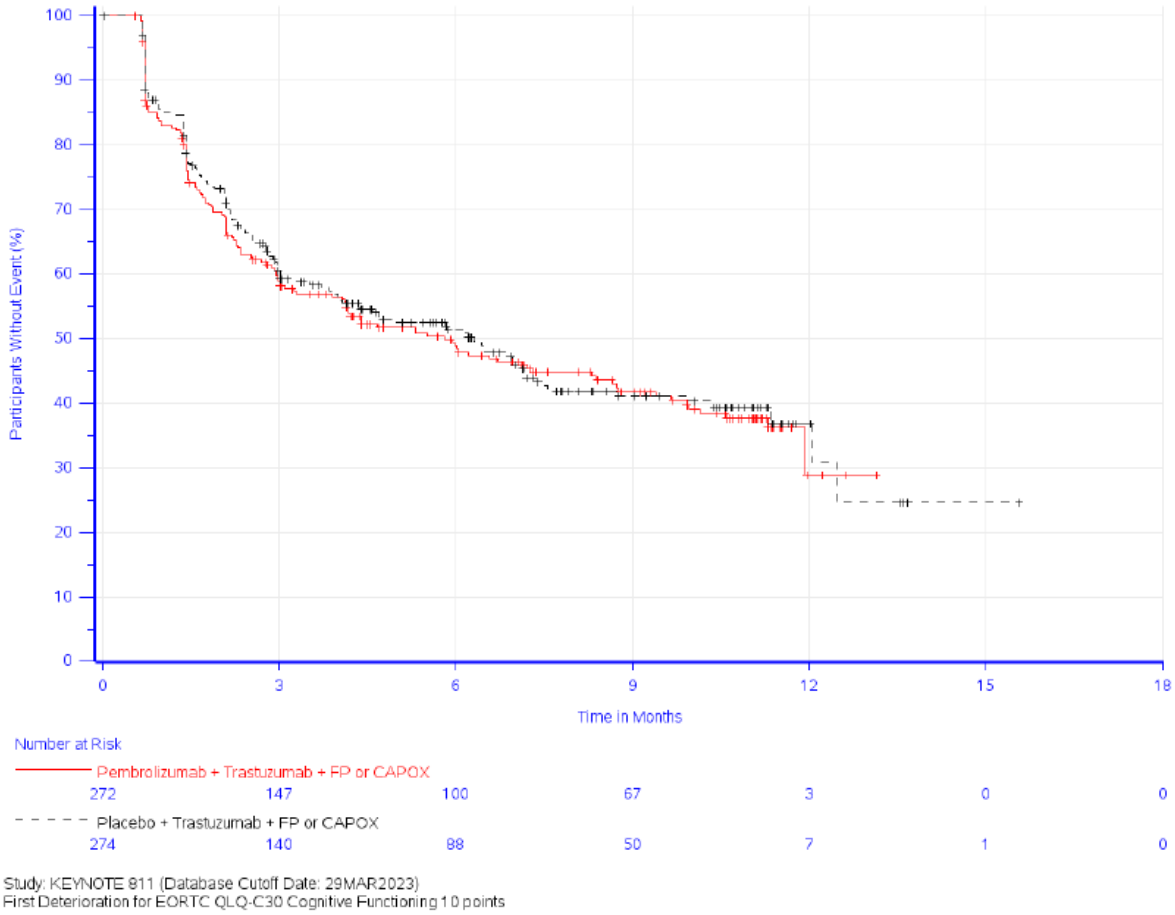

Figure 23: Kaplan-Meier curves for the outcome of cognitive functioning (EORTC QLQ-C30, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

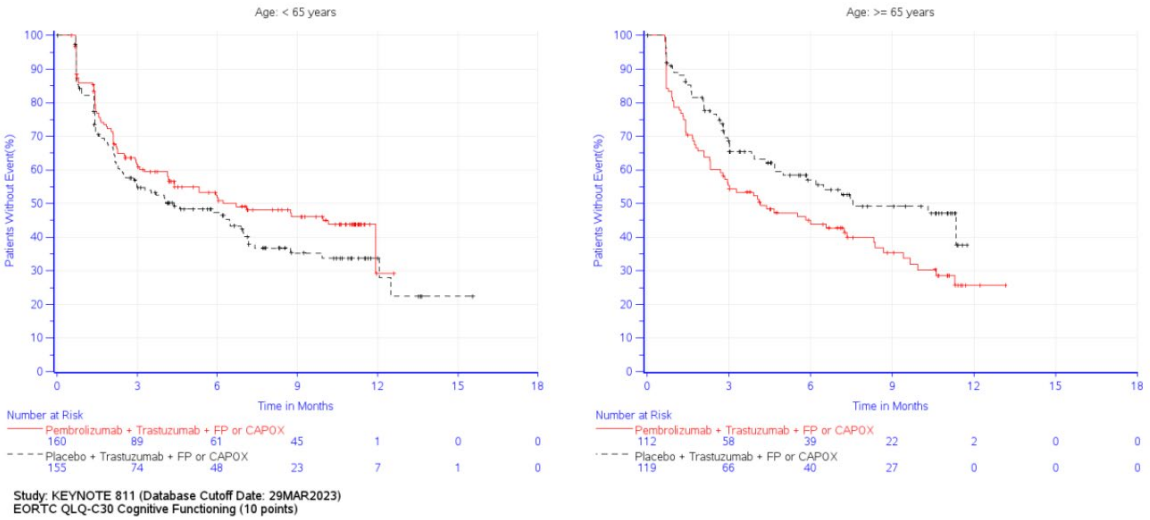

Figure 24: Kaplan-Meier curve for the subgroup analysis by age (years) (< 65 vs. ≥ 65) for the EORTC QLQ-C30 functional scale of cognitive functioning (time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

