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Durvalumab (small cell lung cancer) –

2nd Addendum to Commission A20-87[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
EORTC	European Organisation for Research and Treatment of Cancer
ES-SCLC	extensive-stage small cell lung 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)
MMRM	mixed-effects model with repeated measures
PGIC	Patient Global Impression of Change
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-LC13	Quality of Life Questionnaire-Lung Cancer 13
SAE	serious adverse event
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 9 February 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-87 (Durvalumab – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented results of the CASPIAN study on the comparison of durvalumab in combination with etoposide and either carboplatin or cisplatin (hereinafter referred to as "durvalumab + chemotherapy") versus etoposide with either carboplatin or cisplatin (hereinafter referred to as "chemotherapy") in patients with extensive-stage small cell lung cancer (ES-SCLC). The CASPIAN study recorded patient-reported outcomes using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 and Quality of Life Questionnaire-Lung Cancer 13 (EORTC QLQ-C30 and QLQ-LC13), the European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS), and the Patient Global Impression of Change (PGIC). For the benefit assessment, mixed-effects model with repeated measures (MMRM) analyses were used for the EORTC QLQ-C30 and QLQ-LC13 as well as the EQ-5D VAS, as not all recorded data were included in the event time analyses presented by the company in the dossier. The company's dossier contained no usable data for the PGIC.

With its comments [3,4], the company, on the one hand, subsequently submitted information on the heterogeneity of the results between the cohorts (heterogeneity tests) and subgroup analyses for the MMRM analyses (EORTC QLQ-C30, QLQ-LC13 and EQ-5D VAS). On the other hand, the company subsequently submitted event time analyses over the entire documentation period for these outcomes after the oral hearing [5]. In addition, the company's comments included event time analyses for the PGIC instrument and data on adverse events (AEs) with a follow-up observation period of 90 days, irrespective of the start of subsequent therapy.

The G-BA commissioned IQWiG with the assessment of the following additional data submitted by the company under consideration of the information provided in the dossier:

- analyses of heterogeneity tests for the factor cohort and subgroup analyses for the MMRM analyses or, if subsequently submitted by the company after the oral hearing, analysis of the event time analyses for the patient-reported outcomes recorded using the instruments EORTC QLQ-C30, QLQ-LC13 and EQ-5D VAS
- event time analyses (time to deterioration) of the PGIC
- AEs up to 90 days after discontinuation of the study medication (irrespective of the start of subsequent therapy)

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

2 Assessment

2.1 Morbidity (symptoms and health status) and health-related quality of life

2.1.1 Event time analyses on the instruments EORTC QLQ-C30, QLQ-LC13 and EQ-5D VAS

The event time analyses for the patient-reported outcomes recorded using EORTC QLQ-C30, QLQ-LC13 (time to first deterioration by 10 points) and EQ-5D VAS (time to deterioration by 7 or 10 points) presented in the company's dossier are not suitable for the benefit assessment, as only events up to cycle 6 were included in the analyses [1,2]. After the oral hearing, the company submitted event time analyses for the mentioned outcomes over the entire documentation period based on the meta-analysis (global cohort and cohort in China) [5]. These analyses were incomplete, however. Subgroup analyses as well as heterogeneity tests for the factor cohort and analyses for the individual cohorts were missing.

There was a relevant difference in event rates between the results of the subsequently submitted event time analyses over the entire documentation period and the analyses up to cycle 6 in the company's dossier. This supports the evaluation in the dossier assessment that the analyses presented with the dossier were not adequate. Furthermore, for the outcomes mentioned above, the event time analyses up to cycle 6 showed several effect modifications by the characteristics of age, sex, and brain metastases at baseline, which are relevant to the dossier assessment. Due to the lack of analyses, it cannot be assessed whether there were effect modifications also in the analyses over the entire documentation period. The subsequently submitted event time analyses over the entire documentation period were subject to a high degree of uncertainty due to the missing analyses, in particular on subgroups, and were therefore not used for the benefit assessment (results are presented as supplementary information in Appendix A). As had been the case in dossier assessment A20-87, the MMRM analyses were used for the benefit assessment instead (see Section 2.1.1).

Furthermore, the company submitted only analyses with the response criterion 10 points for the EQ-5D VAS. As explained in the General Methods of the Institute [6,7], for a response criterion to reflect with sufficient certainty a patient-noticeable change, however, it should correspond to at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range). The analysis submitted subsequently by the company (response criterion 10 points) is therefore not suitable for the benefit assessment for this reason alone.

2.1.2 MMRM analyses on the instruments EORTC QLQ-C30, QLQ-LC13 and EQ-5D VAS

For the MMRM analyses for the patient-reported outcomes recorded using EORTC QLQ-C30, QLQ-LC13 and EQ-5D VAS used in the dossier assessment [1], the company subsequently submitted heterogeneity tests and subgroup analyses in its comments [3,4]. These were used for the benefit assessment.

Heterogeneity of the results between the cohorts (heterogeneity tests for the factor cohort)

Homogeneity of data between the global cohort and the cohort in China was shown for the outcomes mentioned above.

Subgroup analyses

The following subgroup characteristics were considered in the present benefit assessment:

- age (< 65/≥ 65 years)
- sex (male/female)
- brain metastases at baseline (yes/no)

Based on the methods described in dossier assessment A20-87 [1], no relevant effect modifications were shown.

2.1.3 Event time analyses on the PGIC instrument

The data on time to deterioration (categories "much worse" and "very much worse") of the PGIC based on the meta-analysis, which were subsequently submitted by the company in its comments [3] are not suitable for the benefit assessment. It is unclear whether all available data were included in the event time analysis or whether only recordings up to cycle 6 were considered, as was the case in the company's dossier for the analyses of the instruments EORTC QLQ-C30, QLQ-LC13 and EQ-5D VAS. Kaplan-Meier curves, subgroup analyses, heterogeneity tests for the factor cohort, and analyses for the individual cohorts for this outcome were additionally missing. Therefore, the analyses of the PGIC were not used for the benefit assessment (results are presented as supplementary information in Appendix A).

2.2 Side effects

2.2.1 Analyses on AEs irrespective of the start of a subsequent therapy

In its comments, the company presented new analyses on AEs based on the meta-analysis. These included all events up to 90 days after the last dose of the study medication, but in contrast to the analyses in the company's dossier, irrespective of the start of a subsequent therapy. In principle, this is the preferable analysis for the benefit assessment, as it represents a longer observation period.

However, the analyses subsequently submitted by the company for the operationalization of AEs irrespective of the start of subsequent therapy were incomplete. Analyses are only available for the following superordinate AE outcomes:

- AEs
- serious AEs (SAEs)
- severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
- discontinuation due to AEs
- immune-related AEs, SAEs and severe AEs (CTCAE grade ≥ 3)

Kaplan-Meier curves as well as subgroup analyses, heterogeneity tests for the factor cohort, analyses for the individual cohorts, analyses based on System Organ Classes (SOCs) and Preferred Terms (PTs) are not available for these analyses, however. Due to this, and because no relevant differences in the observed effects were shown in the overall rates compared with the analyses used for the dossier assessment, the analyses already available with the dossier were still used in the present situation. The subsequently submitted data on the AE outcomes are presented in Appendix A.

2.2.2 Immune-related severe AEs (CTCAE grade ≥ 3) in women

The dossier showed an effect modification by the characteristic of sex for immune-related severe AEs (CTCAE grade ≥ 3). However, the company did not provide a p-value for this outcome (e.g. an unstratified log-rank test would be possible) for the immune-related severe AEs in the subgroup of women in the dossier. The company did not provide a p-value for the immune-related severe AEs in women, neither in the comments nor (despite explicit request) subsequent to the oral hearing. In the final assessment, the effect modification is still taken into account and a possible hint of greater harm is not excluded.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of durvalumab + chemotherapy from dossier assessment A20-87. The subsequently submitted subgroup analyses based on the MMRM analyses for the outcomes of EORTC QLQ-C30, QLQ-LC13 and EQ-5D VAS showed no relevant effect modifications and therefore had no impact on the benefit assessment.

As described in Chapter 2, the data submitted by the company are incomplete. Furthermore, the limitations of the CASPIAN study described in the dossier assessment have not been sufficiently dispelled after the commenting procedure, which is why the certainty of conclusions remains reduced. Therefore, at most hints, e.g. of an added benefit, can still be derived on the basis of the CASPIAN study.

The following Table 1 shows the result of the benefit assessment of durvalumab in combination with chemotherapy under consideration of dossier assessment A20-87 and the present addendum.

Table 1: Durvalumab + chemotherapy[a] – probability and extent of added benefit

Therapeutic indication	**ACT[b]**	**Probability and extent of added benefit**
Extensive-stage small cell lung cancer (ES-SCLC)[c]	Cisplatin in combination with etoposide or carboplatin in combination with etoposide	▪ Men: ▫ hint of considerable added benefit ▪ Women: ▫ Hint of added benefit; extent "non-quantifiable", at most "considerable"

a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide.
b. Presentation of the respective ACT specified by the G-BA.
c. The CASPIAN study only included patients with an ECOG PS of 0 or 1 and with asymptomatic or previously treated brain metastases. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or with symptomatic brain metastases.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

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Appendix A – Event time analyses PGIC, EQ-5D VAS, EORTC QLQ-C30 + QLQ-LC13, AEs irrespective of the start of subsequent therapy

A.1 – Event time analyses PGIC and EQ-5D VAS

Table 2: Results (morbidity, time to event) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a]

Outcome category Outcome Study	Durvalumab + chemotherapy[a]		Chemotherapy[a]		Durvalumab + chemotherapy[a] vs. chemotherapy[a]
	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[b]
Morbidity					
Health status (EQ-5D VAS, time to deterioration[c])					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	6.9 [4.6; 12.9] 147 (45.8)	321	9.2 [6.4; 12.3] 120 (37.4)	1.10 [0.86; 1.40]; 0.470
Health status (PGIC, time to deterioration[d])					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	NA 26 (8.8)	321	NA 28 (9.9)	0.54 [0.31; 0.93]; 0.023

a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide.
b. HR and 95% CI: stratified Cox proportional hazards model; p-value: stratified log-rank test; each stratified by the planned platinum-based chemotherapy at cycle 1 (cisplatin/carboplatin); for the meta-analysis additionally by cohort (Global/China).
c. Time to first deterioration, defined as decrease of the score by at least 10 points compared with baseline.
d. Patients from one study centre in Ukraine were not considered due to incorrect data recording. These were 16 (information in the CSR) or 17 (information in the SAP) randomized patients.
e. Calculated from meta-analysis.
f. A total of 2 patients were included in both the cohort in China and the global cohort. These patients were assigned to the cohort in China for the meta-analysis.
g. Time to first deterioration; deterioration defined as patients in categories “very much worse” and “much worse”.