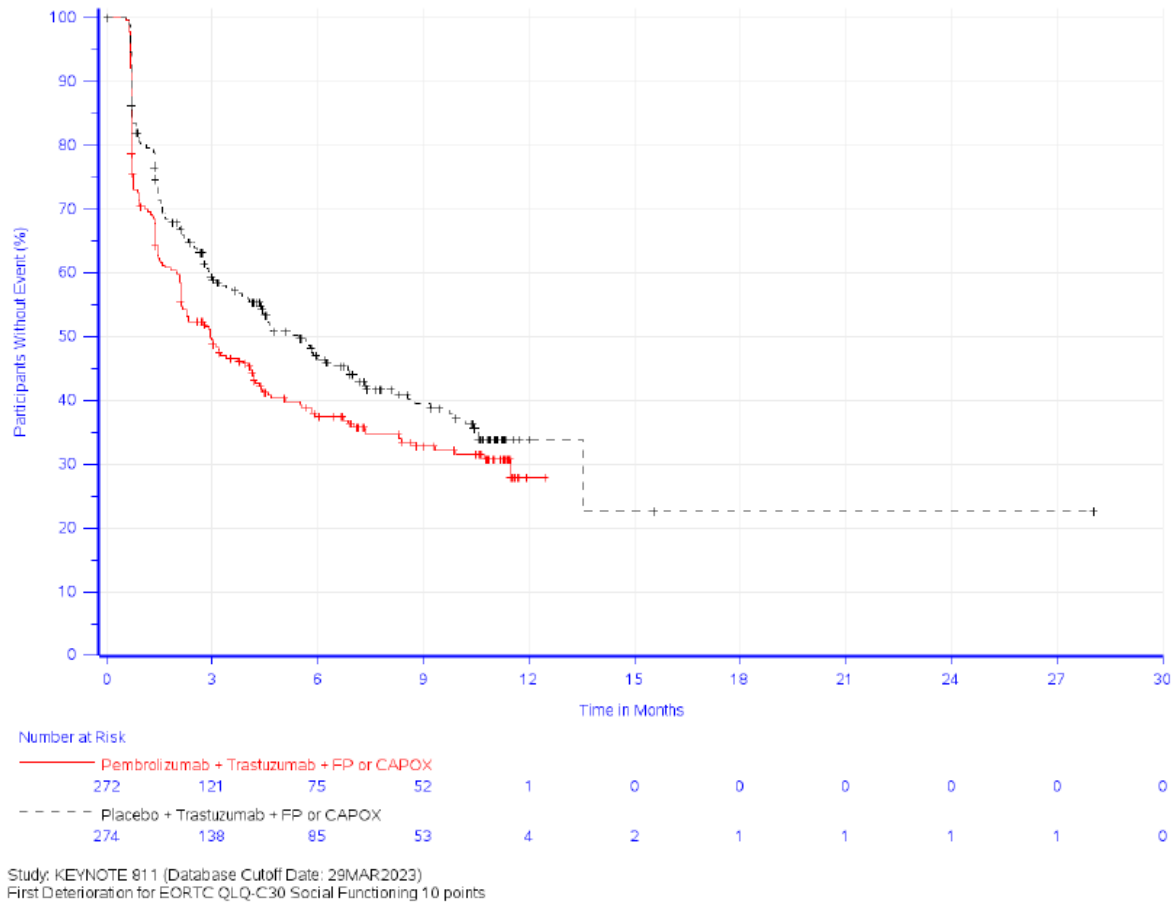

Figure 25: Kaplan-Meier curves for the outcome of social functioning (EORTC QLQ-C30, time to first deterioration by ≥ 10 points, KEYNOTE-811 study, PD-L1-positive population)

A.4 Side effects

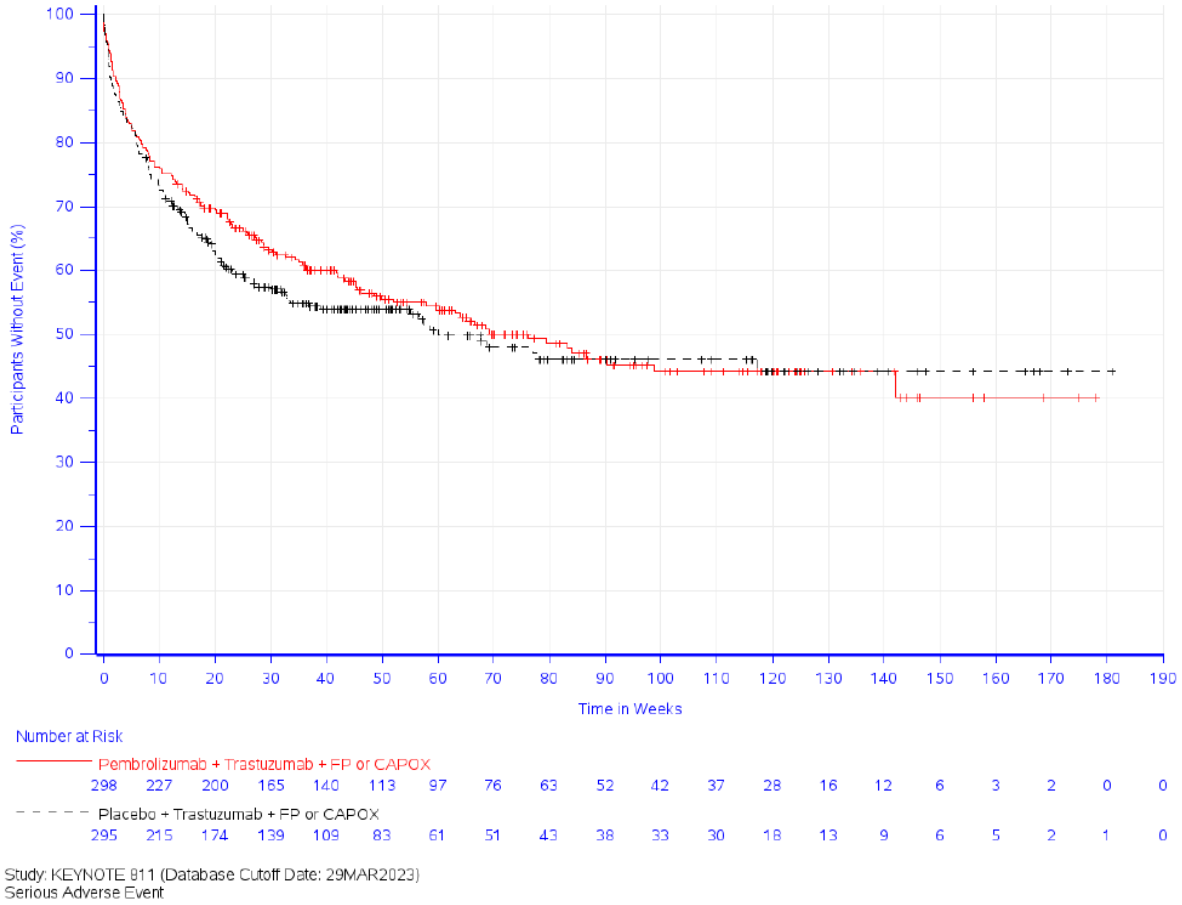

Figure 26: Kaplan-Meier curves for the outcome of SAEs (KEYNOTE-811 study, PD-L1-positive population)