CI: confidence interval; CSR: Clinical Study Report; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; NC: not calculable; PGIC: Patient Global Impression of Change; RCT: randomized controlled trial; SAP: statistical analysis plan; VAS: visual analogue scale; vs.: versus

A.2 – Kaplan-Meier curves EQ-5D VAS

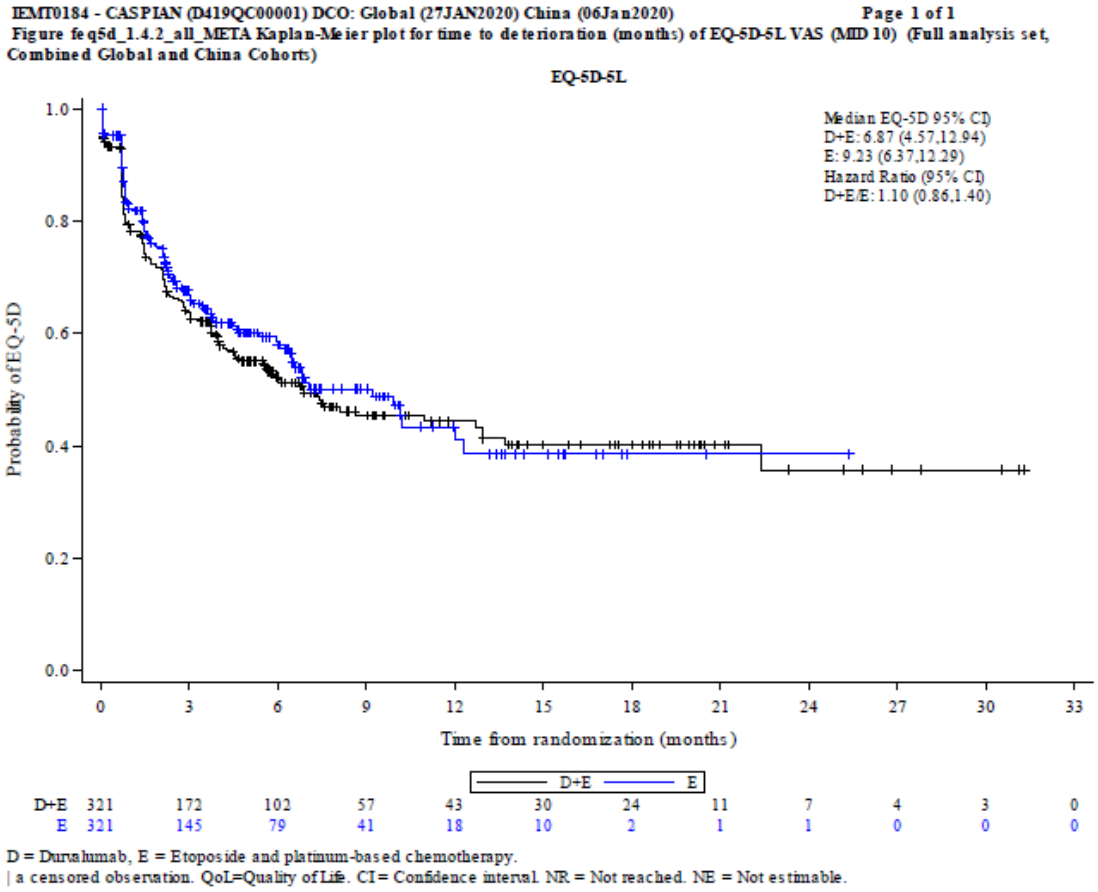

Figure 1: Kaplan-Meier curves on health status, EQ-5D VAS

A.3 – Event time analyses EORTC QLQ-C30 and QLQ-LC13

Table 3: Results (morbidity, health-related quality of life) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category Outcome Study	Durvalumab + chemotherapy[a]		Chemotherapy[a]		Durvalumab + chemotherapy[a] vs. chemotherapy[a]
	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[b]
Morbidity					
EORTC QLQ-C30 (symptom scales, time to deterioration[c])					
Fatigue					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	2.8 [2.1; 3.7] 186 (57.9)	321	2.2 [1.6; 3.0] 178 (55.5)	0.94 [0.76; 1.15]; 0.551
Nausea and vomiting					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	6.2 [3.0; 8.7] 159 (49.5)	321	4.6 [2.8; 7.2] 150 (46.7)	0.92 [0.74; 1.16]; 0.503
Pain					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	5.6 [4.6; 7.2] 167 (52.0)	321	7.4 [5.8; 9.5] 127 (39.6)	1.17 [0.93; 1.48]; 0.181
Dyspnoea					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	NA [8.5; NC] 119 (37.1)	321	10.2 [8.2; NC] 105 (32.7)	1.01 [0.77; 1.31]; 0.960
Insomnia					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	11.7 [7.2; NC] 128 (39.9)	321	8.0 [6.5; NC] 120 (37.4)	0.90 [0.70; 1.16]; 0.433
Appetite loss					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	6.8 [4.7; 12.0] 154 (48.0)	321	6.4 [4.4; 9.0] 140 (43.6)	0.93 [0.74; 1.17]; 0.552

Table 3: Results (morbidity, health-related quality of life) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category Outcome Study	Durvalumab + chemotherapy[a]		Chemotherapy[a]		Durvalumab + chemotherapy[a] vs. chemotherapy[a]
	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[b]
Constipation					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	13.0 [7.6; 19.1] 132 (41.1)	321	NA [9.3; NC] 106 (33.0)	1.11 [0.86; 1.44]; 0.415
Diarrhoea					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	31.1 [31.1; NC] 80 (24.9)	321	NA [11.2; NC] 86 (26.8)	0.75 [0.55; 1.03]; 0.073
EORTC QLQ-LC13 (symptom scales, time to deterioration[c])					
Alopecia					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	0.8 [0.8; 0.8] 265 (82.6)	321	0.8 [0.8; 0.8] 256 (79.8)	1.02 [0.86; 1.22]; 0.809
Haemoptysis					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	NA 38 (11.8)	321	NA 37 (11.5)	0.81 [0.51; 1.29]; 0.377
Dysphagia					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	NA [17.6; NC] 90 (28.0)	321	25.9 [NC] 74 (23.1)	0.98 [0.72; 1.34]; 0.911
Dyspnoea					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	5.6 [3.7; 7.4] 164 (51.1)	321	3.8 [2.6; 6.4] 155 (48.3)	0.91 [0.73; 1.14]; 0.412

Table 3: Results (morbidity, health-related quality of life) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category Outcome Study	Durvalumab + chemotherapy[a]		Chemotherapy[a]		Durvalumab + chemotherapy[a] vs. chemotherapy[a]
	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[b]
Cough					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	NA [13.8; NC] 105 (32.7)	321	NA [10.2; NC] 93 (29.0)	0.96 [0.73; 1.28]; 0.788
Sore mouth					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	22.8 [11.5; NC] 104 (32.4)	321	17.1 [17.1; 25.9] 85 (26.5)	1.02 [0.76; 1.36]; 0.902
Peripheral neuropathy					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	7.9 [6.0; 12.9] 135 (42.1)	321	6.3 [4.8; 10.2] 122 (38.0)	0.87 [0.68; 1.12]; 0.275
Pain (arm/shoulder)					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	13.9 [9.5; NC] 120 (37.4)	321	8.7 [6.2; NC] 116 (36.1)	0.83 [0.64; 1.07]; 0.150
Pain (chest)					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	NA [12.9; NC] 109 (34.0)	321	NA [11.1; NC] 90 (28.0)	1.05 [0.8; 1.4]; 0.717
Pain (other)					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	6.5 [4.9; 12.0] 153 (47.7)	321	10.0 [5.6; 12.7] 122 (38.0)	1.06 [0.83; 1.34]; 0.661

Table 3: Results (morbidity, health-related quality of life) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category Outcome Study	Durvalumab + chemotherapy[a]		Chemotherapy[a]		Durvalumab + chemotherapy[a] vs. chemotherapy[a]
	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[b]
Health-related quality of life					
EORTC QLQ-C30 (functional scales)[g]					
Global health status					
CASPIAN – Global[d]	261	ND	260	ND	
CASPIAN – China	61	ND	62	ND	
Total[d, e, f]	321	12.7 [7.9; NC] 127 (39.6)	321	8.4 [6.5; 14.1] 118 (36.8)	0.87 [0.67; 1.12]; 0.267
Physical functioning					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	13.1 [7.9; NC] 126 (39.3)	321	6.3 [4.4; 9.5] 135 (42.1)	0.74 [0.58; 0.95]; 0.019
Role functioning					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	5.6 [3.6; 7.7] 164 (51.1)	321	4.5 [3.1; 6.7] 149 [46.4]	0.97 [0.77; 1.21]; 0.801
Emotional functioning					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	NA [12.9; NC] 102 (31.8)	321	17.8 [7.3; NC] 99 (30.8)	0.79 [0.60; 1.05]; 0.110
Cognitive functioning					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	5.7 [4.6; 8.8] 157 (48.9)	321	5.6 [4.6; 6.5] 142 (44.2)	0.88 [0.70; 1.11]; 0.298
Social functioning					
CASPIAN – Global[d]	261	ND	260	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[d, e, f]	321	5.6 [2.8; 6.9] 170 (53.0)	321	4.4 [3.0; 7.2] 153 (47.7)	0.93 [0.75; 1.17]; 0.545

Table 3: Results (morbidity, health-related quality of life) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category Outcome Study	Durvalumab + chemotherapy[a]		Chemotherapy[a]		Durvalumab + chemotherapy[a] vs. chemotherapy[a]
	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[b]
a. Etoposide + carboplatin or etoposide + cisplatin. b. HR and 95% CI: stratified Cox proportional hazards model; p-value: stratified log-rank test; each stratified by the planned platinum-based chemotherapy at cycle 1 (cisplatin/carboplatin); for the meta-analysis additionally by cohort (Global/China). c. Time to first deterioration, defined as increase of the score by at least 10 points compared with baseline. d. Patients from one study centre in Ukraine were not considered due to incorrect data recording. These were 16 (information in the CSR) or 17 (information in the SAP) randomized patients. e. Calculated from meta-analysis. f. A total of 2 patients were included in both the cohort in China and the global cohort. These patients were assigned to the cohort in China for the meta-analysis. g. Time to first deterioration, defined as decrease of the score by at least 10 points compared with baseline. CI: confidence interval; CSR: Clinical Study Report; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; NC: not calculable; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAP: statistical analysis plan; vs.: versus					

A.4 – Kaplan-Meier curves on EORTC QLQ-C30 and QLQ-LC13 symptom scales

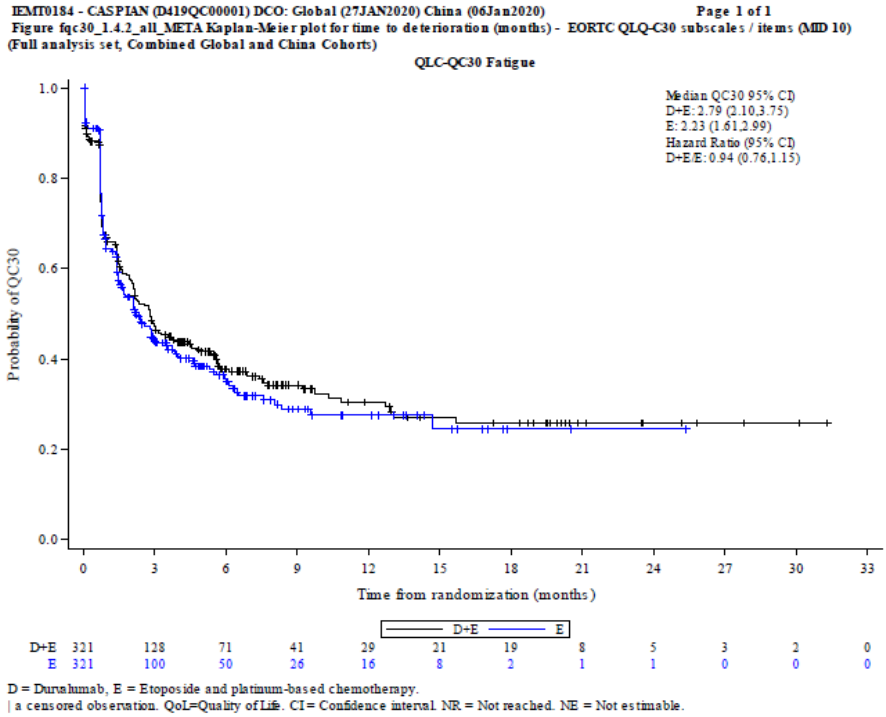

Figure 2: Kaplan-Meier curves on symptoms, symptom scale “fatigue” (EORTC QLQ-C30)

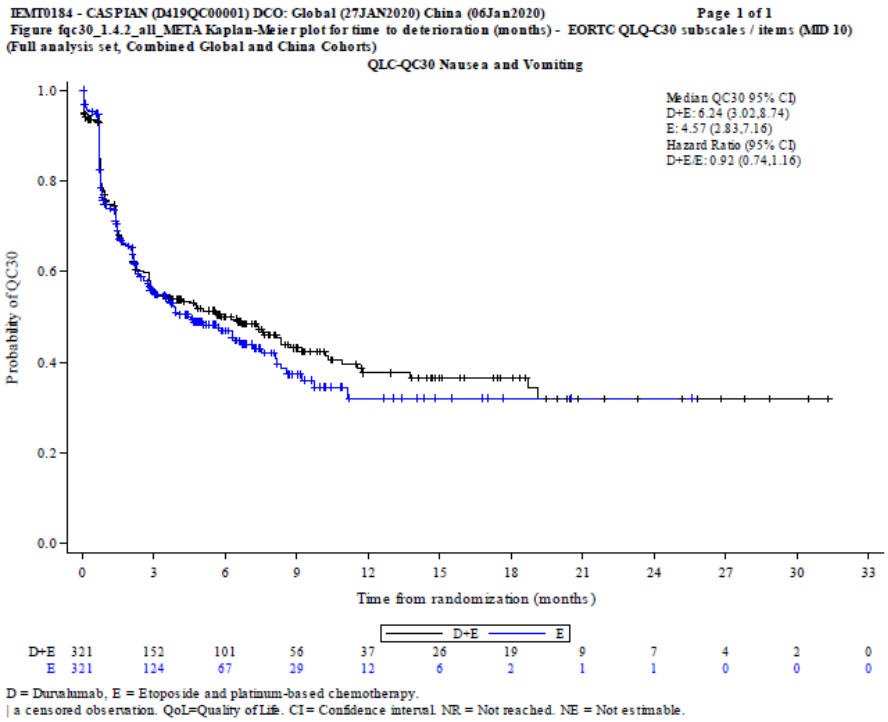

Figure 3: Kaplan-Meier curves on symptoms, symptom scale “nausea and vomiting” (EORTC QLQ-C30)

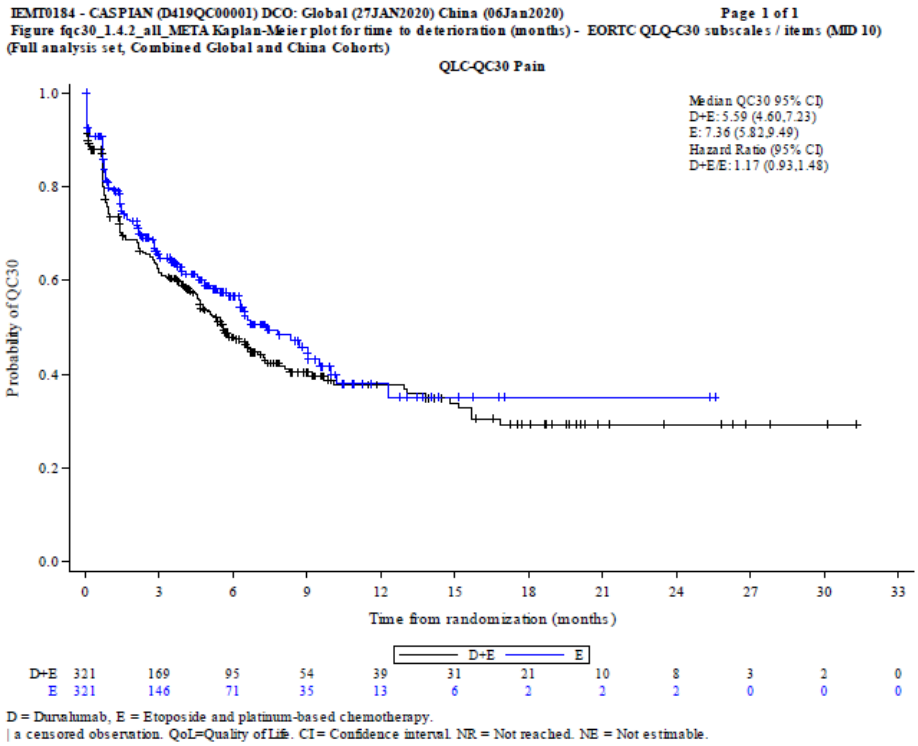

Figure 4: Kaplan-Meier curves on symptoms, symptom scale “pain” (EORTC QLQ-C30)

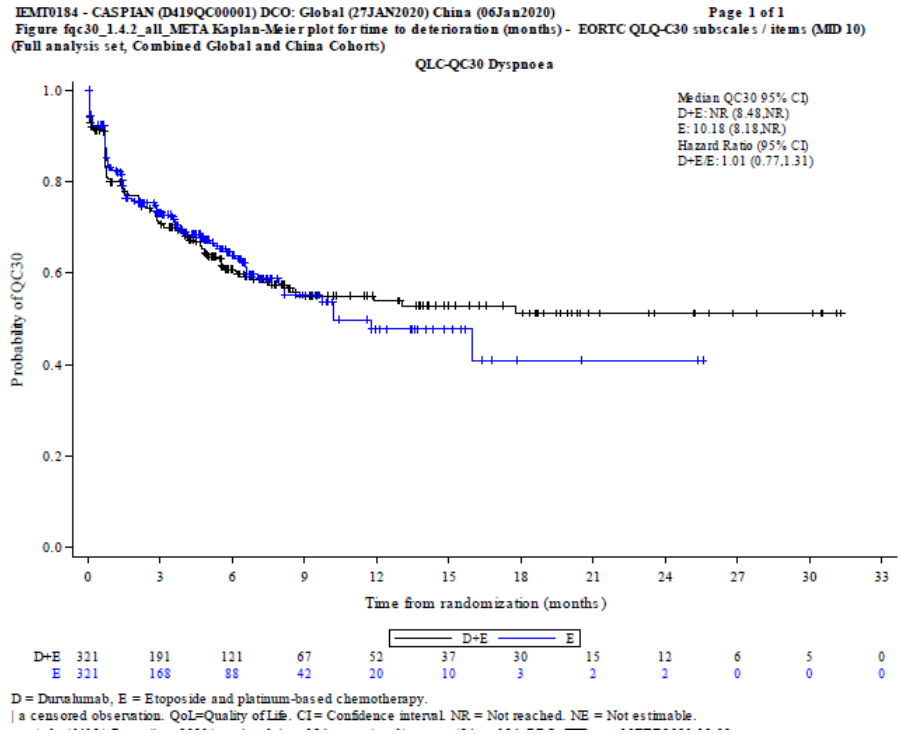

Figure 5: Kaplan-Meier curves on symptoms, symptom scale “dyspnoea” (EORTC QLQ-C30)