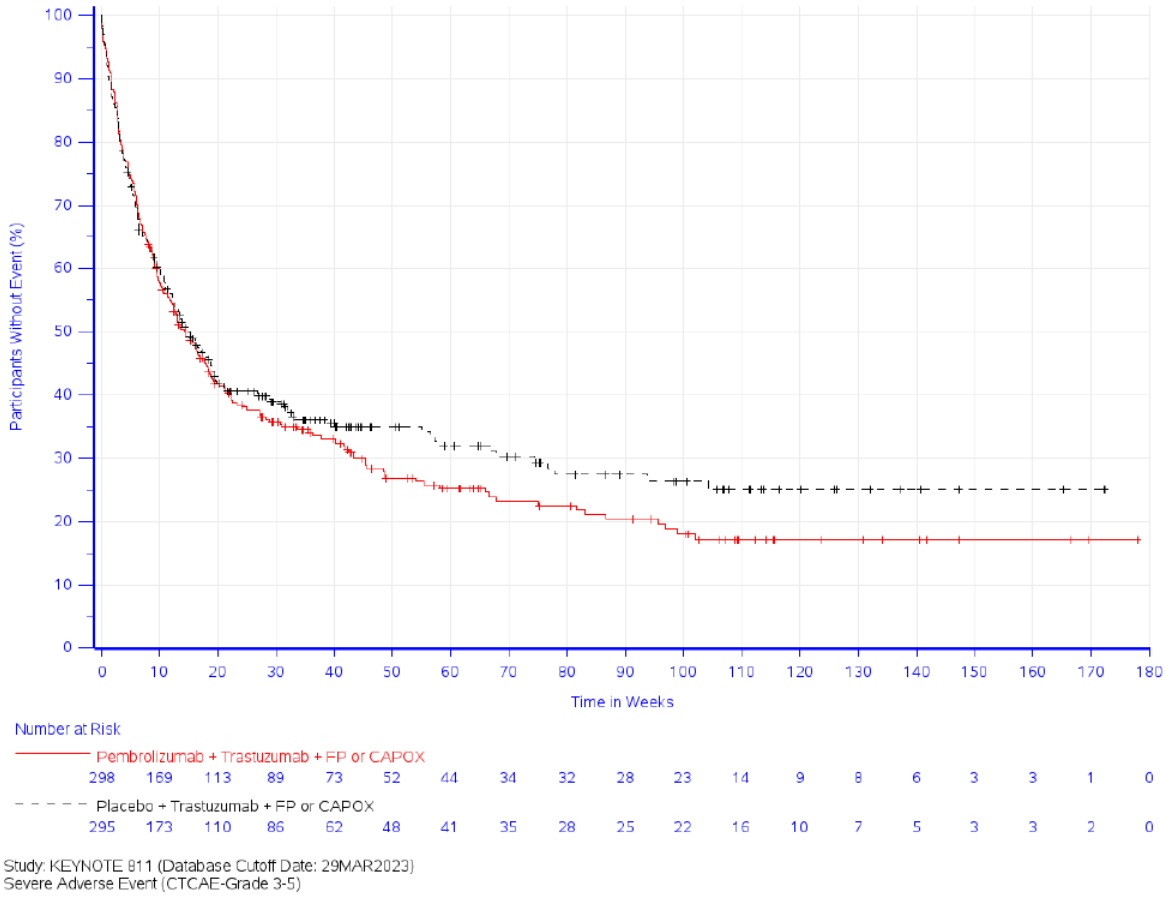

Figure 27: Kaplan-Meier curves for the outcome of severe AEs (KEYNOTE-811 study, PD-L1-positive population)

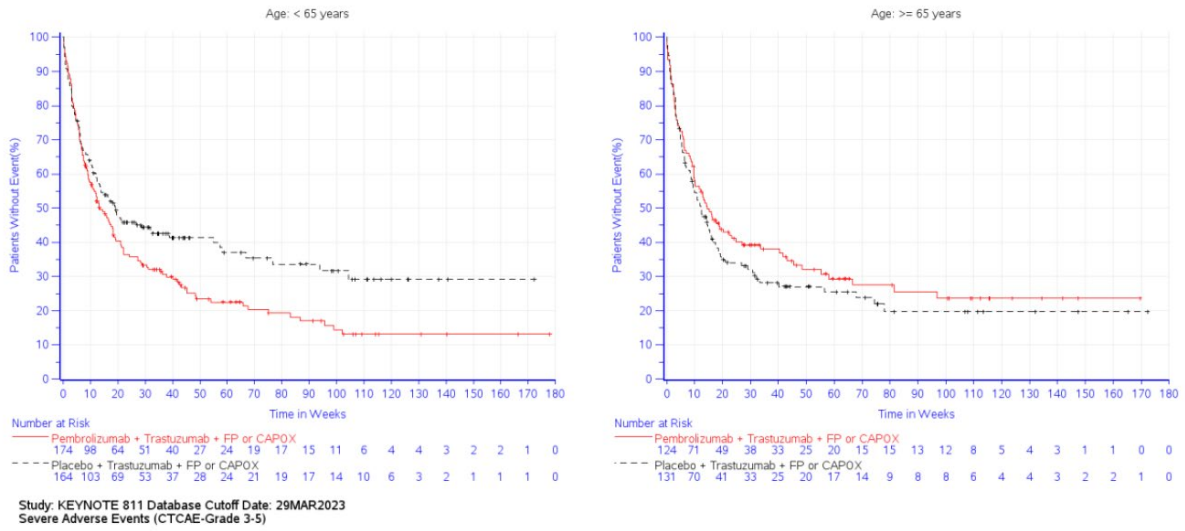

Figure 28: Kaplan-Meier curve for the subgroup analysis by age (years) (< 65 vs. ≥ 65) for the outcome of severe AEs (CTCAE grade 3-5)