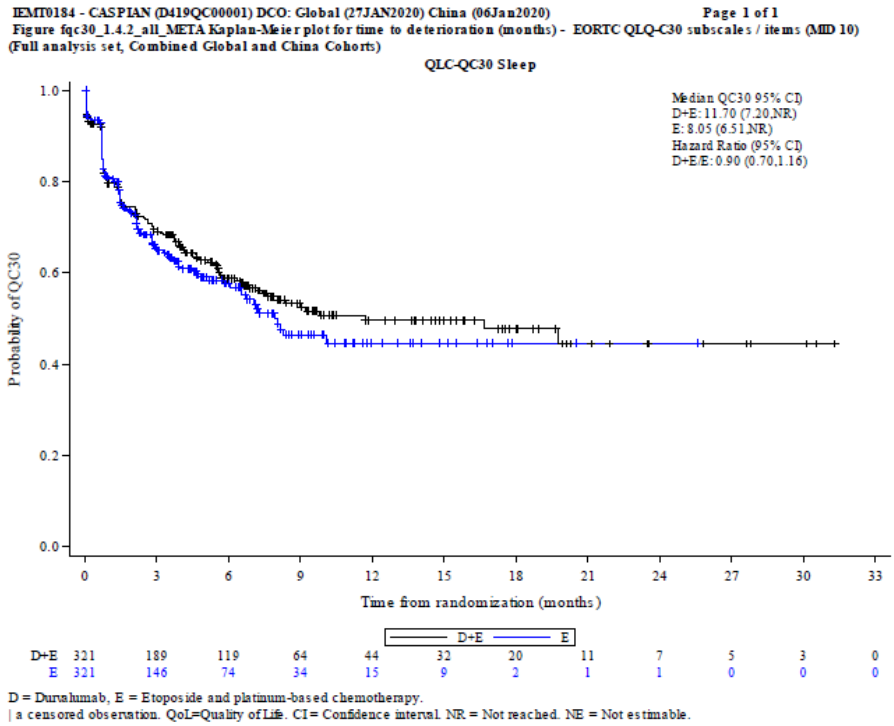

Figure 6: Kaplan-Meier curves on symptoms, symptom scale “insomnia” (EORTC QLQ-C30)

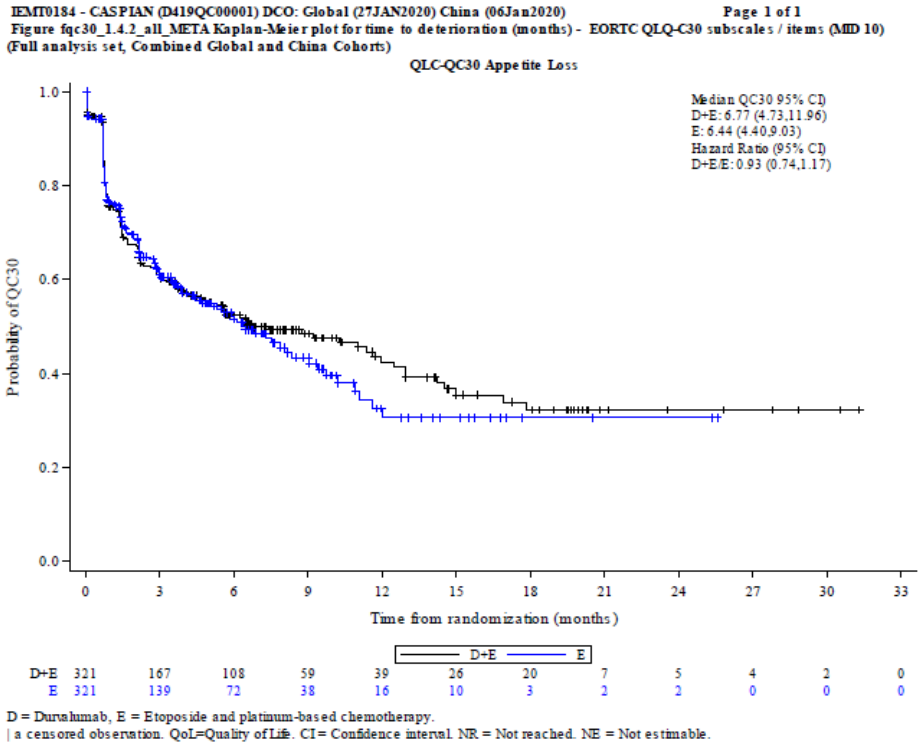

Figure 7: Kaplan-Meier curves on symptoms, symptom scale “appetite loss” (EORTC QLQ-C30)

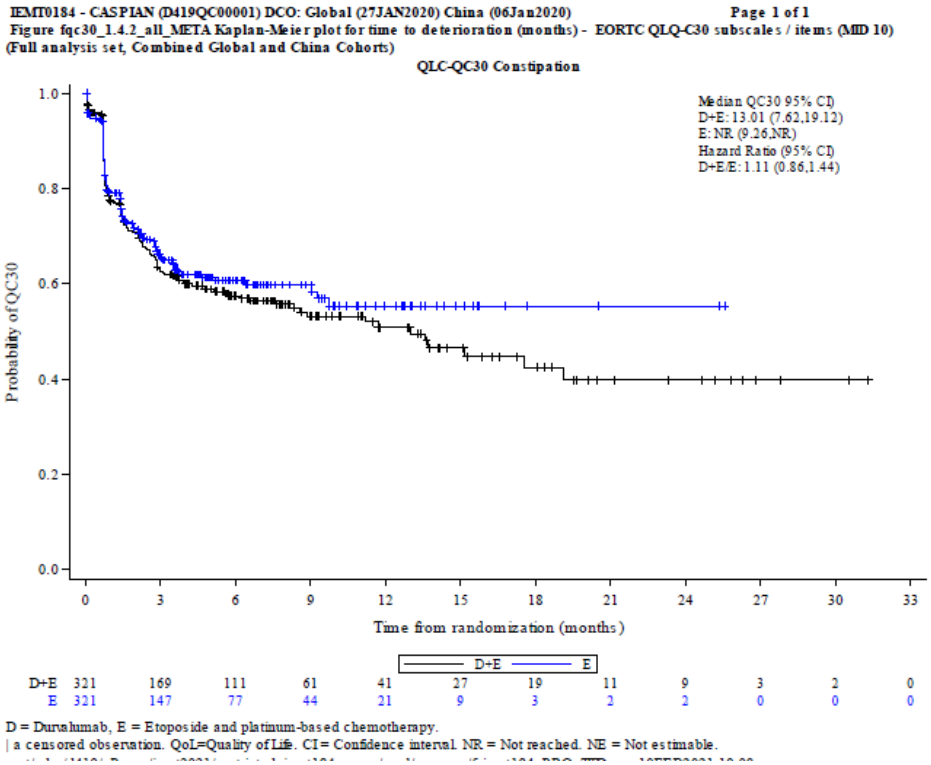

Figure 8: Kaplan-Meier curves on symptoms, symptom scale “constipation” (EORTC QLQ-C30)

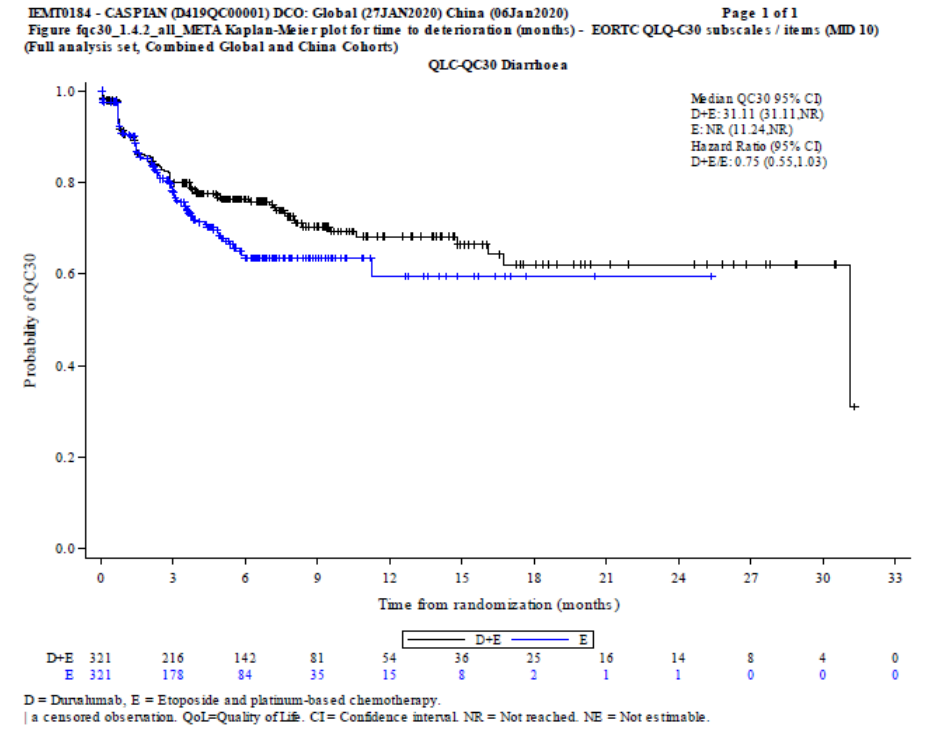

Figure 9: Kaplan-Meier curves on symptoms, symptom scale “diarrhoea” (EORTC QLQ-C30)

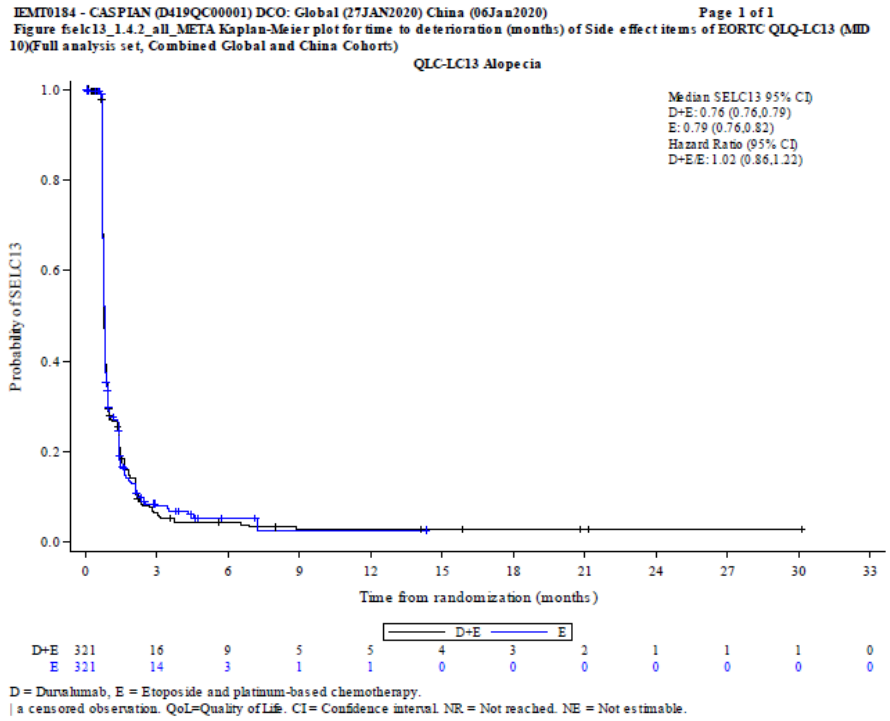

Figure 10: Kaplan-Meier curves on symptoms, symptom scale “alopecia” (EORTC QLQ-LC13)

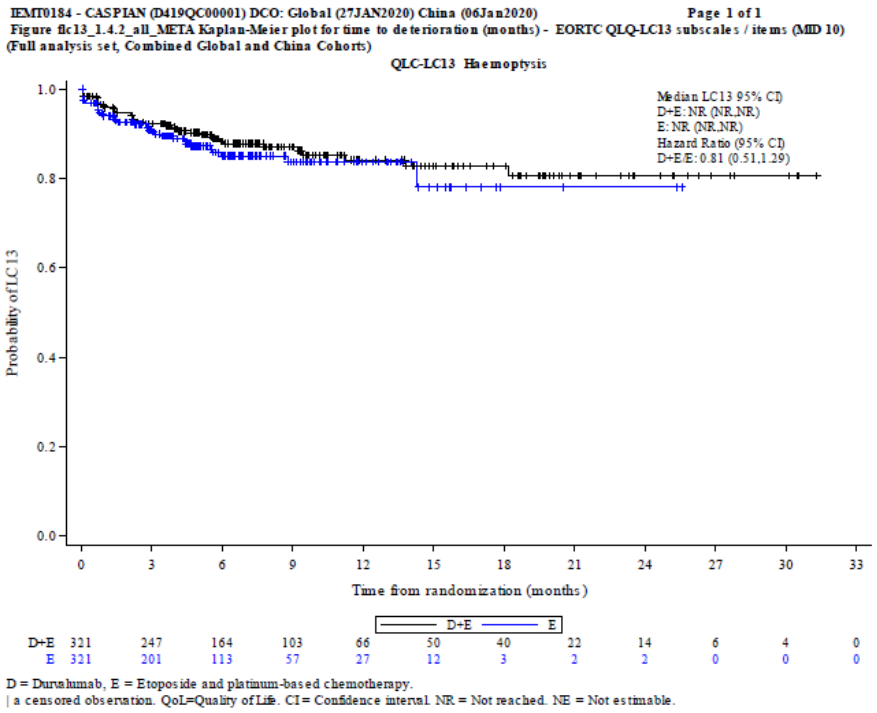

Figure 11: Kaplan-Meier curves on symptoms, symptom scale “haemoptysis” (EORTC QLQ-LC13)

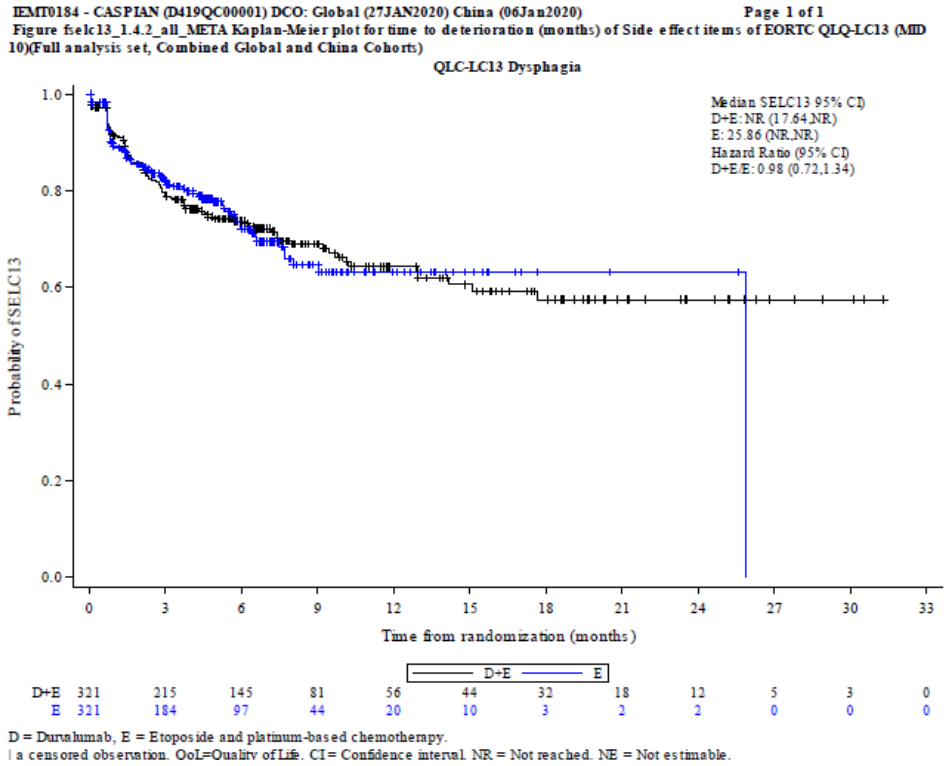

Figure 12: Kaplan-Meier curves on symptoms, symptom scale “dysphagia” (EORTC QLQ-LC13)

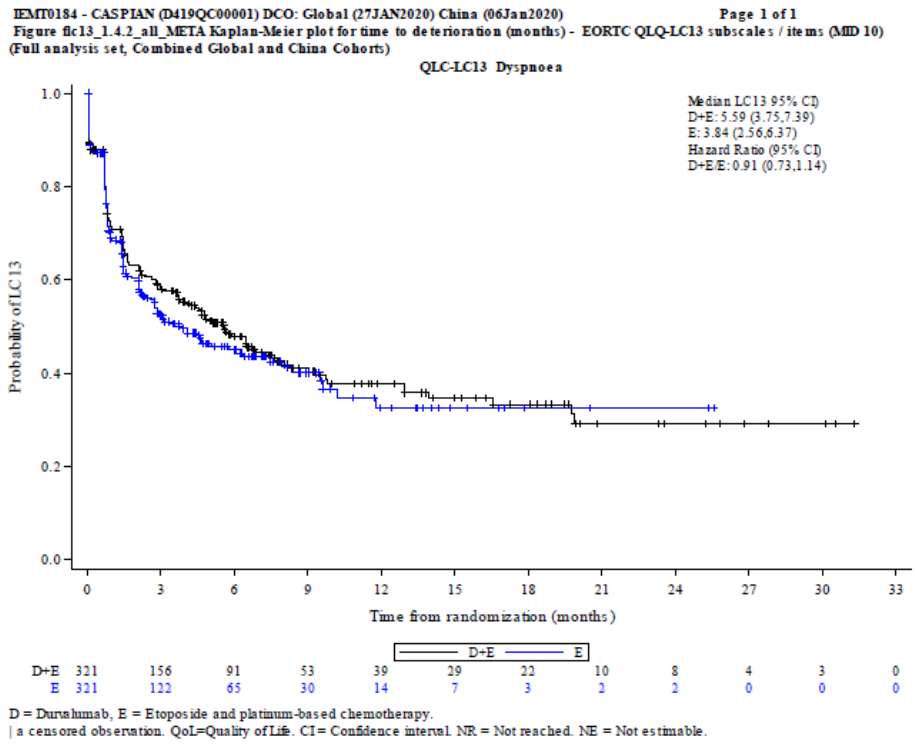

Figure 13: Kaplan-Meier curves on symptoms, symptom scale “dyspnoea” (EORTC QLQ-LC13)