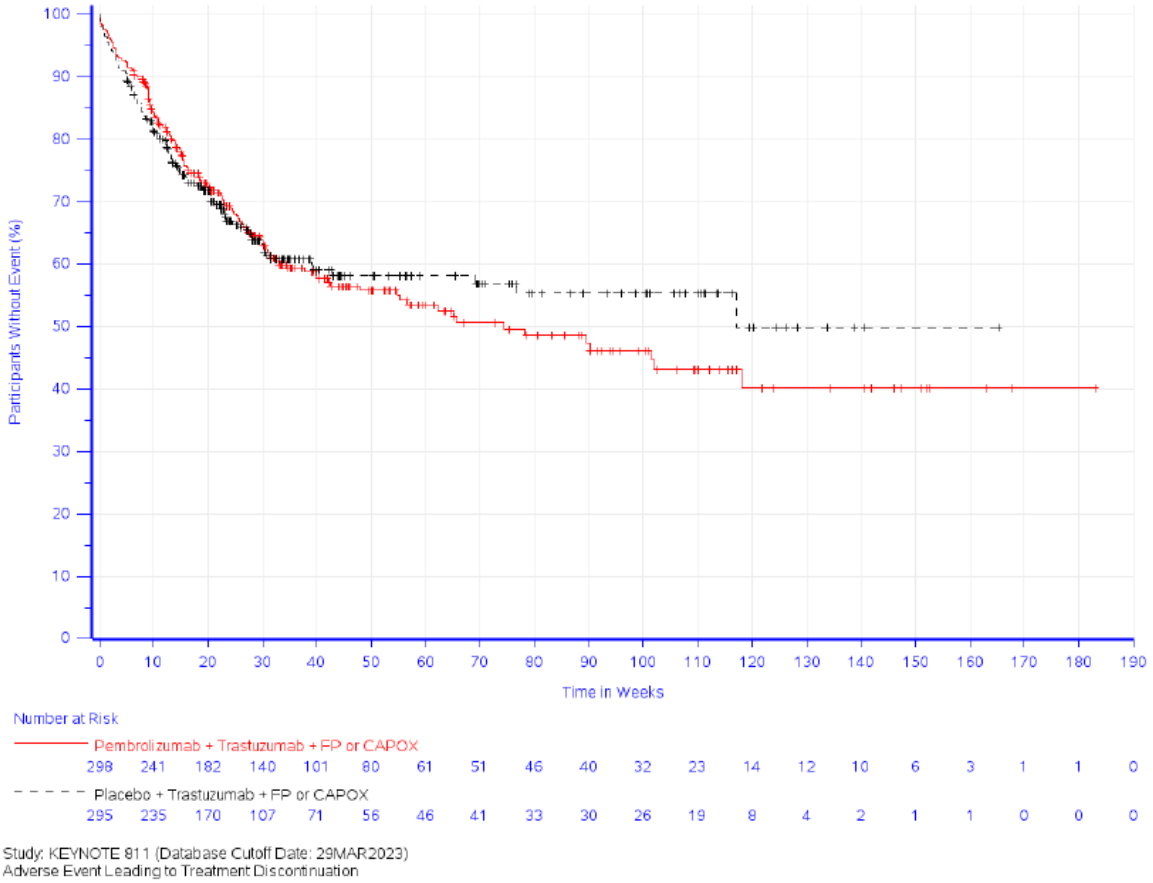

Figure 29: Kaplan-Meier curves for the outcome of discontinuation due to AEs (KEYNOTE-811 study, PD-L1-positive population)

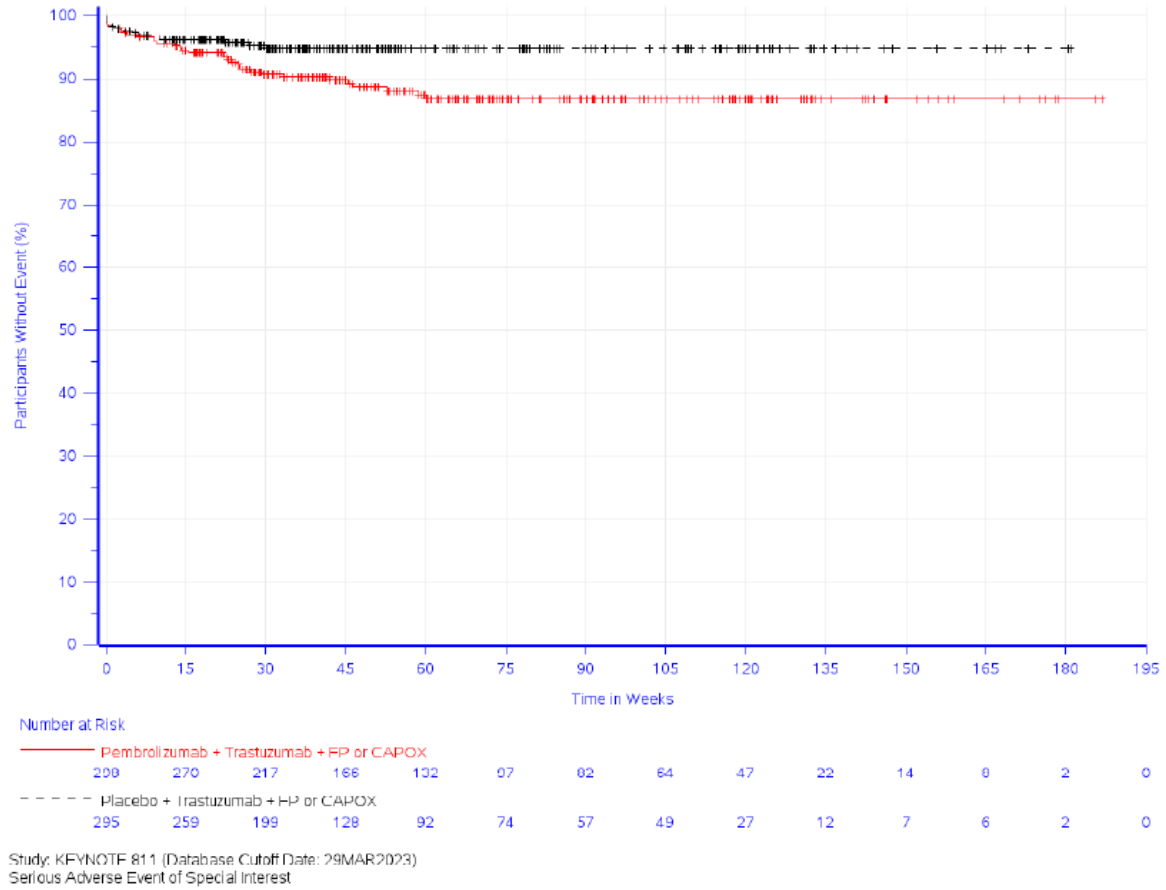

Figure 30: Kaplan-Meier curves for the outcome of immune-related SAEs (KEYNOTE-811 study, PD-L1-positive population)

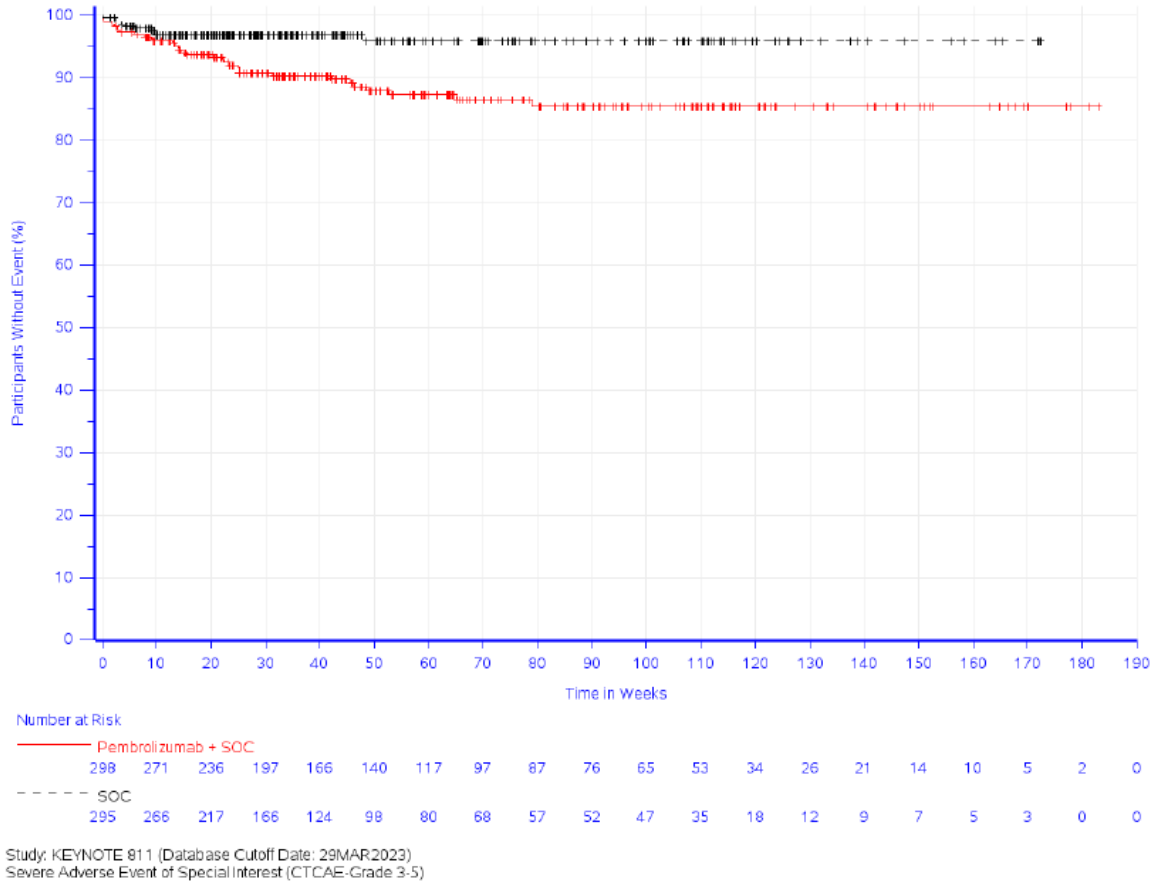

Figure 31: Kaplan-Meier curves for the outcome of immune-related severe AEs (KEYNOTE-811 study, PD-L1-positive population)

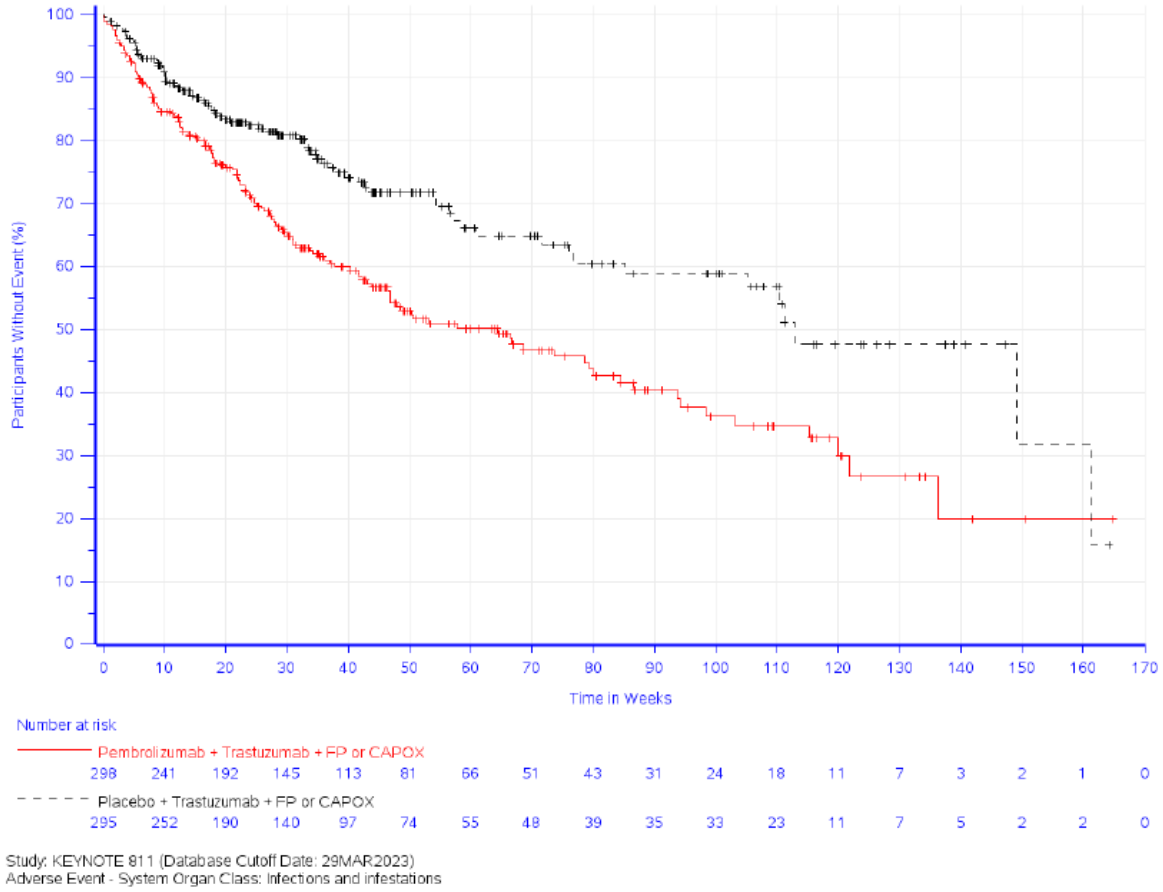

Figure 32: Kaplan-Meier curves for the outcome of infections and infestations (SOC, AE) (KEYNOTE-811 study, PD-L1-positive population)

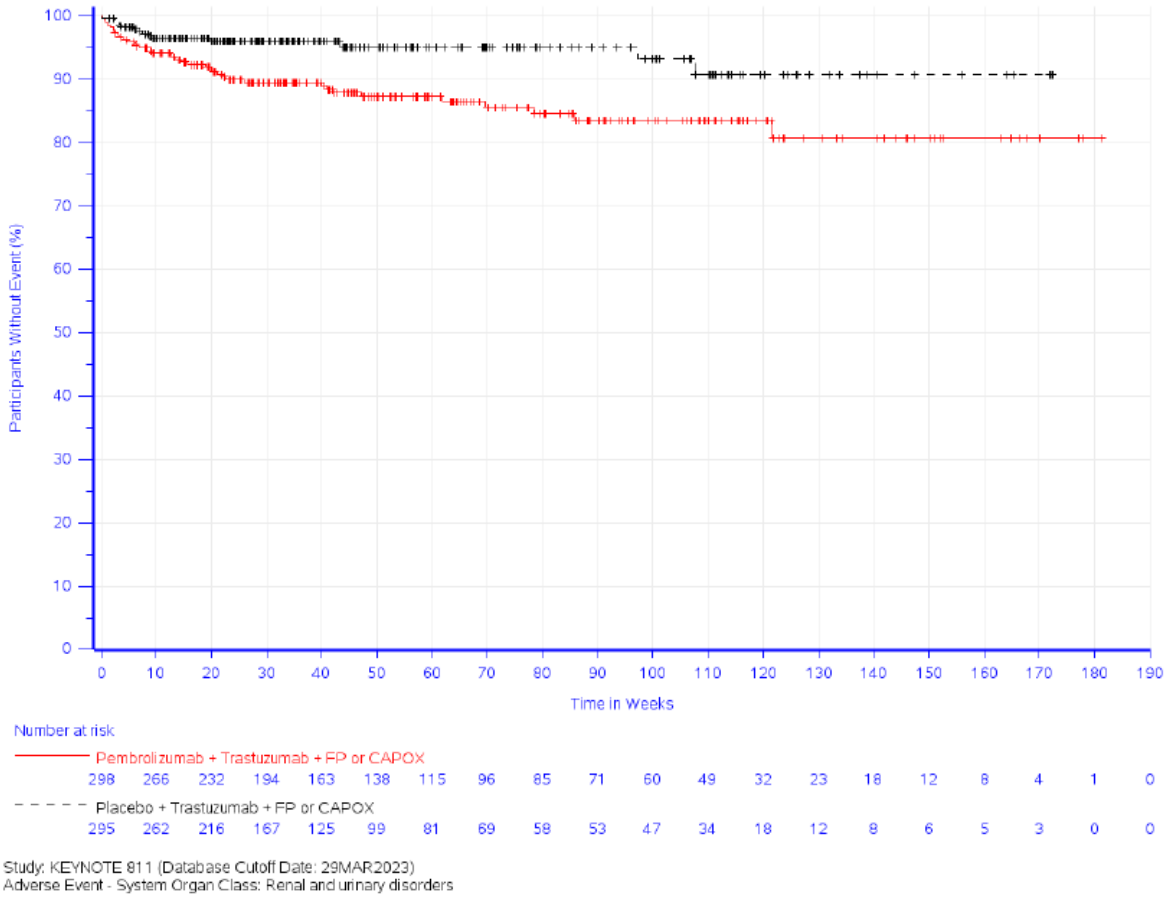

Figure 33: Kaplan-Meier curves for the outcome of renal and urinary disorders (SOC, AE) (KEYNOTE-811 study, PD-L1-positive population)

Appendix B Results on side effects

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

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

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

Table 11: Common AEs[a] – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Pembrolizumab + trastuzumab + FP/CAPOX** **N[c] = 298**	**Placebo + trastuzumab + FP/CAPOX** **N[c] = 295**
KEYNOTE-811		
Overall AE rate	296 (99.3)	295 (100.0)
Blood and lymphatic system disorders	174 (58.4)	165 (55.9)
Anaemia	138 (46.3)	138 (46.8)
Leukopenia	11 (3.7)	21 (7.1)
Neutropenia	53 (17.8)	46 (15.6)
Thrombocytopenia	38 (12.8)	39 (13.2)
Cardiac disorders	33 (11.1)	29 (9.8)
Ear and labyrinth disorders	22 (7.4)	14 (4.7)
Tinnitus	10 (3.4)	8 (2.7)
Endocrine disorders	51 (17.1)	22 (7.5)
Hyperthyroidism	12 (4.0)	10 (3.4)
Hypothyroidism	32 (10.7)	11 (3.7)
Eye disorders	23 (7.7)	15 (5.1)

Table 11: Common AEs[a] – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Pembrolizumab + trastuzumab + FP/CAPOX** **N[c] = 298**	**Placebo + trastuzumab + FP/CAPOX** **N[c] = 295**
Gastrointestinal disorders	257 (86.2)	248 (84.1)
Abdominal distension	11 (3.7)	9 (3.1)
Abdominal pain	34 (11.4)	35 (11.9)
Abdominal pain upper	17 (5.7)	23 (7.8)
Colitis	10 (3.4)	6 (2.0)
Constipation	56 (18.8)	59 (20.0)
Diarrhoea	160 (53.7)	138 (46.8)
Dyspepsia	20 (6.7)	13 (4.4)
Dysphagia	24 (8.1)	26 (8.8)
Gastrooesophageal reflux disease	12 (4.0)	11 (3.7)
Nausea	151 (50.7)	143 (48.5)
Stomatitis	35 (11.7)	22 (7.5)
Vomiting	105 (35.2)	90 (30.5)
General disorders and administration site conditions	186 (62.4)	177 (60.0)
Asthenia	39 (13.1)	55 (18.6)
Chills	10 (3.4)	9 (3.1)
Fatigue	72 (24.2)	64 (21.7)
Malaise	27 (9.1)	20 (6.8)
Mucosal inflammation	24 (8.1)	23 (7.8)
Oedema peripheral	27 (9.1)	22 (7.5)
Pyrexia	45 (15.1)	38 (12.9)
Hepatobiliary disorders	27 (9.1)	20 (6.8)
Immune system disorders	16 (5.4)	10 (3.4)
Infections and infestations	139 (46.6)	79 (26.8)
COVID-19	22 (7.4)	11 (3.7)
Pneumonia	33 (11.1)	16 (5.4)
Urinary tract infection	11 (3.7)	11 (3.7)
Injury, poisoning and procedural complications	61 (20.5)	49 (16.6)
Infusion-related reaction	37 (12.4)	30 (10.2)

Table 11: Common AEs[a] – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Pembrolizumab + trastuzumab + FP/CAPOX N[c] = 298**	**Placebo + trastuzumab + FP/CAPOX N[c] = 295**
Investigations	208 (69.8)	191 (64.7)
Alanine aminotransferase increased	58 (19.5)	39 (13.2)
Aspartate aminotransferase increased	75 (25.2)	50 (16.9)
Blood alkaline phosphatase increased	16 (5.4)	16 (5.4)
Blood bilirubin increased	46 (15.4)	30 (10.2)
Blood creatinine increased	22 (7.4)	12 (4.1)
Ejection fraction decreased	13 (4.4)	10 (3.4)
Gamma-glutamyltransferase increased	10 (3.4)	11 (3.7)
Lymphocyte count decreased	14 (4.7)	9 (3.1)
Neutrophil count decreased	79 (26.5)	76 (25.8)
Platelet count decreased	83 (27.9)	80 (27.1)
Weight decreased	65 (21.8)	54 (18.3)
Weight increased	10 (3.4)	8 (2.7)
White blood cell count decreased	46 (15.4)	38 (12.9)
Metabolism and nutrition disorders	179 (60.1)	159 (53.9)
Decreased appetite	99 (33.2)	89 (30.2)
Hyperglycaemia	22 (7.4)	14 (4.7)
Hypoalbuminaemia	48 (16.1)	50 (16.9)
Hypocalcaemia	20 (6.7)	13 (4.4)
Hypokalaemia	48 (16.1)	31 (10.5)
Hypomagnesaemia	21 (7.0)	13 (4.4)
Hyponatraemia	17 (5.7)	21 (7.1)
Hypophosphataemia	10 (3.4)	11 (3.7)
Hypoproteinaemia	11 (3.7)	3 (1.0)
Musculoskeletal and connective tissue disorders	66 (22.1)	50 (16.9)
Arthralgia	20 (6.7)	12 (4.1)
Back pain	18 (6.0)	21 (7.1)
Myalgia	10 (3.4)	6 (2.0)

Table 11: Common AEs[a] – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Pembrolizumab + trastuzumab + FP/CAPOX** **N[c] = 298**	**Placebo + trastuzumab + FP/CAPOX** **N[c] = 295**
Nervous system disorders	174 (58.4)	172 (58.3)
Dizziness	16 (5.4)	10 (3.4)
Dysgeusia	15 (5.0)	14 (4.7)
Headache	21 (7.0)	17 (5.8)
Hypoaesthesia	10 (3.4)	11 (3.7)
Peripheral neuropathy	55 (18.5)	56 (19.0)
Neurotoxicity	7 (2.3)	14 (4.7)
Paraesthesia	23 (7.7)	19 (6.4)
Peripheral sensory neuropathy	74 (24.8)	59 (20.0)
Polyneuropathy	2 (0.7)	11 (3.7)
Psychiatric disorders	37 (12.4)	36 (12.2)
Depression	3 (1.0)	10 (3.4)
Insomnia	19 (6.4)	14 (4.7)
Renal and urinary disorders	38 (12.8)	14 (4.7)
Respiratory, thoracic, and mediastinal disorders	96 (32.2)	79 (26.8)
Cough	28 (9.4)	15 (5.1)
Dyspnoea	13 (4.4)	12 (4.1)
Epistaxis	12 (4.0)	11 (3.7)
Hiccups	17 (5.7)	9 (3.1)
Pneumonitis	19 (6.4)	2 (0.7)
Pulmonary embolism	9 (3.0)	12 (4.1)
Skin and subcutaneous tissue disorders	141 (47.3)	105 (35.6)
Dry skin	18 (6.0)	11 (3.7)
Palmar-plantar erythrodysaesthesia syndrome	67 (22.5)	57 (19.3)
Itching	28 (9.4)	14 (4.7)
Rash	27 (9.1)	14 (4.7)
Vascular disorders	44 (14.8)	34 (11.5)
Hypertension	16 (5.4)	12 (4.1)
Hypotension	11 (3.7)	5 (1.7)

Table 11: Common AEs[a] – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Pembrolizumab + trastuzumab + FP/CAPOX** **N[c] = 298**	**Placebo + trastuzumab + FP/CAPOX** **N[c] = 295**

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOCs and PTs used unmodified from Module 4 A.
c. Number of randomized patients with positive PD-L1 status (CPS ≥ 1) who received at least one dose of the study medication. The analysis was carried out based on the treatment actually received.

AE: adverse event; CAPOX: capecitabine + oxaliplatin; CPS: combined positive score; FP: 5-fluorouracil + cisplatin; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 12: Common SAEs[a] – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Pembrolizumab + trastuzumab + FP/CAPOX** **N[c] = 298**	**Placebo + trastuzumab + FP/CAPOX** **N[c] = 295**
KEYNOTE-811		
Overall SAE rate	143 (48.0)	141 (47.8)
Blood and lymphatic system disorders	13 (4.4)	9 (3.1)
Cardiac disorders	10 (3.4)	8 (2.7)
Gastrointestinal disorders	63 (21.1)	64 (21.7)
Diarrhoea	16 (5.4)	14 (4.7)
General disorders and administration site conditions	16 (5.4)	15 (5.1)
Infections and infestations	41 (13.8)	26 (8.8)
Pneumonia	16 (5.4)	8 (2.7)
Investigations	10 (3.4)	8 (2.7)
Metabolism and nutrition disorders	12 (4.0)	15 (5.1)
Respiratory, thoracic, and mediastinal disorders	26 (8.7)	13 (4.4)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOCs and PTs used unmodified from Module 4 A.
c. Number of randomized patients with positive PD-L1 status (CPS ≥ 1) who received at least one dose of the study medication. The analysis was carried out based on the treatment actually received.

CAPOX: capecitabine + oxaliplatin; CPS: combined positive score; FP: 5-fluorouracil + cisplatin; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 13: Common severe AEs[a] (CTCAE ≥ 3) – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Pembrolizumab + trastuzumab + FP/CAPOX** **N[c] = 298**	**Placebo + trastuzumab + FP/CAPOX** **N[c] = 295**
KEYNOTE-811		
Overall rate of severe AEs (CTCAE grade ≥ 3)	220 (73.8)	194 (65.8)
Blood and lymphatic system disorders	63 (21.1)	46 (15.6)
Anaemia	38 (12.8)	30 (10.2)
Neutropenia	23 (7.7)	13 (4.4)
Thrombocytopenia	11 (3.7)	8 (2.7)
Cardiac disorders	10 (3.4)	8 (2.7)
Gastrointestinal disorders	87 (29.2)	82 (27.8)
Diarrhoea	32 (10.7)	25 (8.5)
Nausea	13 (4.4)	17 (5.8)
Vomiting	14 (4.7)	11 (3.7)
General disorders and administration site conditions	38 (12.8)	29 (9.8)
Asthenia	9 (3.0)	11 (3.7)
Fatigue	15 (5.0)	7 (2.4)
Hepatobiliary disorders	11 (3.7)	7 (2.4)
Infections and infestations	36 (12.1)	24 (8.1)
Pneumonia	11 (3.7)	8 (2.7)
Investigations	76 (25.5)	59 (20.0)
Neutrophil count decreased	25 (8.4)	27 (9.2)
Platelet count decreased	22 (7.4)	17 (5.8)
Metabolism and nutrition disorders	48 (16.1)	38 (12.9)
Decreased appetite	11 (3.7)	10 (3.4)
Hypokalaemia	18 (6.0)	13 (4.4)
Nervous system disorders	31 (10.4)	24 (8.1)
Peripheral sensory neuropathy	12 (4.0)	7 (2.4)
Respiratory, thoracic, and mediastinal disorders	24 (8.1)	17 (5.8)
Skin and subcutaneous tissue disorders	10 (3.4)	6 (2.0)
Vascular disorders	12 (4.0)	5 (1.7)

Table 13: Common severe AEs[a] (CTCAE ≥ 3) – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Pembrolizumab + trastuzumab + FP/CAPOX** **N[c] = 298**	**Placebo + trastuzumab + FP/CAPOX** **N[c] = 295**

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOCs and PTs used unmodified from Module 4.
c. Number of randomized patients with positive PD-L1 status (CPS ≥ 1) who received at least one dose of the study medication. The analysis was carried out based on the treatment actually received.

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

Table 14: Discontinuation due to AEs[a] – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Pembrolizumab + trastuzumab + FP/CAPOX N[c] = 298**	**Placebo + trastuzumab + FP/CAPOX N[c] = 295**
KEYNOTE-811		
Total rate of discontinuations due to AEs	127 (42.6)	108 (36.6)
Blood and lymphatic system disorders	11 (3.7)	8 (2.7)
Anaemia	2 (0.7)	0 (0)
Neutropenia	4 (1.3)	4 (1.4)
Thrombocytopenia	4 (1.3)	4 (1.4)
Cardiac disorders	4 (1.3)	6 (2.0)
Gastrointestinal disorders	22 (7.4)	17 (5.8)
Colitis	2 (0.7)	0 (0)
Diarrhoea	3 (1.0)	5 (1.7)
Dysphagia	2 (0.7)	0 (0)
Enterocolitis	2 (0.7)	0 (0)
Gastric haemorrhage	2 (0.7)	0 (0)
Nausea	4 (1.3)	3 (1.0)
Stomatitis	2 (0.7)	0 (0)
Vomiting	6 (2.0)	3 (1.0)
General disorders and administration site conditions	8 (2.7)	10 (3.4)
Asthenia	2 (0.7)	0 (0)
Death	2 (0.7)	1 (0.3)
Fatigue	2 (0.7)	3 (1.0)
Malaise	1 (0.3)	2 (0.7)
Hepatobiliary disorders	3 (1.0)	3 (1.0)
Immune system disorders	3 (1.0)	2 (0.7)
Infections and infestations	9 (3.0)	6 (2.0)
Pneumonia	4 (1.3)	2 (0.7)
Sepsis	2 (0.7)	1 (0.3)
Injury, poisoning and procedural complications	4 (1.3)	6 (2.0)
Infusion-related reaction	4 (1.3)	4 (1.4)

Table 14: Discontinuation due to AEs[a] – RCT, direct comparison: pembrolizumab + trastuzumab + FP/CAPOX vs. placebo + trastuzumab + FP/CAPOX (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Pembrolizumab + trastuzumab + FP/CAPOX** **N[c] = 298**	**Placebo + trastuzumab + FP/CAPOX** **N[c] = 295**
Investigations	25 (8.4)	17 (5.8)
Aspartate aminotransferase increased	2 (0.7)	0 (0)
Blood creatinine increased	5 (1.7)	0 (0)
Ejection fraction decreased	2 (0.7)	1 (0.3)
Neutrophil count decreased	7 (2.3)	5 (1.7)
Platelet count decreased	10 (3.4)	9 (3.1)
Weight decreased	0 (0)	2 (0.7)
Metabolism and nutrition disorders	4 (1.3)	3 (1.0)
Decreased appetite	3 (1.0)	3 (1.0)
Nervous system disorders	36 (12.1)	34 (11.5)
Peripheral neuropathy	16 (5.4)	13 (4.4)
Neurotoxicity	0 (0)	5 (1.7)
Paraesthesia	2 (0.7)	0 (0)
Peripheral sensory neuropathy	14 (4.7)	12 (4.1)
Renal and urinary disorders	3 (1.0)	1 (0.3)
Respiratory, thoracic, and mediastinal disorders	15 (5.0)	5 (1.7)
Aspiration	0 (0)	2 (0.7)
Pneumonitis	7 (2.3)	1 (0.3)
Skin and subcutaneous tissue disorders	12 (4.0)	7 (2.4)
Palmar-plantar erythrodysaesthesia syndrome	11 (3.7)	6 (2.0)
Vascular disorders	0 (0)	3 (1.0)

a. Events that occurred in ≥ 2 patients in at least one study arm.
b. MedDRA version 25.0; SOCs and PTs used unmodified from Module 4.
c. Number of randomized patients with positive PD-L1 status (CPS ≥ 1) who received at least one dose of the study medication. The analysis was carried out based on the treatment actually received.

AE: adverse event; CAPOX: capecitabine + oxaliplatin; CPS: combined positive score; FP: 5-fluorouracil + cisplatin; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class