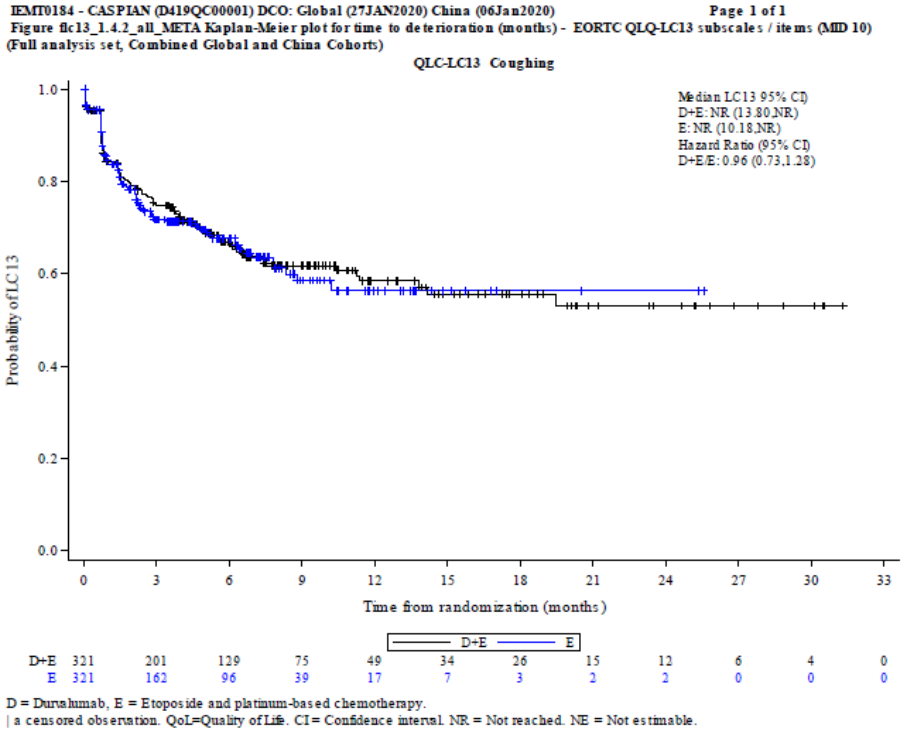

Figure 14: Kaplan-Meier curves on symptoms, symptom scale “cough” (EORTC QLQ-LC13)

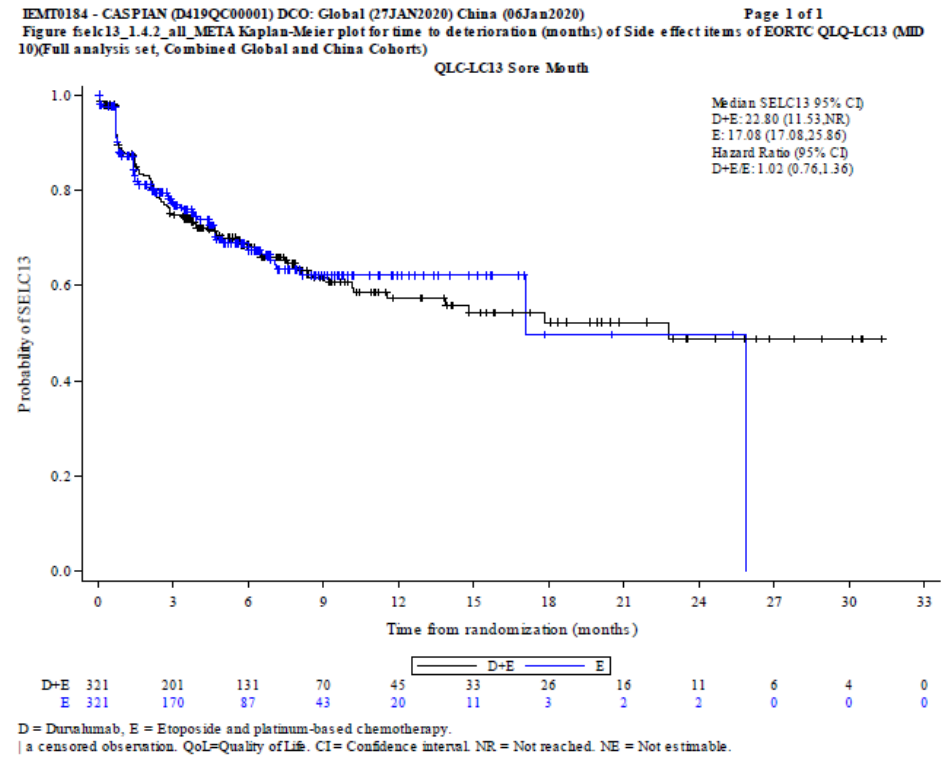

Figure 15: Kaplan-Meier curves on symptoms, symptom scale “sore mouth” (EORTC QLQ-LC13)

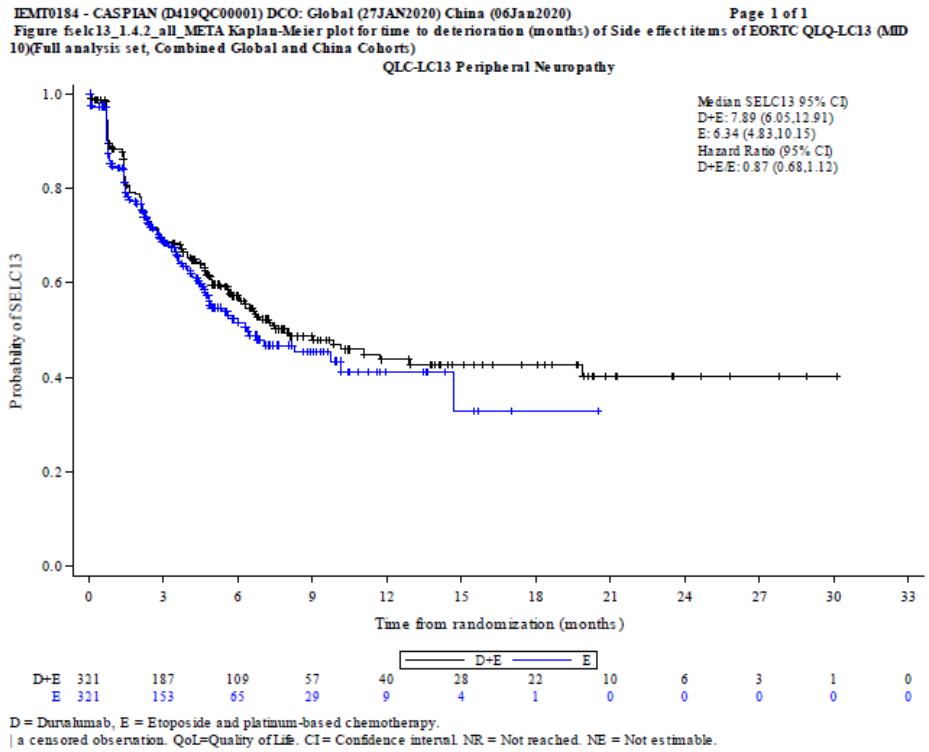

Figure 16: Kaplan-Meier curves on symptoms, symptom scale "peripheral neuropathy" (EORTC QLQ-LC13)

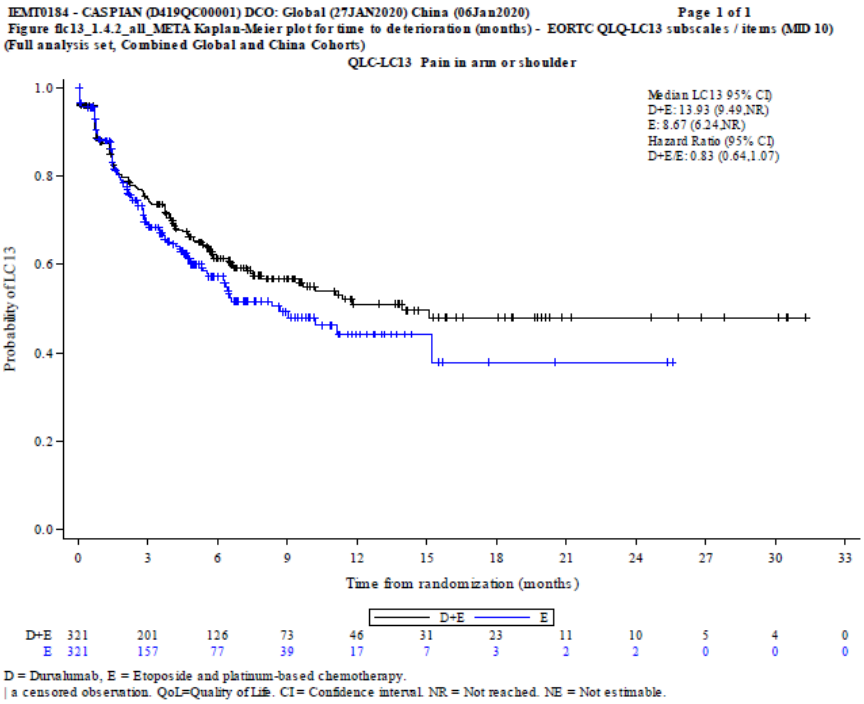

Figure 17: Kaplan-Meier curves on symptoms, symptom scale "pain (arm/shoulder)" (EORTC QLQ-LC13)

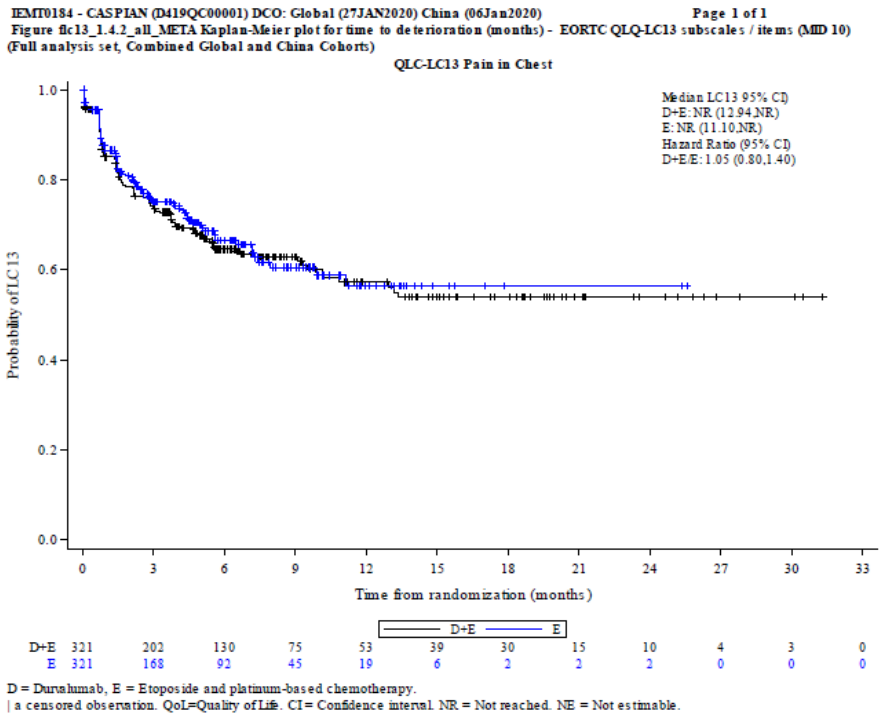

Figure 18: Kaplan-Meier curves on symptoms, symptom scale “pain (chest)” (EORTC QLQ-LC13)

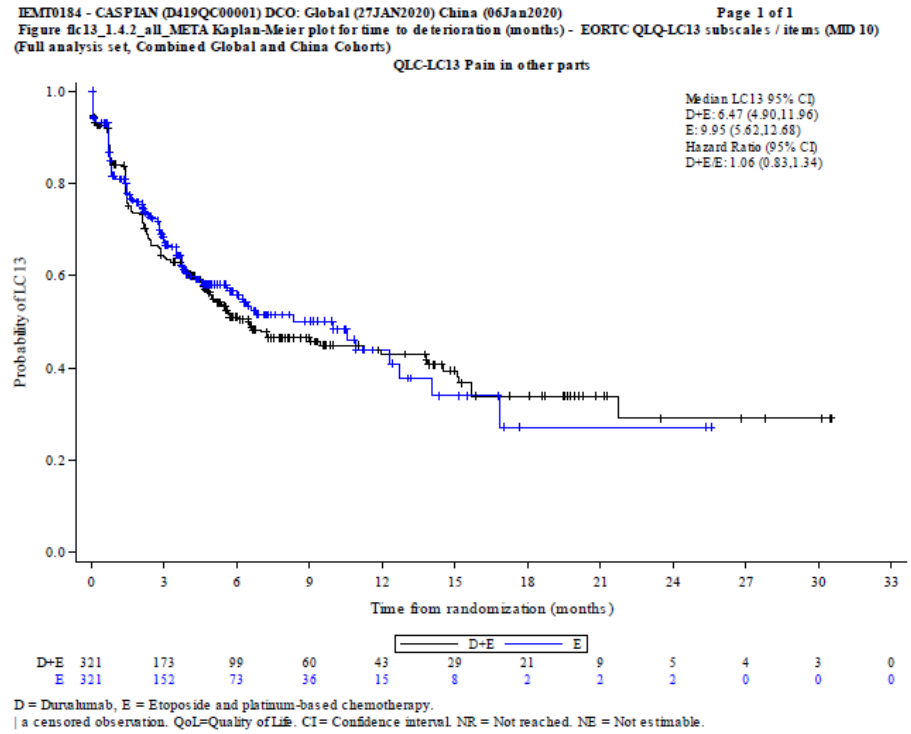

Figure 19: Kaplan-Meier curves on symptoms, symptom scale “pain (other)” (EORTC QLQ-LC13)

A.5 – Kaplan-Meier curves on global health status and EORTC QLQ-C30 functional scales

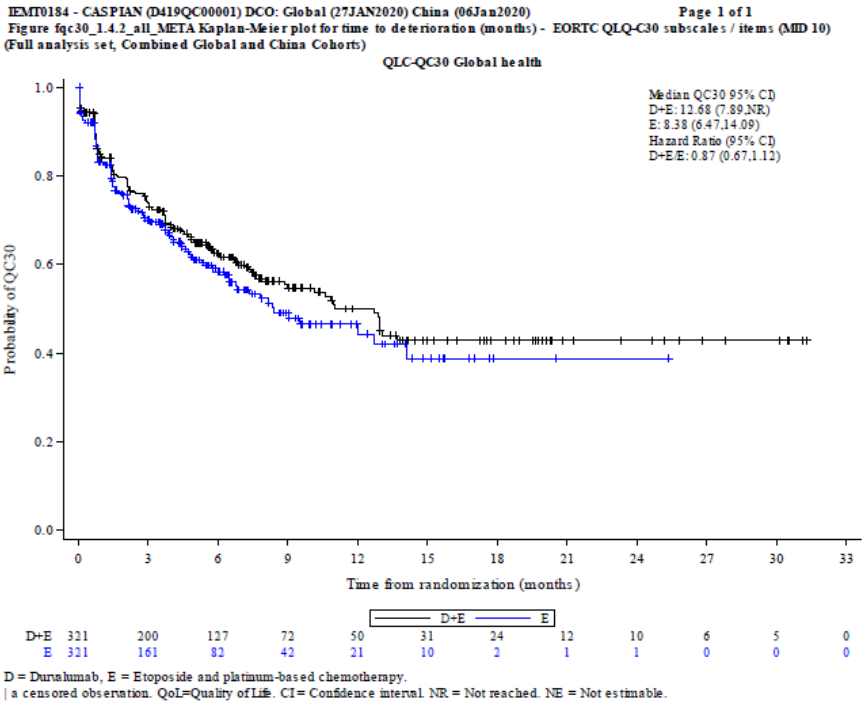

Figure 20: Kaplan-Meier curves on health-related quality of life, scale “global health status” (EORTC QLQ-C30)

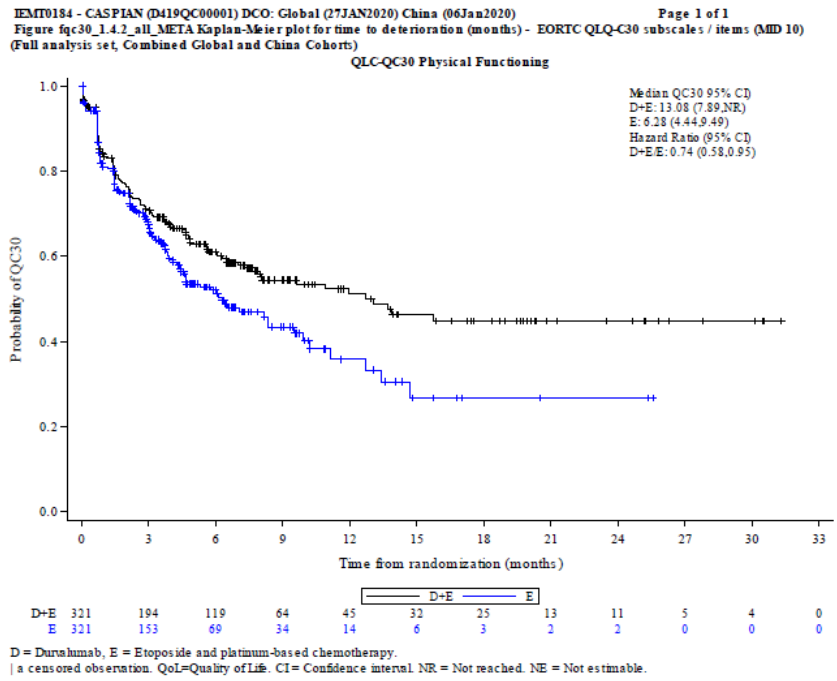

Figure 21: Kaplan-Meier curves on health-related quality of life, scale “physical functioning” (EORTC QLQ-C30)

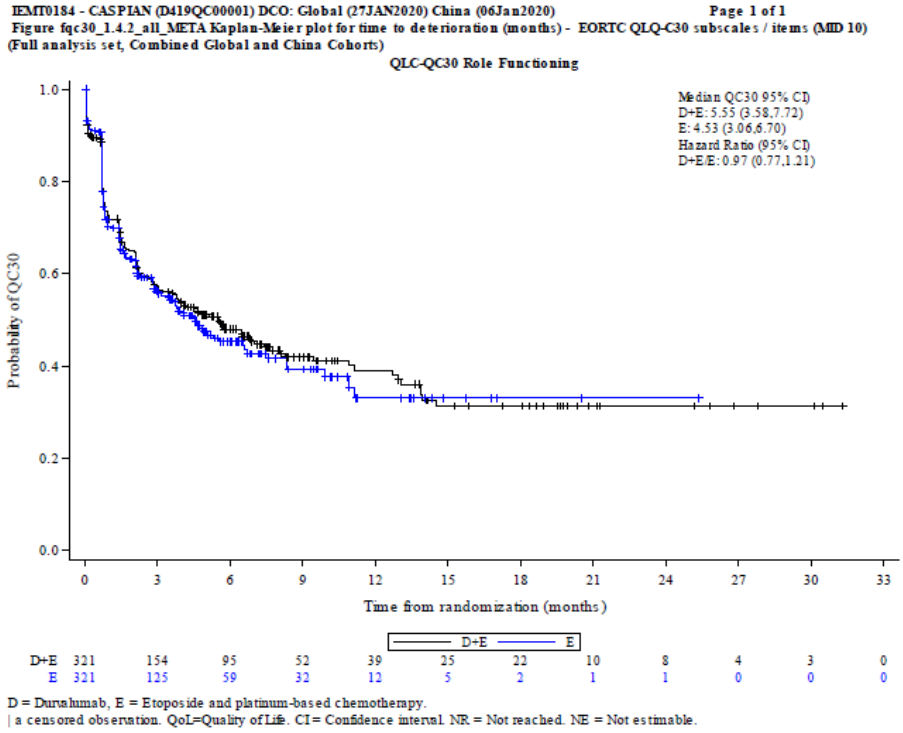

Figure 22: Kaplan-Meier curves on health-related quality of life, scale “role functioning” (EORTC QLQ-C30)

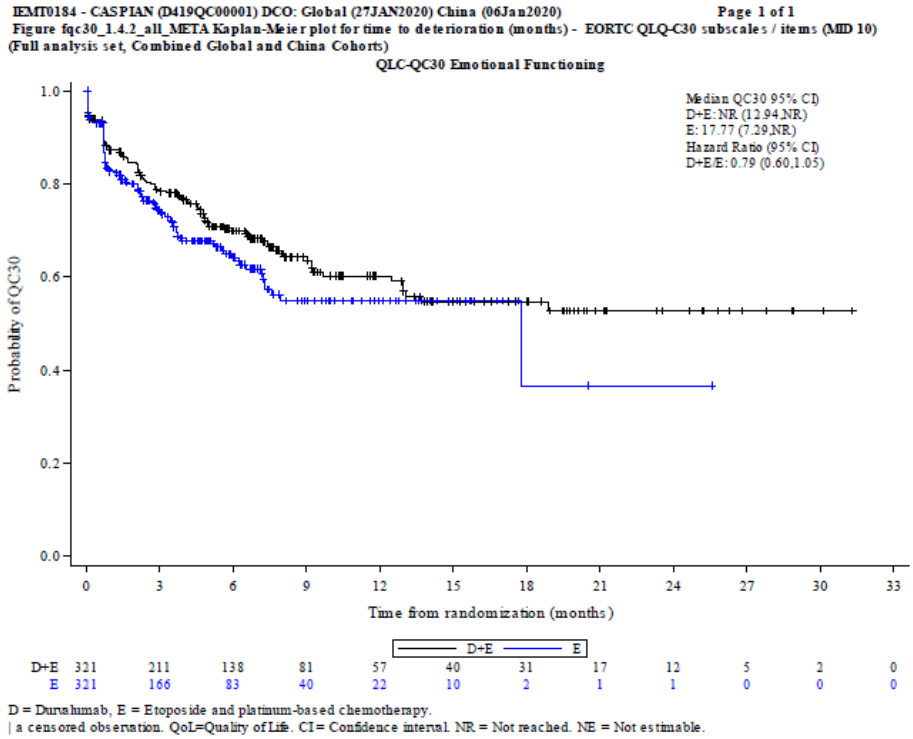

Figure 23: Kaplan-Meier curves on health-related quality of life, scale “emotional functioning” (EORTC QLQ-C30)

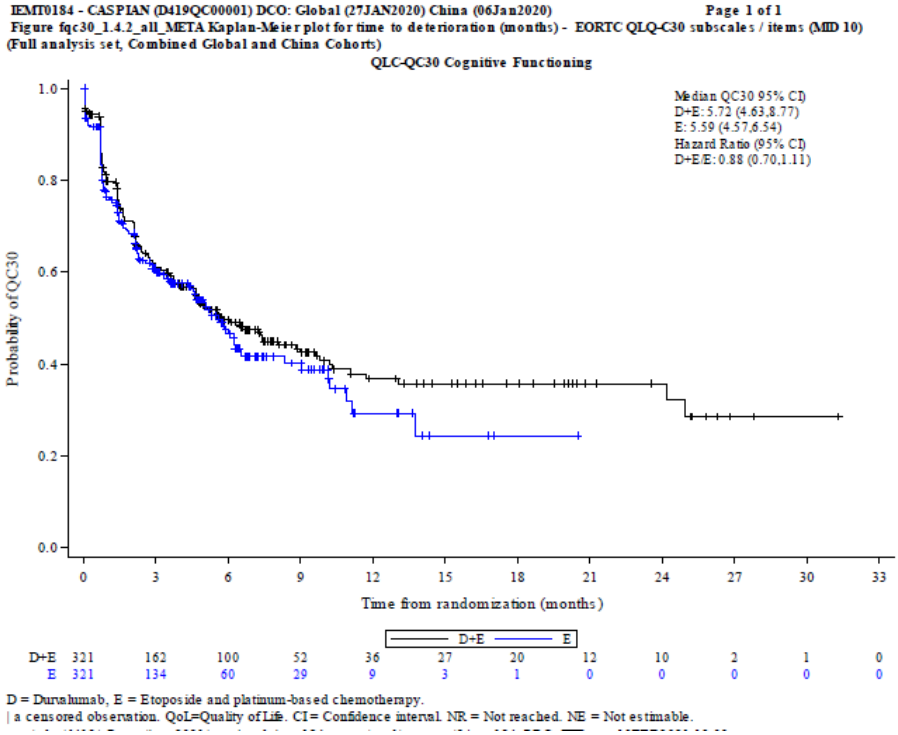

Figure 24: Kaplan-Meier curves on health-related quality of life, scale “cognitive functioning” (EORTC QLQ-C30)

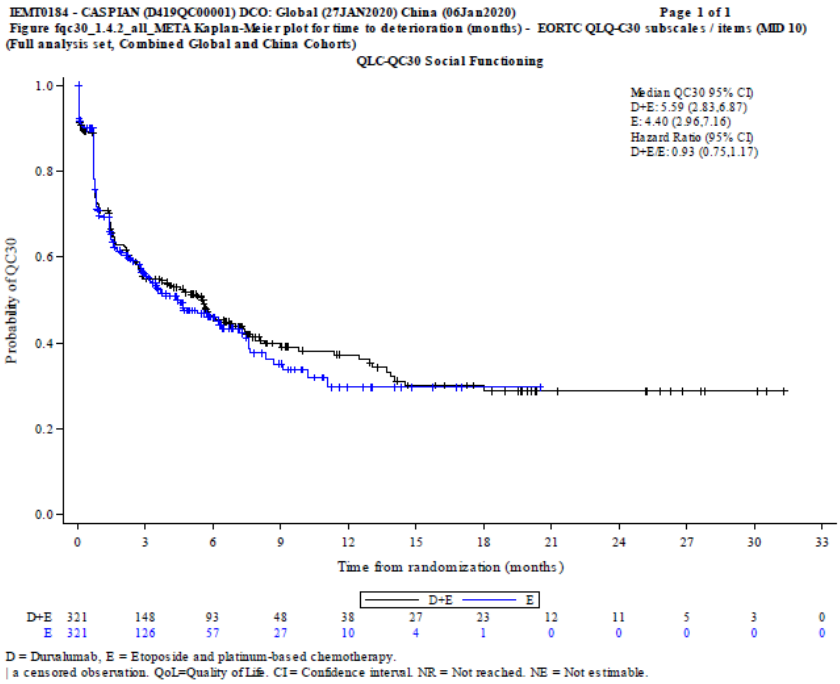

Figure 25: Kaplan-Meier curves on health-related quality of life, scale “social functioning” (EORTC QLQ-C30)

A.6 – AEs irrespective of the start of a subsequent therapy

Table 4: Results (side effects) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category Outcome Study	Durvalumab + chemotherapy[a]		Chemotherapy[a]		Durvalumab + chemotherapy[a] vs. chemotherapy[a]
	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[b]
Side effects					
AEs (supplementary information; until 90 days after the last dose of the study medication)					
CASPIAN – Global	265	ND	266	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[c, d]	325	0.3 [0.2; 0.3] 320 (98.5)	327	0.3 [0.2; 0.3] 318 (97.2)	–
SAEs (until 90 days after the last dose of the study medication)					
CASPIAN – Global	265	ND	266	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[c, d]	325	NA [22.9; NC] 110 (33.8)	327	NA 119 (36.4)	0.78 [0.60; 1.02]; 0.072
Severe AEs[e] (until 90 days after the last dose of the study medication)					
CASPIAN – Global	265	ND	266	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[c, d]	325	0.5 [0.3; 0.7] 219 (67.4)	327	0.5 [0.3; 0.7] 222 (67.9)	0.98 [0.82; 1.18]; 0.855
Discontinuation due to AEs[f] (until 90 days after the last dose of the study medication)					
CASPIAN – Global	265	ND	266	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[c, d]	325	NA 37 (11.4)	327	NA 32 (9.8)	0.99 [0.61; 1.62]; 0.974
Immune-related AEs (supplementary information; until 90 days after the last dose of the study medication)					
CASPIAN – Global	265	ND	266	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[c, d]	325	21.6 [11.2; NC] 123 (37.8)	327	NA 71 (21.7)	–
Immune-related SAEs (until 90 days after the last dose of the study medication)					
CASPIAN – Global	265	ND	266	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[c, d]					Heterogeneity unclear[g]

Table 4: Results (side effects) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category Outcome Study	Durvalumab + chemotherapy[a]		Chemotherapy[a]		Durvalumab + chemotherapy[a] vs. chemotherapy[a]
	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[b]
Immune-related severe AEs[e] (until 90 days after the last dose of the study medication)					
CASPIAN – Global	265	ND	266	ND	–
CASPIAN – China	61	ND	62	ND	–
Total[c, d]	325	14 (4.3)	327	6 (1.8)	1.91 [0.73; 5.50]; 0.188

a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide.
b. HR [95% CI] from unstratified Cox regression model, p-value based on likelihood ratio test.
c. Calculated from meta-analysis.
d. A total of 2 patients were included in both the cohort in China and the global cohort. These patients were assigned to the cohort in China for the meta-analysis.
e. Operationalized as CTCAE grade ≥ 3.
f. Discontinuation of at least one drug component.
g. For the analysis used in the dossier assessment, there is a statistically significant heterogeneity for the factor cohort for the outcome "immune-related SAEs". As the company did not provide any heterogeneity tests for the factor cohort for the subsequently submitted analyses on AEs up to 90 days after the last dose of the study medication, irrespective of the start of a subsequent therapy, statistically significant heterogeneity cannot be excluded. The data are therefore not presented.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus