Elacestrant (breast cancer 1)

Addendum to Project A23-104 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CDK	cyclin-dependent kinase
CTCAE	Common Terminology Criteria for Adverse Events
EORTC	European Organisation for Research and Treatment of Cancer
ER	oestrogen receptor
ESR1	oestrogen receptor 1
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
PRO	patient-reported outcome
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
RCT	**randomized** controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class

1 Background

On 12 March 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-104 (Elacestrant – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprised the assessment of the data [2,3] subsequently submitted by the pharmaceutical company (hereinafter referred to as “the company”) in the commenting procedure [4] on the total population of patients with oestrogen receptor 1 (ESR1) mutation (ESR1-mut population) of the EMERALD study, taking into account the information in the dossier [5].

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 of the EMERALD study

The aim of benefit assessment A23-104 [1] was to assess the added benefit of elacestrant compared with the appropriate comparator therapy (ACT) in postmenopausal women and men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease had progressed after at least one line of endocrine therapy, including a cyclin-dependent kinase (CDK) 4/6 inhibitor. The specification of the ACT by the G-BA resulted in 2 research questions, separated by sex; in Research question 1: postmenopausal women and Research question 2: men.

In the dossier, the company presented the randomized controlled trial (RCT) EMERALD for the comparison of elacestrant with treatment of physician's choice choosing from fulvestrant, anastrozole, letrozole and exemestane. The study is relevant for the benefit assessment and was used for Research question 1. No assessment-relevant data were available for Research question 2, as the label-enabling ESR1-mut population of the EMERALD study did not include any men (see [1]).

In the dossier, the company only presented a post hoc subpopulation of the ESR1-mut population for Research question 1, excluding approx. 13% of the patients. This approach is not appropriate and the data were not used for the benefit assessment. In the context of the commenting procedure, the company subsequently submitted data on the complete ESR1-mut population for Research question 1, which are used for the benefit assessment below.

2.1 Study characteristics

A detailed description of the EMERALD study can be found in dossier assessment A23-104 [1].

Data cut-offs

As described in the dossier assessment, the following 3 data cut-offs are available:

- first data cut-off of 06 September 2021
- second data cut-off of 08 July 2022
- third data cut-off of 02 September 2022

Analogous to the company's approach, the second data cut-off is considered for the results on patient-reported outcomes (PROs) and side effects, and the third data cut-off is used for the results on the outcome "overall survival” (for details, see [1]).

Implementation of the ACT

The dossier assessment describes that data on prior therapies in relation to the chosen treatment option are required for the final assessment of the implementation of the ACT.

These were not presented by the company. However, in the context of the comments, the company states that only one patient did not change endocrine therapy according to the study protocol and refers to one patient who received further fulvestrant treatment after pre-treatment with fulvestrant [4]. In the present situation, adequate implementation of the ACT can therefore be assumed for the majority of patients.

2.1.1 Patient characteristics

The characteristics of the patients in the assessment-relevant ESR1-mut population are shown in Table 1.

Table 1: Characteristics of the ESR1-mut population as well as study/treatment discontinuation – RCT, direct comparison: elacestrant vs. treatment of physician's choice choosing from fulvestrant, anastrozole, letrozole and exemestane (multipage table)

Study characteristic category	**Elacestrant N[a] = 115**	**Treatment of physician's choice[b] N[a] = 113**
EMERALD		
Age [years], mean (SD)	63 (12)	62 (12)
Family origin, n (%)		
Missing	21 (18[c])	21 (19[c])
Asian	5 (4[c])	8 (7[c])
Black or African American	4 (3[c])	4 (4[c])
White/Caucasian	84 (73[c])	80 (71[c])
Other	1 (1[c])	0 (0)
Region, n (%)		
Europe	63 (55)	50 (44)
North America	33 (29)	42 (37)
Asia	10 (9)	16 (14)
Other	9 (8)	5 (4)
ECOG PS, n (%)		
0	67 (58)	62 (55)
1	48 (42)	51 (45)
Years since initial diagnosis, mean (SD)	7.5 (6.5)	8.4 (7.0)
Presence of visceral[d] metastases, n (%)		
Yes	78 (68)	77 (68)
No	37 (32)	36 (32)

Table 1: Characteristics of the ESR1-mut population as well as study/treatment discontinuation – RCT, direct comparison: elacestrant vs. treatment of physician's choice choosing from fulvestrant, anastrozole, letrozole and exemestane (multipage table)

Study characteristic category	**Elacestrant N[a] = 115**	**Treatment of physician's choice[b] N[a] = 113**
Prior therapies in advanced/metastatic stage, n (%)		
Aromatase inhibitors	101 (88)	96 (85)
Tamoxifen	9 (8)	9 (8)
CDK 4/6 inhibitor	115 (100)	113 (100)
Fulvestrant	27 (23)	28 (25)
Immunotherapy	1 (1)	0 (0)
Other therapy	0 (0)	4 (4)
Prior endocrine treatment lines in advanced/metastatic stage, n (%)		
1	73 (63)	69 (61)
2	42 (37)	44 (39)
Prior chemotherapy in advanced/metastatic stage, n (%)	26 (23[c])	32 (28[c])
Treatment discontinuation, n (%)[e]	110 (96)	106 (94)
Study discontinuation, n (%)[f]	74 (64)	69 (61)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Fulvestrant, anastrozole, letrozole or exemestane according to physician's choice.
c. Institute's calculation.
d. Visceral includes lungs, liver, brain, pleura and peritoneum; based on information at the time of randomization according to interactive randomization technology (IRT). According to the information on patient characteristics at baseline, 81 (70%) patients in the intervention arm had visceral metastases compared to 84 (74%) patients in the comparator arm.
e. Data based on the time point of the second data cut-off (8 July 2022). Common reasons for treatment discontinuation in the intervention vs. the control arm were: disease progression (85% vs. 88%), physician's decision (3% vs. 3%), AEs, abnormal lab results or concomitant disease that precludes further therapy (3% vs. 1%) and withdrawal of consent for further treatment (3% vs. 0%).
f. Data based on the time point of the second data cut-off (08 July 2022). Common reasons for study discontinuation in the intervention arm vs. the control arm were death (51% vs. 49%) and withdrawal of consent (7% vs. 10%).

AE: adverse event; CDK 4/6: cyclin-dependent kinase 4/6; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IRT: interactive randomization technology; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics were largely comparable between the treatment arms of the EMERALD study. The mean age of the patients in the intervention and was 63 years and in the comparator arm 62 years and more than 80% of them came from Europe or North America. 68% of the patients had visceral metastases. According to the inclusion criteria, all patients had to have experienced progression during or after pretreatment with a CDK 4/6 inhibitor either in combination with fulvestrant or an aromatase inhibitor. Accordingly, all patients had

received pretreatment with a CDK 4/6 inhibitor. The vast majority of patients had already received aromatase inhibitors as a prior endocrine therapy (88% vs. 85%), and 23% vs. 25% fulvestrant, in relation to the intervention arm vs. the comparator arm respectively. Around one third (37% in the intervention arm vs. 39% in the comparator arm) had already received 2 prior lines of endocrine therapy.

At the time of the second data cut-off (8 July 2022), almost all patients in both treatment arms had discontinued treatment. The most common reason for treatment discontinuation was disease progression.

2.1.2 Planned duration of follow-up observation

Table 2 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 2: Planned duration of follow-up observation – RCT, direct comparison: elacestrant versus treatment of physician's choice, choosing from fulvestrant, anastrozole, letrozole and exemestane

Study **outcome category** **outcome**	**Planned follow-up observation**
EMERALD	
Mortality	
Overall survival	Until death, lost to follow-up or end of study
Morbidity	
Health status (EQ-5D VAS), symptoms (EORTC QLQ-C30)	Until 30 days after the last dose of the study medication[a]
Health-related quality of life	
EORTC QLQ-C30	Until 30 days after the last dose of the study medication[a]
Side effects	
All outcomes in the side effects category	Up to 30 days after the last dose of the study medication[b]
a. According to the study protocol, no questionnaires on patient-reported outcomes were collected if the safety follow-up visit (30 days after the last dose of study medication) was conducted by telephone. b. SAEs that, in the opinion of the investigator, were related to the study medication were to be followed up until the end of the study. EORTC: European Organization for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale	

In the EMERALD study, only overall survival was recorded until study end. The observation periods for the outcomes on morbidity, health-related quality of life and side effects were systematically shortened because they were only recorded until 30 days after the end of

treatment. However, drawing a reliable conclusion on the entire study period or the time until patient death would require for the outcomes of the categories of morbidity, health-related quality of life, and side effects to be recorded over the total period of time, as was the case for survival.

2.1.3 Data on treatment and observation periods

Table 3 shows the mean and median treatment durations of the patients and the mean and median observation periods for individual outcomes.

Table 3: Information on the course of the study – RCT, direct comparison: elacestrant versus treatment of physician's choice, choosing from fulvestrant, anastrozole, letrozole and exemestane

Study **duration of the study phase** **outcome category**	**Elacestrant** **N = 115**	**Treatment of physician's choice[a]** **N = 113**
EMERALD		
Treatment duration [months]		
Median [min; max]	2.9 [0.4; 32.1]	2.8 [0.5; 20.3][b] 2.1 [0.0; 22.8][c]
Mean (SD)	5.9 (6.8)	4.2 (3.6)[b] 3.4 (4.4)[c]
Observation period [months]		
Overall survival		
Median [min; max]	27.5[d] [0.5; 38.3][e]	25.8[d] [0.03; 37.6][e]
Mean (SD)	19.0 (ND)[e]	16.9 (ND)[e]
Symptoms, health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	ND[f]	ND[f]
Mean (SD)	ND[f]	ND[f]
Health status (EQ-5D VAS)		
Median [min; max]	ND[f]	ND[f]
Mean (SD)	ND[f]	ND[f]
Side effects[g]		
Median [min; max]	3.8 [0.03; 31.4][h]	2.9 [0.03; 23.8][h]
Mean (SD)	6.2 (ND)[h]	4.1 (ND)[h]

a. Fulvestrant, anastrozole, letrozole or exemestane according to physician's choice.
b. Data refer to patients who were treated with fulvestrant (N = 79).
c. Data refer to patients who were treated with an aromatase inhibitor (N = 27).
d. Median follow-up duration calculated using the inverse Kaplan-Meier method; deceased patients are censored at the time of death, non-deceased patients are counted as an event at the time of the end of observation.
e. Calculated based on the observed time to event/censoring or end of study of all patients (deceased and non-deceased).
f. No information available; see body of text for explanation.
g. Data refer to patients who received at least one dose of the study drug ("safety population"); elacestrant arm N = 115 vs. comparator arm N = 106.
h. Observation period is defined as the time from the first dose up to safety follow-up (or withdrawal from the study, if earlier).

EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of analysed patients; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

As far as the duration of treatment is concerned, only separate data are available for the patients in the comparator arm who received fulvestrant or aromatase inhibitors. This shows that the median and mean duration of treatment with an aromatase inhibitor was significantly shorter than with fulvestrant and elacestrant.

The median observation period for overall survival in accordance with the inverse Kaplan-Meier method was 27.5 months in the intervention arm and 25.8 months in the control arm.

The data on the observation periods of the outcomes on morbidity, health-related quality of life and side effects in the company's dossier were not comprehensible. As part of the commenting procedure, the company subsequently submitted plausible observation periods for the side effects that reflect the time from the first dose to the safety follow-up (or withdrawal from the study, if this occurred earlier). Accordingly, the median observation period for the outcomes on side effects was 3.8 months in the intervention arm and 2.9 months in the comparator arm.

The company did not present any data on the observation periods for the outcomes on morbidity and health-related quality of life as part of the commenting procedure. According to the study protocol, the observation period for the outcomes on morbidity and health-related quality of life was planned to be up to 30 days after the last dose of study medication, analogous to the outcomes on side effects (see Section 2.1.2). Therefore, a similar observation period is assumed for these outcomes as for the side effects.

2.1.4 Follow-up therapies

The study protocol provides no information on requirements for the use of possible subsequent therapies. Information on follow-up therapies is only available for the first data cut-off of 6 September 2021. Table 4 shows the follow-up therapies patients received after having discontinued the study medication.

Table 4: Information on subsequent antineoplastic therapies – RCT, direct comparison: elacestrant versus treatment of physician's choice, choosing from fulvestrant, anastrozole, letrozole and exemestane

Study drug class	Patients with follow-up therapy n (%)	
	elacestrant N = 115	treatment of physician's choice[a] N = 113
EMERALD (1st data cut-off of 06 September 2021)		
Overall rate of patients with any systemic therapy, n (%)	83 (72)	90 (80)
Endocrine therapy	23 (20[b])	15 (13[b])
Targeted therapy	6 (5[b])	11 (10[b])
Chemotherapy	50 (43[b])	59 (52[b])
Immunotherapy	1 (1[b])	0 (0[b])
CDK 4/6 inhibitor	0 (0[b])	1 (1[b])
Other	3 (3[b])	4 (4[b])

a. Fulvestrant, anastrozole, letrozole or exemestane according to physician's choice.
b. Institute's calculation.

CDK 4/6: cyclin-dependent kinase 4/6; n: number of patients with follow-up therapy; N: number of analysed patients; RCT: randomized controlled trial

In the EMERALD study, a large proportion of patients had already received follow-up therapy at the first data cut-off. The proportion of patients with systemic follow-up therapy in the intervention arm was slightly lower than in the control arm (72% vs. 80%). The most common follow-up therapy was chemotherapy (43% vs. 52%), followed by endocrine therapy (20% vs. 13%).

2.1.5 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: elacestrant versus treatment of physician's choice, choosing from fulvestrant, anastrozole, letrozole and exemestane

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			
EMERALD	Yes	Yes	No	No	Yes	No[a]	High

a. Relevant difference between the treatment groups regarding the proportion of patients who discontinued the study before the first treatment with the study medication: 0 (0%) in the elacestrant arm and 7 (6.2%) patients in the comparator arm. Of these 7 patients, 6 (8.7%) patients had received one prior line of endocrine therapy in the advanced/metastatic stage and one (2.3%) patient had received 2 prior lines of endocrine therapy in the advanced/metastatic stage.

RCT: randomized controlled trial

The risk of bias across outcomes was rated as high for the EMERALD study, since there was a relevant difference (6.2 percentage points; 0 patients in the intervention arm and 7 patients in the comparator arm) between the two study arms in the proportion of patients who had already discontinued the study before the first administration of the study medication. Upon the analysis of all outcomes, this results in a high difference between the treatment groups (> 5 percentage points) regarding the proportion of patients not included in the analysis. The information provided by the company in the commenting procedure shows that of these 7 patients in the control arm, 6 patients had one prior line of endocrine therapy in the advanced/metastatic stage (8.7% of this subgroup in the control arm) and 1 patient had two prior lines of endocrine therapy in the advanced/metastatic stage (2.3% of this subgroup in the control arm). The distribution of missing patients in the analyses is taken into account for the certainty of conclusions within the subgroup analyses, separately for one vs. two prior endocrine therapies (see Section 2.2.4)

Limitations resulting from the open-label study design are described in Section 2.2.2 under "Outcome-specific risk of bias".

Transferability of the study results to the German health care context

In Module 4 A of its dossier, the company states that the results of the EMERALD study are transferable to the German health care context, referring to the population presented in the dossier. In the company's view, the study population corresponds to the target population in Germany in terms of demographic and disease-specific characteristics, and the low proportion of men in the EMERALD study reflects the health care reality in Germany.

The company described that although hardly any data regarding the disease-specific characteristics were available for the target population in Germany, it could be assumed that the disease-specific characteristics also essentially corresponded to those of patients in Germany. According to the company, treatment in the comparator arm also corresponded to the German health care reality and covered the options named as ACT for the present benefit assessment very well.

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

2.2 Results on added benefit

2.2.1 Outcomes included

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)
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded with 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
  - specific AEs

The choice of patient-relevant outcomes deviates from that taken by the company, which used other 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: elacestrant versus treatment of physician's choice, choosing from fulvestrant, anastrozole, letrozole and exemestane

Study	Outcomes							
	Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Specific AEs[b]
EMERALD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (MedDRA coding): gastrointestinal disorders (SOC, AEs) and musculoskeletal and connective tissue disorders (SOC, severe AEs).

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

Comments on outcomes and the company's comments

Discrepancy in the assessment of progression events

With reference to the European Public Assessment Report (EPAR) [6], the dossier assessment [1] described that as early as at the first data cut-off in the EMERALD study, the assessment of progression by the investigators differed significantly from the retrospectively conducted, blinded assessment and that there were also corresponding differences between the intervention arm and the comparator arm. This discrepancy could not be plausibly explained during the commenting procedure either.

A discrepant assessment of progression might have a distorting effect on the results of other outcomes, as the decision to remain on treatment depended on the investigators' assessment of progression. In the present case, however, the extent of discrepancy is not large enough for a relevant distorting effect to be assumed. No consequences arise for the benefit assessment.

Symptoms, health status, and health-related quality of life

For the PROs, the company presented analyses of the ESR1-mut population for the first deterioration by at least 10 points for the EORTC QLQ-C30 and by at least 15 points for the EQ-5D VAS in the form of event time analyses. These are used for the benefit assessment.

However, the company still does not present correctly calculated response rates. The number of expected responses at the respective time points should correspond to the number of all patients who have not died by this point in time. Despite this uncertainty regarding the response rates, the analyses are used for the benefit assessment in the present data situation.

Side effects

AEs, SAEs, and severe AEs

For the overall rates of AEs, SAEs, and severe AEs, the company presents in Module 4 A not only analyses including all AEs but also analyses excluding disease-related events. It categorizes all events in the System Organ Class (SOC) "neoplasms benign, malignant and unspecified" (including cysts and polyps) as disease-related events. In the ESR1-mut population, 4 events (2 of which occurred in the same patient) occurred in this SOC in the following Preferred Terms (PTs): breast cancer with metastases, cancer pain, tumour pain. The analyses including the SOC of neoplasms benign, malignant and unspecified (including cysts and polyps) were used in the present data situation. On the one hand, this is due to the fact that it was already planned in the study protocol not to record events which were clearly attributable to the progression of the underlying disease as AEs. On the other hand, the effect estimates without disease-related events differ only slightly from those with disease-related events.

Patient-Reported Outcome – Common Terminology Criteria for Adverse Events (PRO-CTCAE)

As per study protocol, side effects in the EMERALD study were also recorded using the PRO-CTCAE instrument for descriptive presentation. Overall, the PRO-CTCAE system is a valuable addition to the usual recording and analysis of AEs. The system comprises a total of 78 symptomatic AEs of the CTCAE system, which are compiled into a questionnaire adapted to the respective study situation. The selection process is to be planned a priori and carried out transparently. The individual symptomatic AEs must be transparently selected, e.g. all important potential AEs of the drug in the intervention and the control arm must be recorded. For a detailed description of the PRO-CTCAE system, see the corresponding explanations in benefit assessment A20-87 [7].

In Appendix 4 G to Module 4 A, the company presents descriptive analyses on the following symptomatic AEs, which it does not use itself to derive the added benefit: abdominal pain, anxiety, shortness of breath, cough, loss of appetite, despondency, dizziness, fatigue, pain, headache, heartburn, hot flushes, unexpected or profuse sweating during the day or night (not associated with hot flushes), problems sleeping, joint pain, muscle pain, nausea, sadness, swollen arms or legs, vomiting.

The selection of symptomatic AEs was not planned a priori in the study protocol or statistical analysis plan of the study, and the company did not provide any information on its procedure,

for example on the search or the type of documents reviewed. It can only be inferred from the study report that the selected symptomatic AEs are those that are frequently reported in patients with metastatic breast cancer and/or were frequently reported in prior studies on elacestrant. Due to the nontransparent selection process and the incomprehensible selection of items to depict symptomatic AEs, the outcome of PRO-CTCAE is not used for the benefit assessment, as also by the company itself.

2.2.2 Risk of bias

Table 7 describes the risk of bias for the results of the relevant outcomes.

Table 7: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: elacestrant versus treatment of physician's choice, choosing from fulvestrant, anastrozole, letrozole and exemestane

Study	Study level	Outcomes							
		Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Specific AEs[b]
EMERALD	H	H[c]	H[c, d, e]	H[c, d, e]	H[c, d, e]	H[c, e]	H[c, e]	H[c, d]	H[c, d, e]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (MedDRA coding): gastrointestinal disorders (SOC, AEs) and musculoskeletal and connective tissue disorders (SOC, severe AEs).
c. High risk of bias across outcomes.
d. Lack of blinding with subjective recording of outcomes (except specific AEs with CTCAE grade ≥ 3) or subjective decision to discontinue treatment (discontinuation due to AEs).
e. Incomplete observations for potentially informative reasons.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; MedDRA: Medical Dictionary for Regulatory Activities; QLQ-C30: Quality of Life Questionnaire–Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Due to the high risk of bias across outcomes that already exists, there is a high risk of bias for the results on all outcomes (see Section 2.1.5).

Apart from the outcomes "overall survival" and "discontinuation due to AEs", the high risk of bias for the results on all outcomes is additionally due to the fact that the observation of

outcomes was incomplete for potentially informative reasons. Moreover, the results for the outcomes “symptoms”, “health status”, “health-related quality of life”, “discontinuation due to AEs” as well as the specific AE “gastrointestinal disorders” are subject to a high risk of bias due to the lack of blinding in subjective recording of outcomes or subjective decision on treatment discontinuation.

Summary assessment of the certainty of conclusions

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

The high risk of bias of the results on the outcome of overall survival is exclusively due to the high risk of bias across outcomes, which is based on the relevant difference of patients not included in the analysis between the treatment groups (see Table 7). In different subgroups, however, this difference between the treatment arms may be greater or smaller. In the present data situation, it is shown for the subgroup of patients with two prior lines of endocrine therapy in the advanced/metastatic stage that only one (2.3%) patient was not included in the analysis. Thus, the difference in patients not included in the analysis between the treatment groups is < 5%. This means that there is a low risk of bias for the results on the outcome “overall survival” for this subgroup and at most an indication, e.g. of an added benefit, can be determined.

2.2.3 Results

Table 8 summarizes the results of the ESR1-mut population comparing elacestrant versus treatment of physician's choice choosing from fulvestrant, anastrozole, letrozole and exemestane in postmenopausal women with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed after at least one line of endocrine therapy, including a CDK 4/6 inhibitor. Where necessary, the data provided by the company were supplemented with the Institute’s calculations.

Results for common AEs, SAEs, severe AEs, and discontinuations due to AEs can be found in Appendix A of the present addendum. The Kaplan-Meier curves on the presented event time analyses are presented in Appendix B of the full dossier assessment.

Table 8: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: elacestrant versus treatment of physician's choice, choosing from fulvestrant, anastrozole, letrozole and exemestane (multipage table)

Study outcome category outcome	Elacestrant		Treatment of physician's choice[a]		Elacestrant vs. treatment of physician's choice[a]
	N	median time to event in months [95% CI] patients with event n(%)	N[b]	median time to event in months [95% CI] patients with event n(%)	HR [95% CI]; p-value[c]
EMERALD					
Mortality (third data cut-off of 02 September 2022)					
Overall survival	115	24.2 [20.5; 28.7] 61 (53.0)	113	23.5 [15.6; 29.9] 60 (53.1)	0.90 [0.63; 1.30]; 0.582
Morbidity (second data cut-off: 08 July 2022)					
Symptoms (EORTC QLQ-C30[d])					
Fatigue	115	1.5 [1.0; 2.0] 59 (51.3)	113	1.5 [1.0; 2.8] 55 (48.7)	0.87 [0.59; 1.27]; 0.462
Nausea/vomiting	115	1.1 [1.0; 1.9] 61 (53.0)	113	2.1 [1.9; 3.3] 31 (27.4)	1.46 [0.94; 2.31]; 0.101
Pain	115	1.9 [1.0; 2.8] 66 (57.4)	113	1.9 [1.0; 2.8] 48 (42.5)	1.09 [0.74; 1.62]; 0.659
Dyspnoea	115	3.1 [1.9; 8.3] 37 (32.2)	113	2.8 [1.9; 3.8] 39 (34.5)	0.74 [0.47; 1.18]; 0.233
Insomnia	115	4.0 [2.0; 8.5] 45 (39.1)	113	2.0 [1.9; 2.9] 44 (38.9)	0.74 [0.48; 1.14]; 0.178
Appetite loss	115	2.3 [1.8; 4.7] 51 (44.3)	113	3.9 [2.8; 6.3] 25 (22.1)	1.84 [1.12; 3.11]; 0.018
Constipation	115	4.9 [2.8; 8.4] 33 (28.7)	113	3.0 [2.8; 4.7] 34 (30.1)	0.72 [0.44; 1.18]; 0.172
Diarrhoea	115	8.3 [2.3; NC] 32 (27.8)	113	3.4 [2.8; 5.9] 26 (23.0)	0.97 [0.57; 1.68]; 0.901
Health status (EQ-5D VAS[e])	115	8.3 [4.8; NC] 37 (32.2)	113	10.3 [5.9; NC] 31 (27.4)	0.93 [0.57; 1.52]; 0.751

Table 8: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: elacestrant versus treatment of physician's choice, choosing from fulvestrant, anastrozole, letrozole and exemestane (multipage table)

Study outcome category outcome	Elacestrant		Treatment of physician's choice[a]		Elacestrant vs. treatment of physician's choice[a]
	N	median time to event in months [95% CI] patients with event n(%)	N[b]	median time to event in months [95% CI] patients with event n(%)	HR [95% CI]; p-value[c]
Health-related quality of life (second data cut-off: 08 July 2022)					
EORTC QLQ-C30[f]					
Global health status	115	3.7 [2.3; 6.5] 54 (47.0)	113	2.1 [1.5; 4.7] 39 (34.5)	0.75 [0.49; 1.17]; 0.190
Physical functioning	115	2.8 [1.9; 4.7] 49 (42.6)	113	2.8 [1.9; 4.7] 36 (31.9)	0.96 [0.62; 1.51]; 0.916
Role functioning	115	1.9 [1.0; 3.9] 62 (53.9)	113	2.8 [1.9; 5.9] 35 (31.0)	1.23 [0.81; 1.89]; 0.347
Emotional functioning	115	6.5 [2.8; 8.4] 40 (34.8)	113	2.9 [2.8; 5.9] 30 (26.5)	0.88 [0.53; 1.48]; 0.627
Cognitive functioning	115	4.0 [2.3; 8.3] 46 (40.0)	113	2.8 [2.2; 3.5] 35 (31.0)	0.99 [0.62; 1.60]; 0.944
Social functioning	115	3.9 [1.9; 6.6] 49 (42.6)	113	2.2 [1.0; 3.0] 42 (37.2)	0.78 [0.50; 1.22]; 0.267
Side effects (second data cut-off of 08 July 2022)					
AEs (supplementary information)	115	0.3 [0.1; 0.5] 105 (91.3)	106	0.5 [0.3; 0.5] 92 (86.8)	–
SAEs	115	NA 14 (12.2)	106	NA 12 (11.3)	0.85 [0.39; 1.88]; 0.678[g]
Severe AEsh	115	NA 33 (28.7)	106	13.1 [13.1; NC] 24 (22.6)	1.11 [0.66; 1.90]; 0.701[g]
discontinuation due to AEs	115	NA 6 (5.2)	106	NA 4 (3.8)	1.28 [0.36; 5.03]; 0.701[g]
Gastrointestinal disorders (SOC, AEs)	115	1.8 [1.0; 2.7] 75 (65.2)	106	NA [5.9; NC] 33 (31.1)	2.56 [1.71; 3.92]; < 0.001[g]
Musculoskeletal and connective tissue disorders (SOC, severe AEsh)	115	NA 10 (8.7)	106	NA 1 (0.9)	7.41 [1.40; 136.55]; 0.026[g]

Table 8: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: elacestrant versus treatment of physician's choice, choosing from fulvestrant, anastrozole, letrozole and exemestane (multipage table)

Study outcome category outcome	Elacestrant		Treatment of physician's choice[a]		Elacestrant vs. treatment of physician's choice[a]
	N	median time to event in months [95% CI] patients with event n(%)	N[b]	median time to event in months [95% CI] patients with event n(%)	HR [95% CI]; p-value[c]
a. Fulvestrant, anastrozole, letrozole or exemestane according to physician's choice. b. For the outcomes on mortality, morbidity and health-related quality of life, 113 patients were formally included in the analysis, but as 7 patients had withdrawn their consent before the first study medication was administered, it is assumed that they were censored at baseline and were therefore included in the analysis without any information. c. Unless specified otherwise: HR and CI: Cox proportional hazards model, stratified by pretreatment with fulvestrant and the presence of visceral metastases; p-value: stratified log-rank test. d. Time to first deterioration; a score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100). e. Time to first deterioration; a score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100). f. Time to first deterioration; a score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100). g. HR and CI: unstratified Cox proportional hazards model; p-value: unstratified log-rank test. h. Operationalized as CTCAE grade ≥ 3. AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale					

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes. For the outcome "overall survival", at most an indication, e.g. of an added benefit, can be determined in the subgroup of patients with 2 prior lines of endocrine therapy in the advanced/metastatic stage (see Section 2.2.2).

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. However, there was an effect modification by the characteristic "number of prior endocrine therapy lines in advanced/metastatic stage" (see Table 9). There is an indication of an added benefit of elacestrant compared to treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane in patients with 2 prior lines of endocrine therapy. For patients with one prior line of endocrine therapy, there is no hint of

an added benefit of elacestrant in comparison with treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane; an added benefit is therefore not proven.

Morbidity

Symptoms

Symptom outcomes were recorded using the EORTC QLQ-C30. Below, the symptom outcomes with statistically significant differences are described first.

Appetite loss

A statistically significant difference to the disadvantage of elacestrant was shown for the outcome "appetite loss". For this outcome, there is a hint of lesser benefit of elacestrant in comparison with treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane.

Insomnia

No statistically significant difference between the treatment groups was shown for the outcome "insomnia". However, there was an effect modification by the characteristic "number of prior endocrine therapy lines" (see Table 9). There is a hint of an added benefit of elacestrant compared to treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane in patients with 1 prior line of endocrine therapy. For patients with two prior lines of endocrine therapy, there is no hint of an added benefit of elacestrant in comparison with treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane; an added benefit is therefore not proven.

Further symptom outcomes

No statistically significant difference between treatment groups was shown for any of the outcomes of fatigue, nausea/vomiting, pain, dyspnoea, constipation, or diarrhoea. There are not hints of an added benefit of elacestrant in comparison with treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane; an added benefit is therefore not proven for these outcomes.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups for the outcome "health status" recorded with the EQ-5D VAS. There is no hint of an added benefit of elacestrant in comparison with treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane; an added benefit is therefore not proven for this outcome.

Health-related quality of life

EORTC QLQ-C30

Health-related quality of life outcomes were recorded using the EORTC QLQ-C30 instrument.

There was no statistically significant difference between the treatment groups for any of the outcomes on health-related quality of life. There is no hint of an added benefit of elacestrant in comparison with treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane; an added benefit is therefore not proven for these outcomes.

Side effects

SAEs, severe AEs and discontinuation due to AEs

There were no statistically significant differences between treatment groups for the outcomes of SAEs, severe AEs and discontinuation due to AEs. There is no hint of greater or lesser harm from elacestrant in comparison with treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane; greater or lesser harm is therefore not proven for these outcomes.

Specific AEs

Gastrointestinal disorders (SOC, AEs) and musculoskeletal and connective tissue disorders (SOC, severe AEs)

For each of the outcomes of gastrointestinal disorders (SOC, AEs) and musculoskeletal and connective tissue disorders (SOC, severe AEs), there is a statistically significant difference to the disadvantage of elacestrant. For each of these outcomes, there is a hint of greater harm from elacestrant in comparison with treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane.

2.2.4 Subgroups and effect modifiers

The following potential effect modifiers were taken into account for the present addendum:

- Age (< 65 years versus ≥ 65 years)
- Presence of visceral metastasis (yes versus no)
- Number of prior endocrine therapy lines in advanced/metastatic stage (1 vs. 2)
- Bilateral oophorectomy (yes versus no)

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 B.5 of the full dossier assessment.

Table 9: Subgroups (mortality, morbidity) – RCT, direct comparison: elacestrant versus treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane

Study outcome characteristic subgroup	Elacestrant N	Elacestrant median time to event in months [95% CI] patients with event n(%)	Treatment of physician's choice[a] N	Treatment of physician's choice[a] median time to event in months [95% CI] patients with event n(%)	Elacestrant vs. treatment of physician's choice[a] HR [95% CI][b]	Elacestrant vs. treatment of physician's choice[a] p-value[c]
EMERALD						
Mortality						
Overall survival						
Number of prior endocrine therapy lines in advanced/metastatic stage						
1	73	24.2 [18.3; 31.9] 38 (52.1)	69	29.9 [21.3; NC] 29 (42.0)	1.34 [0.82; 2.21]	0.239
2	42	26.3 [19.8; 33.0] 23 (54.8)	44	15.6 [12.2; 19.8] 31 (70.5)	0.50 [0.28; 0.852]	0.010
Total					Interaction:	0.008[d]
Morbidity						
Symptoms (EORTC QLQ-C30[e])						
Insomnia						
Number of prior endocrine therapy lines in advanced/metastatic stage						
1	73	6.5 [2.3; 12.8] 25 (34.2)	69	1.5 [1.0; 2.8] 29 (42.0)	0.43 [0.25; 0.75]	0.002
2	42	1.9 [0.9; 19.1] 20 (47.6)	44	2.8 [2.0; NC] 15 (34.1)	1.41 [0.71; 2.84]	0.309
Total					Interaction:	0.012[d]

a. Fulvestrant, anastrozole, letrozole or exemestane according to physician's choice.
b. Effect and CI: unstratified Cox proportional hazards model.
c. p-value: unstratified log-rank test.
d. p-value from interaction test from unstratified Cox proportional hazards model.
e. Time to first deterioration; a score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100).

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NC: not calculable; QLQ-C30: Quality of Life Questionnaire; RCT: randomized controlled trial

Mortality

Overall survival

For the outcome of overall survival, there was an effect modification by the characteristic "number of prior endocrine therapy lines in advanced/metastatic stage". For patients with 2 prior lines of endocrine therapy in the advanced/metastatic stage, there is a statistically significant difference between the treatment arms in favour of elacestrant. There is an indication of an added benefit of elacestrant compared to treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane in patients with 2 prior lines of endocrine therapy. For patients with one prior line of endocrine therapy, there is no hint of an added benefit of elacestrant in comparison with treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane; an added benefit is therefore not proven.

Morbidity

Symptoms

Insomnia

For the outcome of insomnia, there was an effect modification by the characteristic "number of prior endocrine therapy lines in advanced/metastatic stage". For patients with 1 prior line of endocrine therapy in the advanced/metastatic stage, there is a statistically significant difference between the treatment arms in favour of elacestrant. There is a hint of an added benefit of elacestrant compared to treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane in patients with 1 prior line of endocrine therapy. For patients with two prior lines of endocrine therapy, there is no hint of an added benefit of elacestrant in comparison with treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane; an added benefit is therefore not proven.

Note on the characteristic "bilateral oophorectomy"

According to the G-BA's advice, it is viewed critically to consider premenopausal women with suppressed ovarian function as postmenopausal and to treat them as postmenopausal women. In accordance with the inclusion criteria of the EMERALD study, patients with bilateral oophorectomy were also included in the study. The ESR1-mut population included 46 patients (20.2%) who were included as postmenopausal due to bilateral oophorectomy. To assess the influence of these patients on the results, the company presented subgroup analyses as part of the commenting procedure. There was no effect modification by the characteristic "bilateral oophorectomy".

2.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [8].

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

2.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.2 (see Table 10).

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they are serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Determination of the outcome category for symptom outcomes

Insomnia and appetite loss (EORTC QLQ-C30)

For the outcomes of insomnia and appetite loss, insufficient information is available to classify the severity category as serious/severe. The outcomes of insomnia and appetite loss were therefore allocated to the outcome category of non-serious/non-severe symptoms.

Table 10: Extent of added benefit at outcome level: elacestrant versus treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Elacestrant vs. treatment of physician's choice[a]** **median time to event (months)** **HR [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival		
Number of prior endocrine therapy lines in advanced/metastatic stage		
1	24.2 vs. 29.9 1.34 [0.82; 2.21] p = 0.239	Lesser/added benefit not proven
2	26.3 vs. 15.6 0.50 [0.28; 0.852] p = 0.010 probability: "indication"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent: "considerable"
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30 – time to first deterioration)		
Fatigue	1.5 vs. 1.5 0.87 [0.59; 1.27] p = 0.462	Lesser/added benefit not proven
Nausea/vomiting	1.1 vs. 2.1 1.46 [0.94; 2.31] p = 0.101	Lesser/added benefit not proven
Pain	1.9 vs. 1.9 1.09 [0.74; 1.62] p = 0.659	Lesser/added benefit not proven
Dyspnoea	3.1 vs. 2.8 0.74 [0.47; 1.18] p = 0.233	Lesser/added benefit not proven

Table 10: Extent of added benefit at outcome level: elacestrant versus treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Elacestrant vs. treatment of physician's choice**[a] **median time to event (months)** **HR [95% CI];** **p-value** **probability**[b]	**Derivation of extent**[c]
Insomnia		
Number of prior endocrine therapy lines in advanced/metastatic stage		
1	6.5 vs. 1.5 0.43 [0.25; 0.75] p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit; extent: "considerable"
2	1.9 vs. 2.8 1.41 [0.71; 2.84] p = 0.309	Lesser/added benefit not proven
Appetite loss	2.3 vs. 3.9 1.84 [1.12; 3.11] 0.54 [0.32; 0.89][d] p = 0.018 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ lesser benefit, extent: "minor"
Constipation	4.9 vs. 3.0 0.72 [0.44; 1.18] p = 0.172	Lesser/added benefit not proven
Diarrhoea	8.3 vs. 3.4 0.97 [0.57; 1.68] p = 0.901	Lesser/added benefit not proven
Health status		
EQ-5D VAS - time to first deterioration	8.3 vs. 10.3 0.93 [0.57; 1.52] p = 0.751	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 – time to first deterioration		
Global health status	3.7 vs. 2.1 0.75 [0.49; 1.17] p = 0.190	Lesser/added benefit not proven
Physical functioning	2.8 vs. 2.8 0.96 [0.62; 1.51] p = 0.916	Lesser/added benefit not proven

Table 10: Extent of added benefit at outcome level: elacestrant versus treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Elacestrant vs. treatment of physician's choice**[a] **median time to event (months)** **HR [95% CI];** **p-value** **probability**[b]	**Derivation of extent**[c]
Role functioning	1.9 vs. 2.8 1.23 [0.81; 1.89] p = 0.347	Lesser/added benefit not proven
Emotional functioning	6.5 vs. 2.9 0.88 [0.53; 1.48] p = 0.627	Lesser/added benefit not proven
Cognitive functioning	4.0 vs. 2.8 0.99 [0.62; 1.60] p = 0.944	Lesser/added benefit not proven
Social functioning	3.9 vs. 2.2 0.78 [0.50; 1.22] p = 0.267	Lesser/added benefit not proven
Side effects		
SAEs	NA vs. NA 0.85 [0.39; 1.88] p = 0.678	Greater/lesser harm not proven
Severe AEs	NA vs. 13.1 1.11 [0.66; 1.90] p = 0.701	Greater/lesser harm not proven
Discontinuation due to AEs	NA vs. NA 1.28 [0.36; 5.03]; p = 0.701	Greater/lesser harm not proven
Gastrointestinal disorders (AEs)	1.8 vs. NA 2.56 [1.71; 3.92] 0.39 [0.26; 0.58][d] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Musculoskeletal and connective tissue disorders (severe AEs)	NA vs. NA 7.41 [1.40; 136.55] 0.14 [0.01; 0.72][d] p = 0.026 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: "major"

Table 10: Extent of added benefit at outcome level: elacestrant versus treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Elacestrant vs. treatment of physician's choice**[a] **median time to event (months)** **HR [95% CI];** **p-value** **probability**[b]	**Derivation of extent**[c]
a. Fulvestrant, anastrozole, letrozole or exemestane according to physician's choice. b. Probability provided if a statistically significant and relevant effect is present. c. Depending on the outcome category, estimations of effect size use different limits based on the upper limit of the confidence interval (CI_u). d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; VAS: visual analogue scale		

2.3.2 Overall conclusion on added benefit

Table 11 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 11: Positive and negative effects from the assessment of elacestrant in comparison with treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival: ▫ 2 prior lines of endocrine therapy in the advanced/metastatic stage Indication of an added benefit - extent: “considerable”	–
Outcomes with shortened observation period	
Non-serious/non-severe symptoms/late complications symptoms (EORTC QLQ-C30) ▪ insomnia: ▫ 1 prior line of endocrine therapy in the advanced/metastatic stage Indication of an added benefit - extent: “considerable”	Non-serious/non-severe symptoms/late complications Symptoms (EORTC QLQ-C30) ▪ appetite loss: hint of lesser benefit – extent: "minor"
–	Serious/severe side effects ▪ musculoskeletal and connective tissue disorders (severe AEs): hint of greater harm – extent: “major”
–	Non-serious/non-severe side effects ▪ gastrointestinal disorders (AEs): hint of greater harm – extent: “considerable”
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire – Core 30	

Overall, there were both positive and negative effects of different extents of elacestrant in comparison with treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane. Only for overall survival are the observed effects based on the entire observation period. For the outcome categories of morbidity, health-related quality of life and side effects, in contrast, they are based exclusively on the shortened observation period of up to 30 days after the last dose of study medication (see Section 2.1.2).

For the outcome of overall survival, there was an effect modification by the characteristic “number of prior endocrine therapy lines in advanced/metastatic stage”. For patients with 2 prior lines of endocrine therapy, there was an indication of a considerable added benefit; for patients with 1 prior line of endocrine therapy, there is no added benefit.

In the subgroup of patients with 1 prior line of endocrine therapy, there was a hint of a considerable added benefit in the outcome of insomnia for non-serious/non-severe symptoms/consequential complications.

The positive effects were offset by negative effects for the entire ESR1-mut population: for the outcome “loss of appetite”, there is a hint of lesser benefit with the extent “minor”. In the outcome categories of serious/severe side effects and non-serious/non-severe side effects, negative effects with the extents “major” or “considerable” were shown for the outcomes of musculoskeletal and connective tissue disorders and gastrointestinal disorders.

Due to the effect modification in the outcome of overall survival, the added benefit is derived separately for patients with one or two prior lines of endocrine therapy. The negative effects described do not call into question the benefit in the outcome of overall survival in patients with 2 prior lines of endocrine therapy. Neither the advantages nor the disadvantages prevail in patients with 1 prior line of endocrine therapy.

In summary, there is an indication of considerable added benefit of elacestrant compared to treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane in patients with 2 prior lines of endocrine therapy in the advanced/metastatic stage. For patients with 1 prior line of endocrine therapy in the advanced/metastatic stage, however, there is no hint of an added benefit.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure have changed the conclusion on the added benefit of elacestrant from dossier assessment A23-104 for Research question 1: postmenopausal women with ER-positive, HER2-negative locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed after at least one line of endocrine therapy, including a CDK 4/6 inhibitor. There is an indication of considerable added benefit of elacestrant compared to treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane for patients with 2 prior lines of endocrine therapy in the advanced/metastatic stage. The added benefit is still not proven for patients with 1 prior line of endocrine therapy in the advanced/metastatic stage.

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of elacestrant from dossier assessment A23-104 for Research question 2. An added benefit of elacestrant is still not proven for men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed following at least one line of endocrine therapy including a CDK 4/6 inhibitor.

Table 12 below shows the result of the benefit assessment of elacestrant, taking into account dossier assessment A23-104 and the present addendum.

Table 12: Elacestrant – probability and extent of added benefit (multipage table)

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
1	Postmenopausal women[b] with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed following at least one line of endocrine therapy including a CDK 4/6 inhibitor[c]	Treatment of physician's choice, taking into account a change of endocrine therapy[d]: ▪ tamoxifen ▪ anastrozole ▪ fulvestrante as monotherapy ▪ letrozolee ▪ exemestane ▪ everolimus in combination with exemestane (only for patients without symptomatic visceral metastases who have progressed after a non-steroidal aromatase inhibitor).	Patients with ▪ 1 prior line of endocrine therapy in the advanced/metastatic stage: added benefit not proven ▪ 2 prior lines of endocrine therapy in the advanced/metastatic stage: indication of considerable added benefit
2	Men[f] with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed following at least one line of endocrine therapy including a CDK 4/6 inhibitor[c]	Treatment of physician's choice, taking into account a change of endocrine therapy[d]: ▪ tamoxifen[f] ▪ aromatase inhibitorf in combination with a gonadotropin-releasing hormone (GnRH) analogue ▪ fulvestrant[f]	Added benefit not proven

Table 12: Elacestrant – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the respective ACT specified by the G-BA. b. According to the G-BA, it is viewed critically to consider premenopausal women with supressed ovarian function as postmenopausal and to treat them as postmenopausal women. c. For the present therapeutic indication, it is assumed that re-treatment with a CDK 4/6 inhibitor is not an option, and that further endocrine therapy is indicated for the patients and there is no therapeutic indication for chemotherapy to achieve a rapid remission. Moreover, it is assumed that (secondary) resection or radiotherapy with curative intent is not indicated. It is also assumed that treatment with elacestrant is not indicated for patients with genomic breast cancer associated gene (BRCA)1/2 mutation for whom BRCA-specific therapy is an option. d. It is assumed that there has been a change in treatment with respect to the drugs used for the previous endocrine-based therapy. e. In this therapeutic indication, the approvals of fulvestrant, letrozole and exemestane only provide for use after prior anti-oestrogen therapy. However, it is clear from the guidelines that the use of fulvestrant is also explicitly based on previous therapy with aromatase inhibitors, and that with regard to the use of the aromatase inhibitors letrozole and exemestane, switching from a steroidal to a non-steroidal aromatase inhibitor or vice versa is also explicitly recommended. According to the G-BA, the use of fulvestrant, letrozole and exemestane is generally preferable to the approved endocrine therapies for the patient group of postmenopausal women for the therapeutic indication after pretreatment with an endocrine therapy other than anti-oestrogens, in particular after prior therapy with aromatase inhibitors. For this reason, the G-BA considers it appropriate to determine the above-mentioned drugs as ACT for this therapeutic indication, even when used beyond the scope of the approval. f. The guidelines recommends the drugs tamoxifen, fulvestrant and aromatase inhibitor + GnRH analogue for the male patient group. However, in the therapeutic indication, aromatase inhibitors and fulvestrant are only approved for women. With regard to the approved drug tamoxifen, it can be assumed that the vast majority of patients have already received treatment with tamoxifen at an earlier stage of the disease or earlier in the treatment sequence. According to the G-BA, the use of fulvestrant and of aromatase inhibitors + GnRH analogue is therefore generally preferable to tamoxifen for the patient group of men in the described therapeutic indication. The G-BA therefore considers it appropriate to determine the off-label use of the above-mentioned drugs as ACT. BRCA: breast cancer susceptibility gene; CDK 4/6: cyclin-dependent kinase 4/6; ER: oestrogen receptor; ESR1: oestrogen receptor 1; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2			

The G-BA decides on the added benefit.

3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

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Appendix A Results on side effects

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

- overall rate of AEs (irrespective of severity): events which occurred in at least 10% of patients in one study arm
- overall rates of severe AEs (CTCAE grade ≥ 3) and SAEs: events which occurred in at least 5% of patients in one study arm
- additionally, for all events irrespective of severity: events which 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 13: Common AEsa – RCT, direct comparison: elacestrant versus treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane (multipage table)

Study	**Patients with event n(%)**	
SOC[b] **PT[b]**	**Elacestrant** **N = 115**	**Treatment of physician's choice[c]** **N = 106**
EMERALD		
Overall AE rate	105 (91.3)	92 (86.8)
Blood and lymphatic system disorders	18 (15.7)	18 (17.0)
Anaemia	12 (10.4)	11 (10.4)
Gastrointestinal disorders	75 (65.2)	33 (31.1)
Constipation	12 (10.4)	8 (7.5)
Diarrhoea	18 (15.7)	13 (12.3)
Dyspepsia	13 (11.3)	3 (2.8)
Nausea	40 (34.8)	19 (17.9)
Vomiting	22 (19.1)	10 (9.4)
General disorders and administration site conditions	45 (39.1)	44 (41.5)
Asthenia	11 (9.6)	9 (8.5)
Fatigue	20 (17.4)	21 (19.8)

Table 13: Common AEsa – RCT, direct comparison: elacestrant versus treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane (multipage table)

Study	**Patients with event n(%)**	
SOC[b] **PT[b]**	**Elacestrant N = 115**	**Treatment of physician's choice[c] N = 106**
Infections and infestations	28 (24.3)	15 (14.2)
Investigations	34 (29.6)	37 (34.9)
Alanine aminotransferase increased	6 (5.2)	13 (12.3)
Aspartate aminotransferase increased	12 (10.4)	15 (14.2)
Metabolism and nutrition disorders	25 (21.7)	9 (8.5)
Decreased appetite	20 (17.4)	8 (7.5)
Musculoskeletal and connective tissue disorders	53 (46.1)	46 (43.4)
Arthralgia	23 (20.0)	19 (17.9)
Back pain	16 (13.9)	9 (8.5)
Musculoskeletal pain	5 (4.3)	10 (9.4)
Pain in extremity	10 (8.7)	5 (4.7)
Nervous system disorders	30 (26.1)	25 (23.6)
Headache	15 (13.0)	11 (10.4)
Psychiatric disorders	23 (20.0)	13 (12.3)
Insomnia	13 (11.3)	7 (6.6)
Reproductive system and breast disorders	12 (10.4)	3 (2.8)
Respiratory, thoracic and mediastinal disorders	21 (18.3)	17 (16.0)
Skin and subcutaneous tissue disorders	21 (18.3)	6 (5.7)
Vascular disorders	15 (13.0)	10 (9.4)
Hot flush	11 (9.6)	8 (7.5)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 23.0; SOC and PT notation taken without adaptation from the data subsequently submitted by the company.
a. Fulvestrant, anastrozole, letrozole or exemestane according to physician's choice.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 14: Common SAEsa – RCT, direct comparison: elacestrant versus treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane

Study	**Patients with event n(%)**	
SOC[b] PT[b]	**Elacestrant N = 115**	**Treatment of physician's choice[c] N = 106**
EMERALD		
Overall SAE rate	14 (12.2)	12 (11.3)
Infections and infestations	3 (2.6)	7 (6.6)

a. Events that occurred in ≥ 5% of patients in at least one study arm.
b. MedDRA version 23.0; SOC and PT notation taken without adaptation from the data subsequently submitted by the company.
a. Fulvestrant, anastrozole, letrozole or exemestane according to physician's choice.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 15: Common severe AEs (CTCAE grade ≥ 3)a – RCT, direct comparison: elacestrant versus treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane

Study	**Patients with event n(%)**	
SOC[b] PT[b]	**Elacestrant N = 115**	**Treatment of physician's choice[c] N = 106**
EMERALD		
Overall rate of severe AEs	33 (28.7)	24 (22.6)
Blood and lymphatic system disorders	4 (3.5)	7 (6.6)
Gastrointestinal disorders	8 (7.0)	5 (4.7)
Infections and infestations	3 (2.6)	6 (5.7)
Investigations	12 (10.4)	11 (10.4)
Musculoskeletal and connective tissue disorders	10 (8.7)	1 (0.9)

a. Events that occurred in ≥ 5% of patients in at least one study arm.
b. MedDRA version 23.0; SOC notation taken without adaptation from the data subsequently submitted by the company.
a. Fulvestrant, anastrozole, letrozole or exemestane according to physician's choice.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 16: Discontinuations due to AEs – RCT, direct comparison: elacestrant versus treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane (multipage table)

Study	**Patients with event n(%)**	
SOC[a] **PT[a]**	**Elacestrant** **N = 115**	**Treatment of physician's choice[b]** **N = 106**
EMERALD		
Total rate of discontinuations due to AEs	6 (5.2)	4 (3.8)
Gastrointestinal disorders	2 (1.7)	1 (0.9)
Abdominal pain	1 (0.9)	1 (0.9)
Nausea	1 (0.9)	0 (0)
Vomiting	1 (0.9)	0 (0)
General disorders and administration site conditions	1 (0.9)	0 (0)
Fatigue	1 (0.9)	0 (0)
Hepatobiliary disorders	1 (0.9)	0 (0)
Cholecystitis acute	1 (0.9)	0 (0)
Investigations	1 (0.9)	2 (1.9)
Alanine aminotransferase increased	0 (0)	2 (1.9)
Aspartate aminotransferase increased	0 (0)	2 (1.9)
Blood alkaline phosphatase increased	1 (0.9)	1 (0.9)
Gamma-glutamyltransferase increased	1 (0.9)	0 (0)
Metabolism and nutrition disorders	2 (1.7)	0 (0)
Decreased appetite	2 (1.7)	0 (0)
Musculoskeletal and connective tissue disorders	2 (1.7)	2 (1.9)
Arthralgia	1 (0.9)	0 (0)
Back pain	1 (0.9)	0 (0)
Bone lesion	0 (0)	1 (0.9)
Flank pain	0 (0)	1 (0.9)
Neck pain	1 (0.9)	0 (0)
Pathological fracture	1 (0.9)	0 (0)
Nervous system disorders	1 (0.9)	0 (0)
Headache	1 (0.9)	0 (0)
Paraesthesia	1 (0.9)	0 (0)
Psychiatric disorders	1 (0.9)	0 (0)
Depression	1 (0.9)	0 (0)
Insomnia	1 (0.9)	0 (0)
Respiratory, thoracic and mediastinal disorders	1 (0.9)	0 (0)
Pulmonary embolism	1 (0.9)	0 (0)

Table 16: Discontinuations due to AEs – RCT, direct comparison: elacestrant versus treatment of physician's choice selecting from fulvestrant, anastrozole, letrozole and exemestane (multipage table)

Study	**Patients with event n(%)**	
SOC[a] **PT[a]**	**Elacestrant** **N = 115**	**Treatment of physician's choice[b]** **N = 106**

a. MedDRA version 23.0; SOC and PT notation taken without adaptation from the data subsequently submitted by the company.
b. Fulvestrant, anastrozole, letrozole or exemestane according to physician's choice.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Appendix B Graphic display of the time-to-event analyses presented in the benefit assessment (Kaplan-Meier curves)

B.1 Mortality

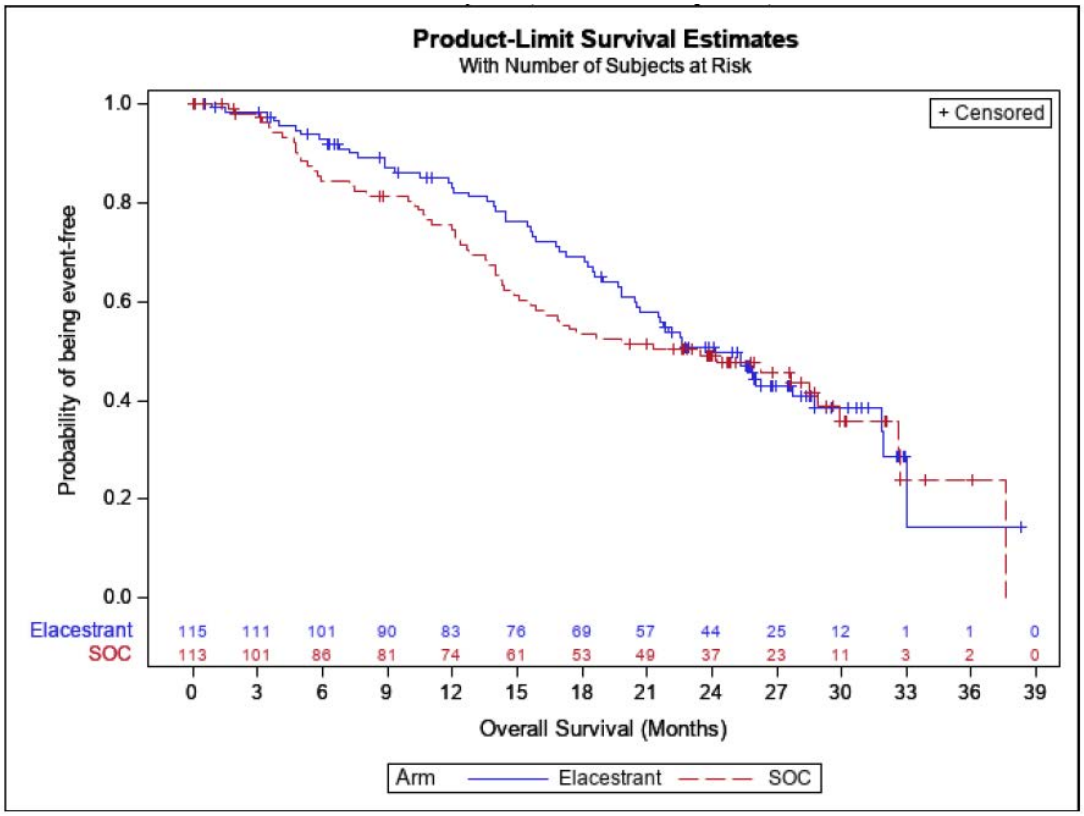

Figure 1: Kaplan-Meier curve, outcome of overall survival (ESR1-mut population)

B.2 Morbidity

Symptoms (EORTC QLQ-C30)

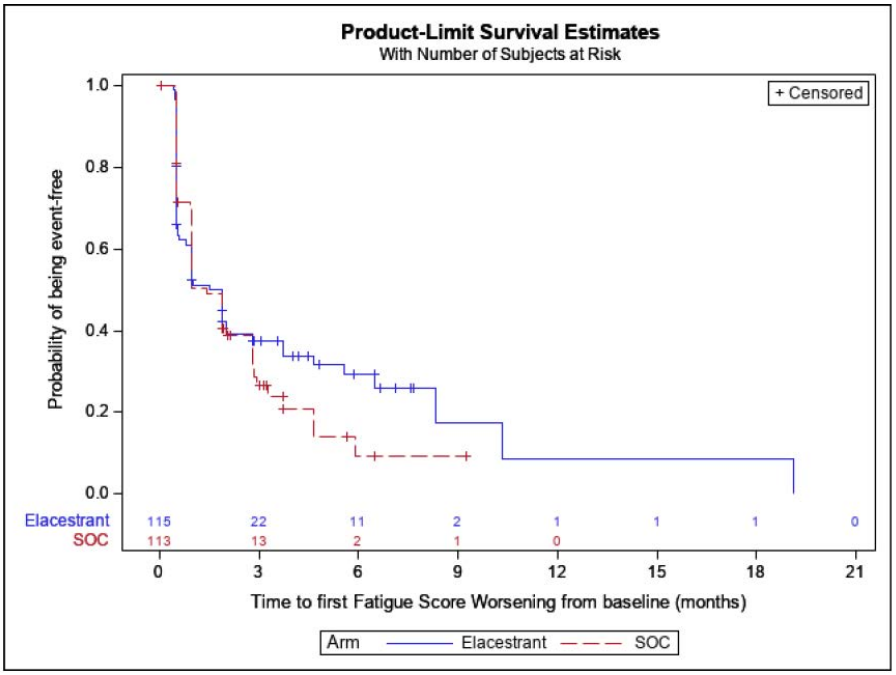

Figure 2: Kaplan-Meier curve for symptoms, outcome of fatigue (EORTC QLQ-C30, first deterioration by ≥ 10 points)

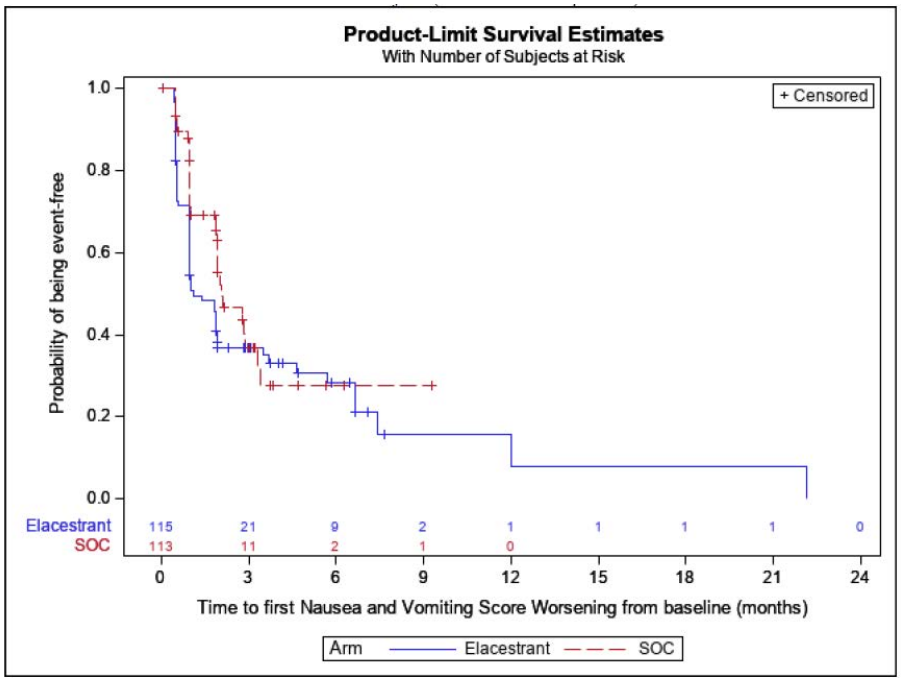

Figure 3: Kaplan-Meier curve for symptoms, outcome of nausea and vomiting (EORTC QLQ-C30, first deterioration by ≥ 10 points)

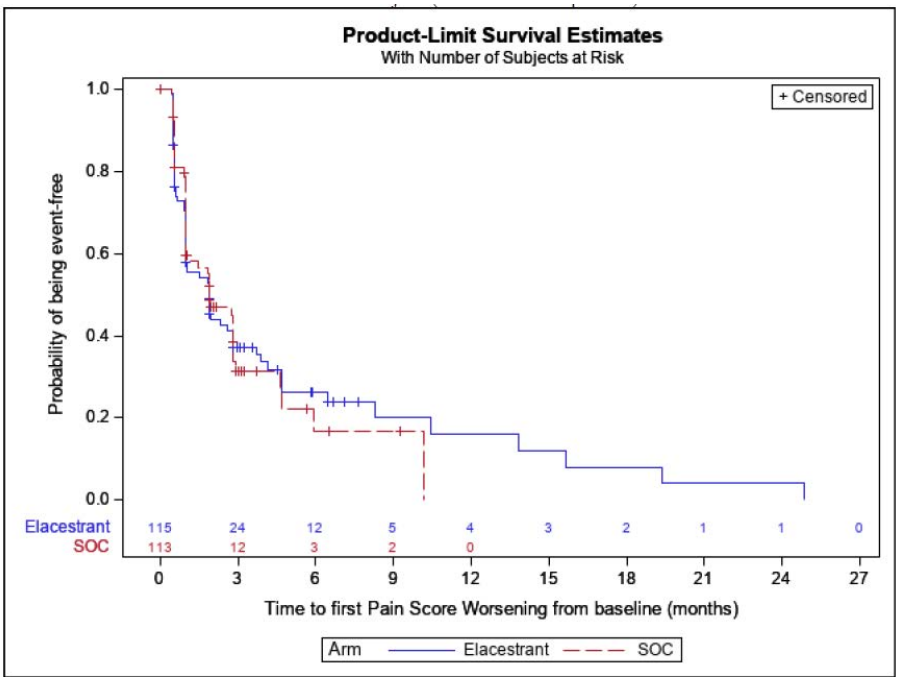

Figure 4: Kaplan-Meier curve for symptoms, outcome of pain (EORTC QLQ-C30, first deterioration by ≥ 10 points)

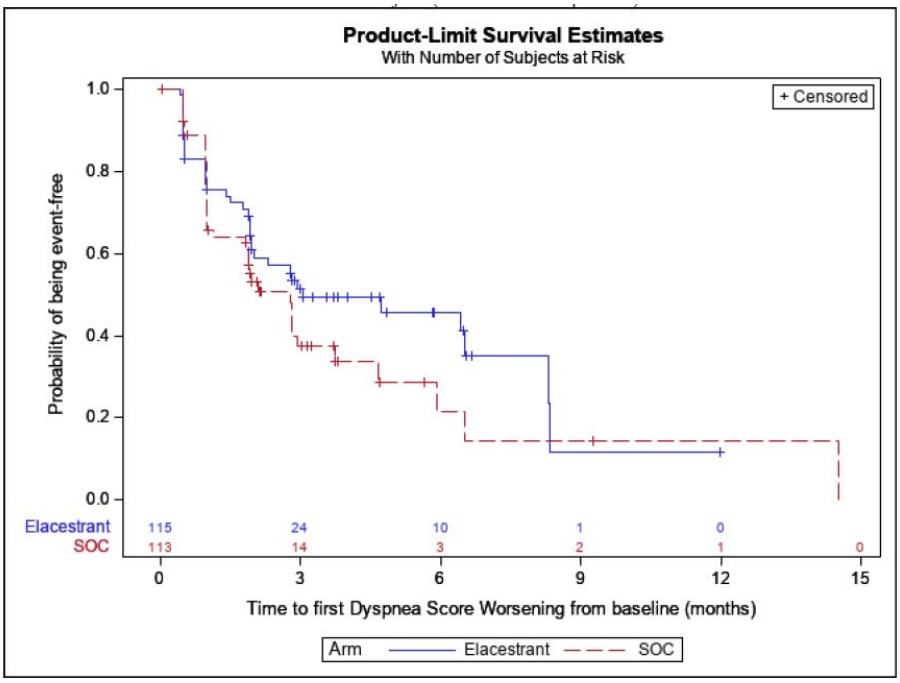

Figure 5: Kaplan-Meier curve for symptoms, outcome of dyspnoea (EORTC QLQ-C30, first deterioration by ≥ 10 points)

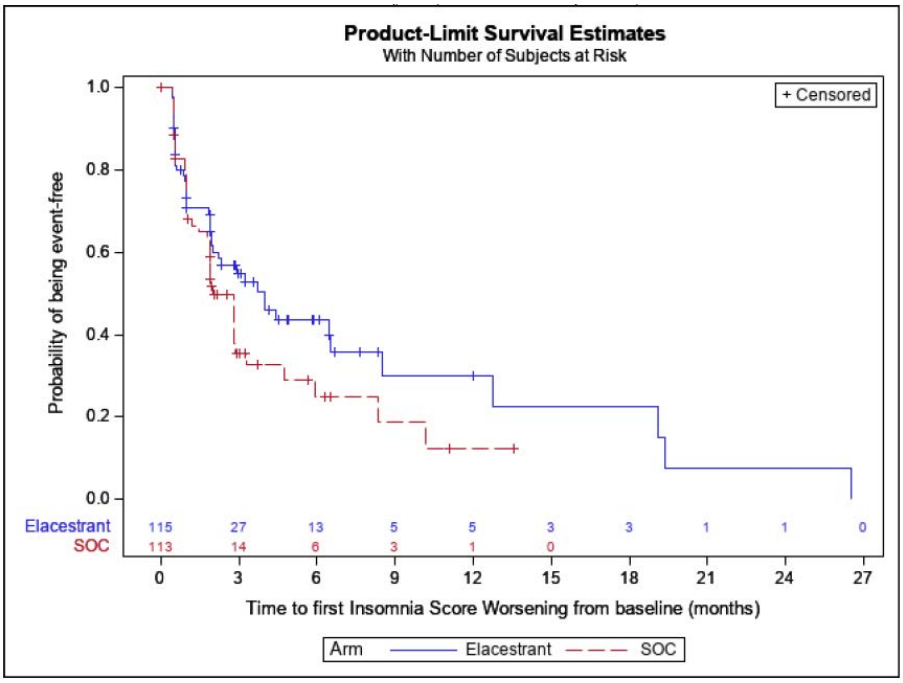

Figure 6: Kaplan-Meier curve for symptoms, outcome of insomnia (EORTC QLQ-C30, first deterioration by ≥ 10 points)

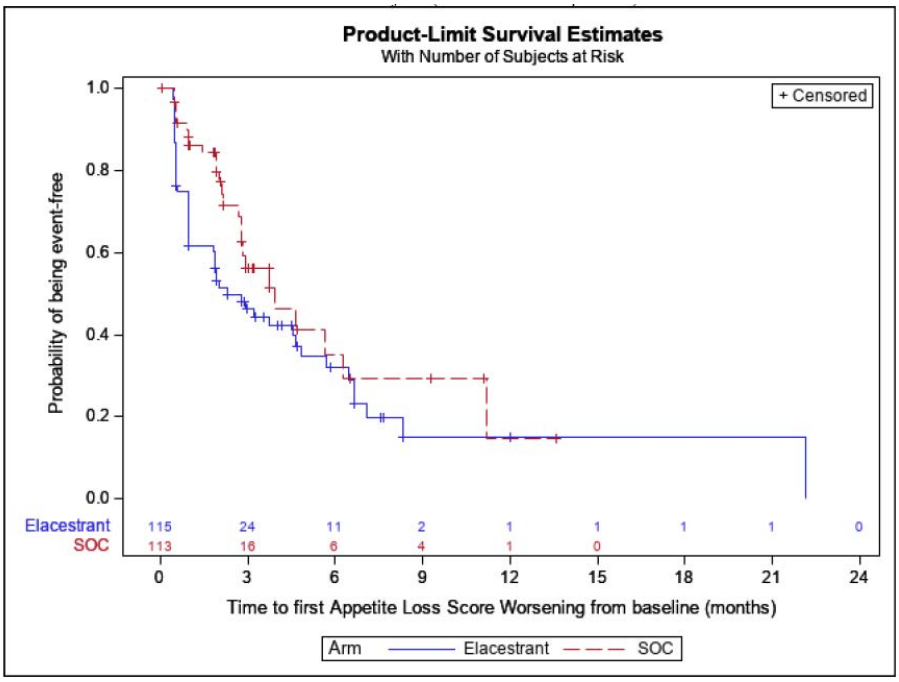

Figure 7: Kaplan-Meier curve for symptoms, outcome of appetite loss (EORTC QLQ-C30, first deterioration by ≥ 10 points)

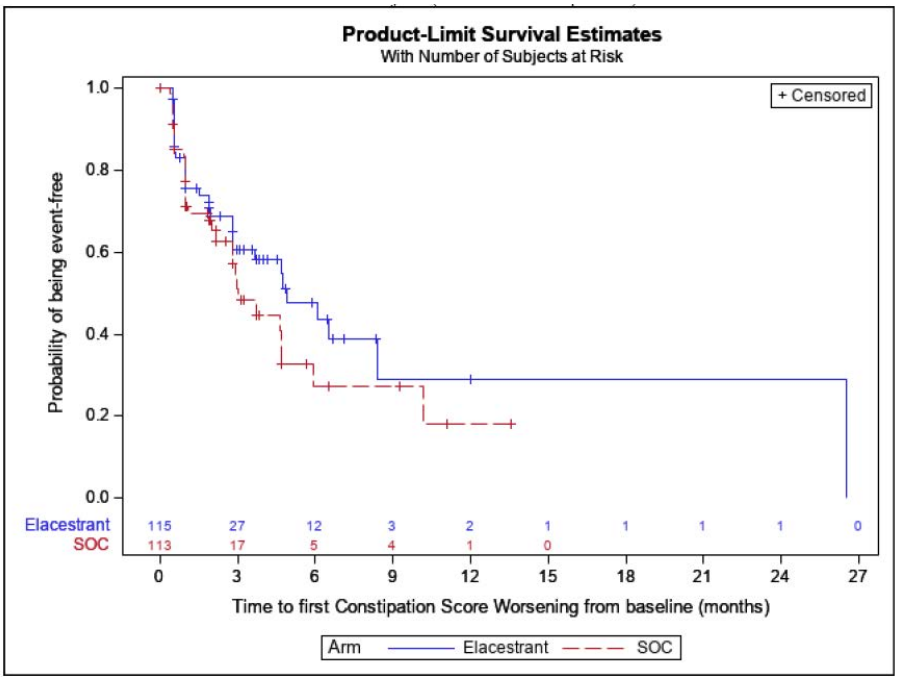

Figure 8: Kaplan-Meier curve for symptoms, outcome of constipation (EORTC QLQ-C30, first deterioration by ≥ 10 points)

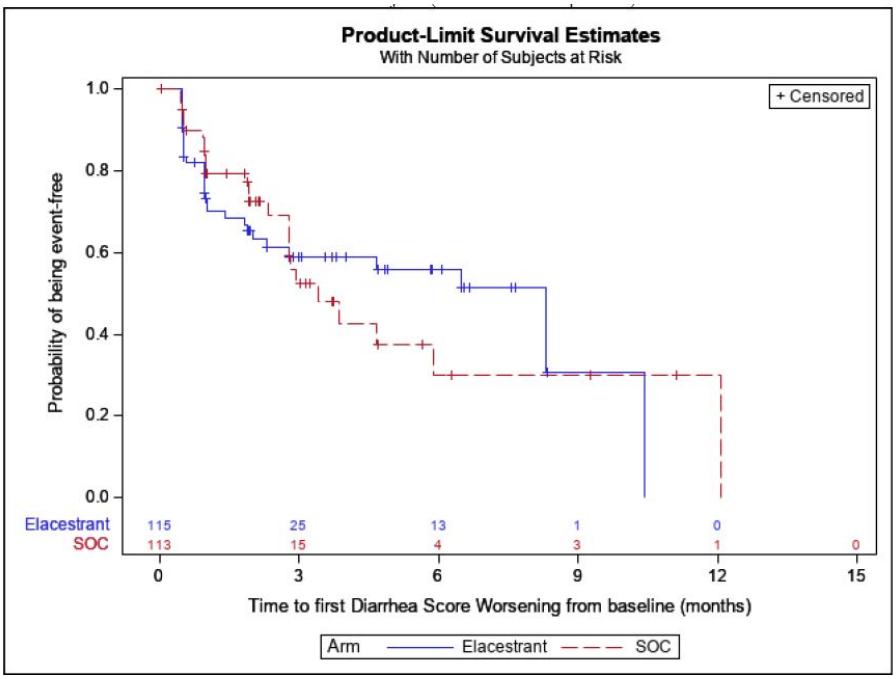

Figure 9: Kaplan-Meier curve for symptoms, outcome of diarrhoea (EORTC QLQ-C30, first deterioration by ≥ 10 points)

Health status (EQ-5D VAS)

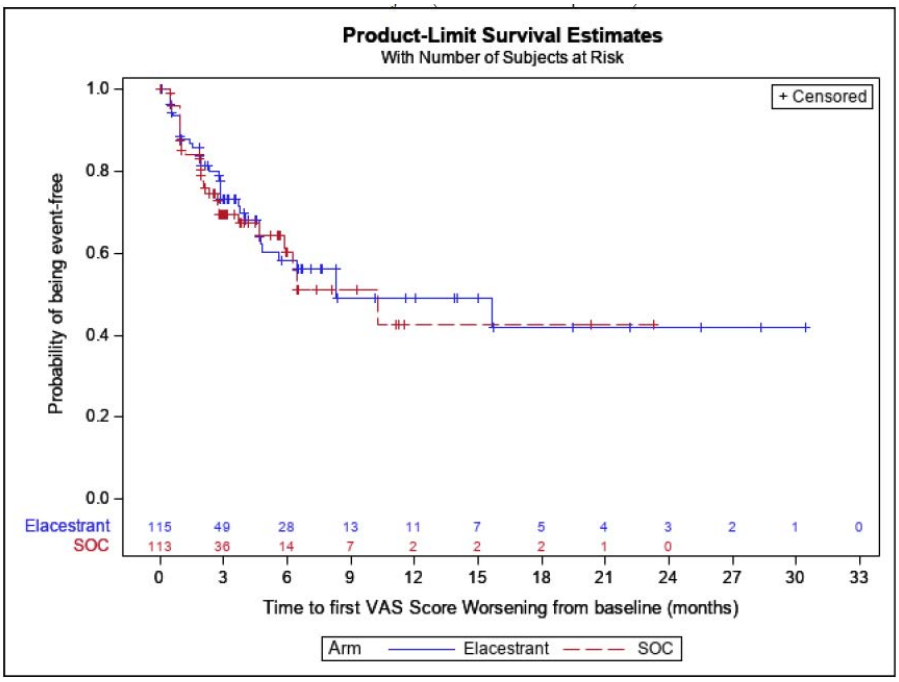

Figure 10: Kaplan-Meier curve, outcome of health status (EORTC QLQ-C30, first deterioration by ≥ 15 points)

B.3 Health-related quality of life

EORTC QLQ-C30

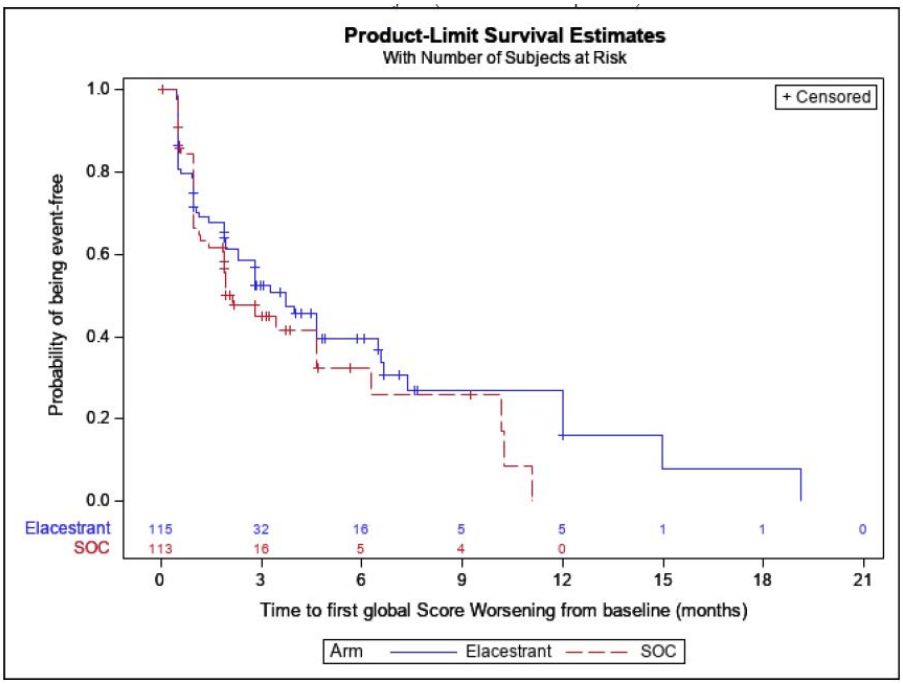

Figure 11: Kaplan-Meier curve for health-related quality of life, outcome of global health status (EORTC QLQ-C30, first deterioration by ≥ 10 points)

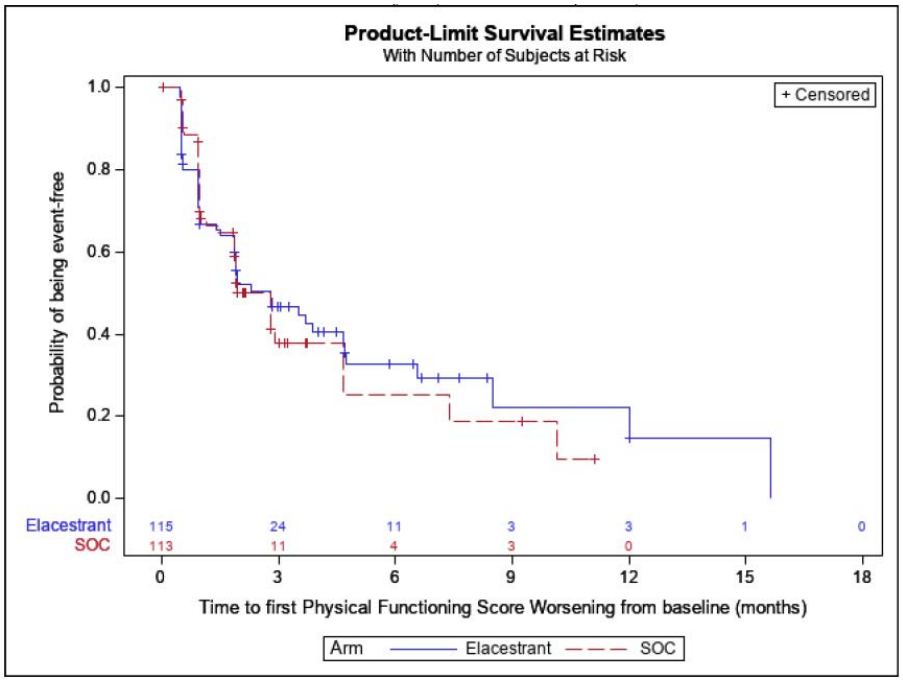

Figure 12: Kaplan-Meier curve for health-related quality of life, outcome of physical functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

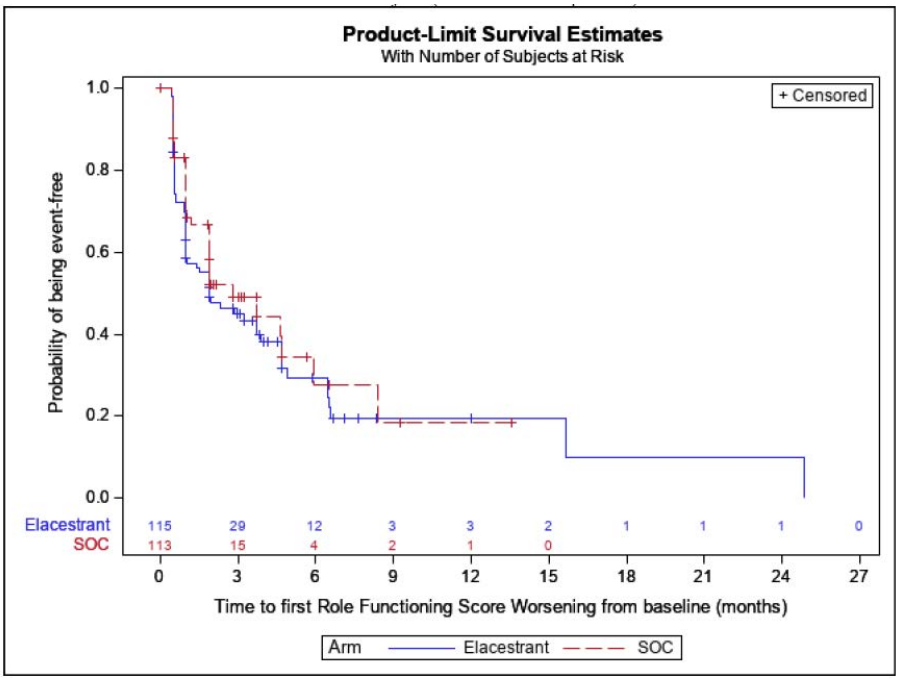

Figure 13: Kaplan-Meier curve for health-related quality of life, outcome of role functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

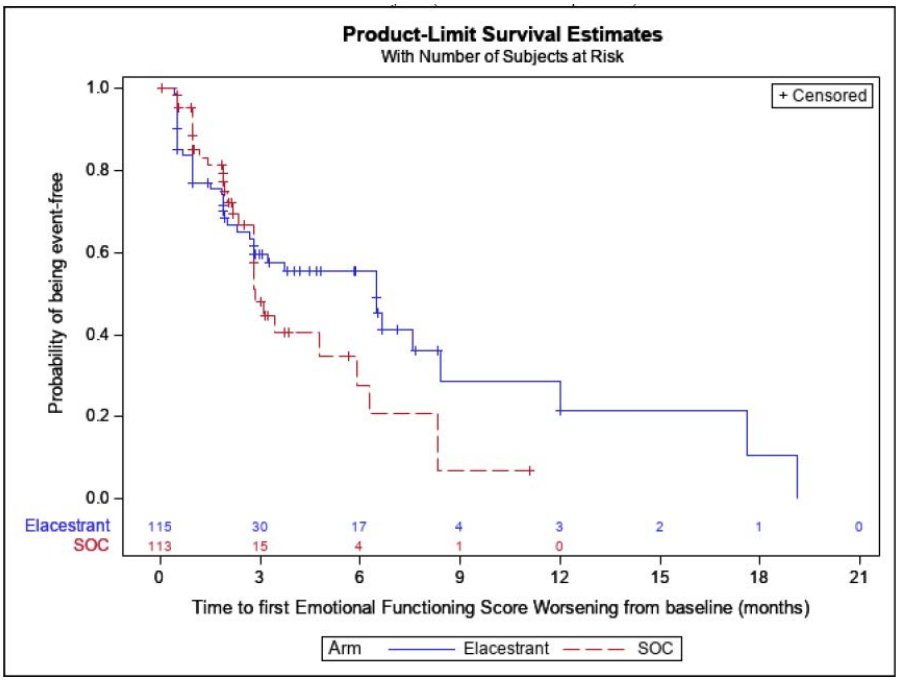

Figure 14: Kaplan-Meier curve for health-related quality of life, outcome of emotional functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

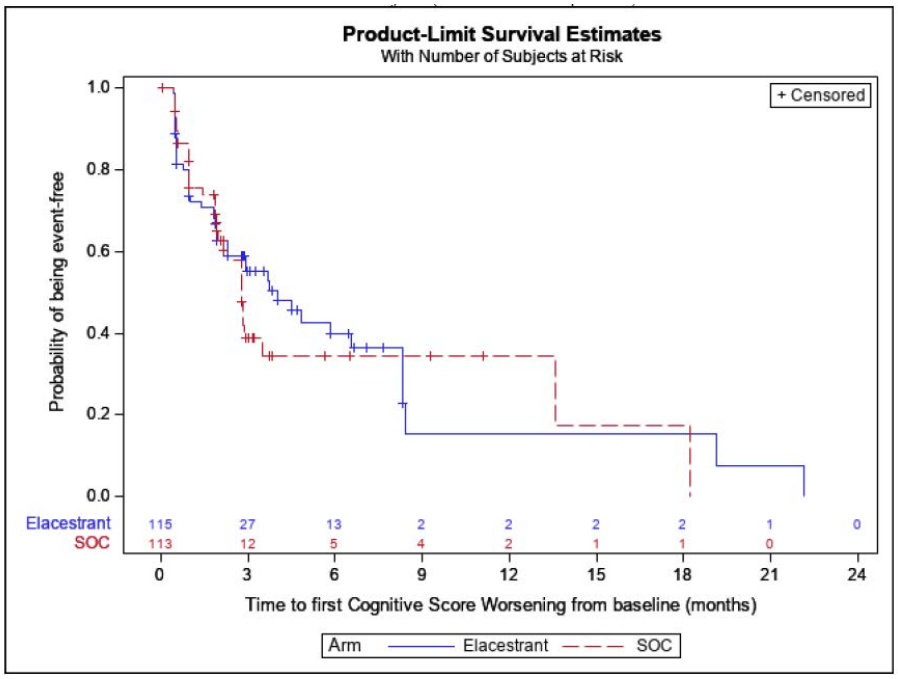

Figure 15: Kaplan-Meier curve for health-related quality of life, outcome of cognitive functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

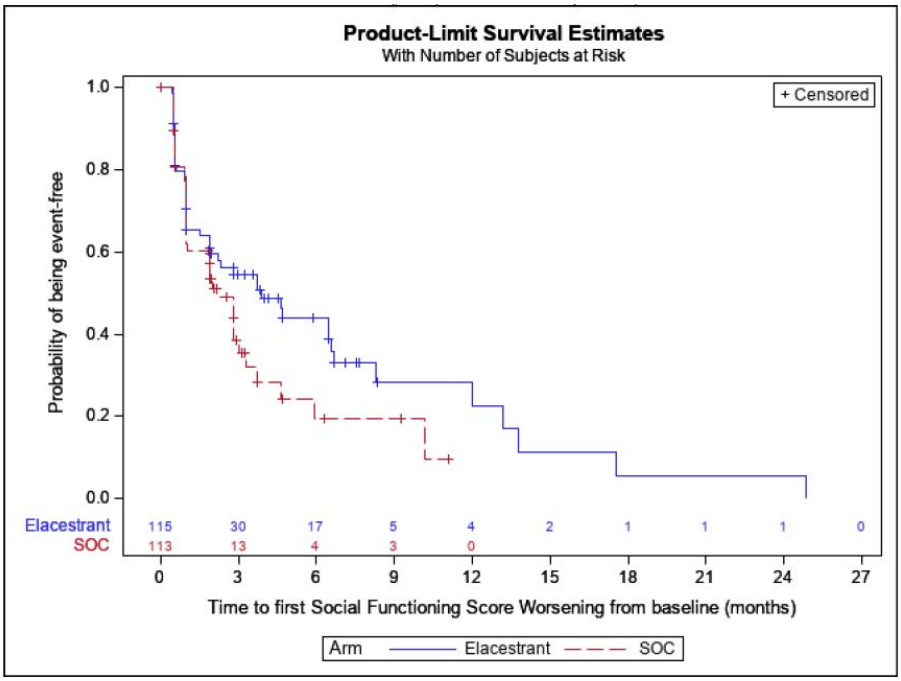

Figure 16: Kaplan-Meier curve for health-related quality of life, outcome of social functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points)

B.4 Side effects

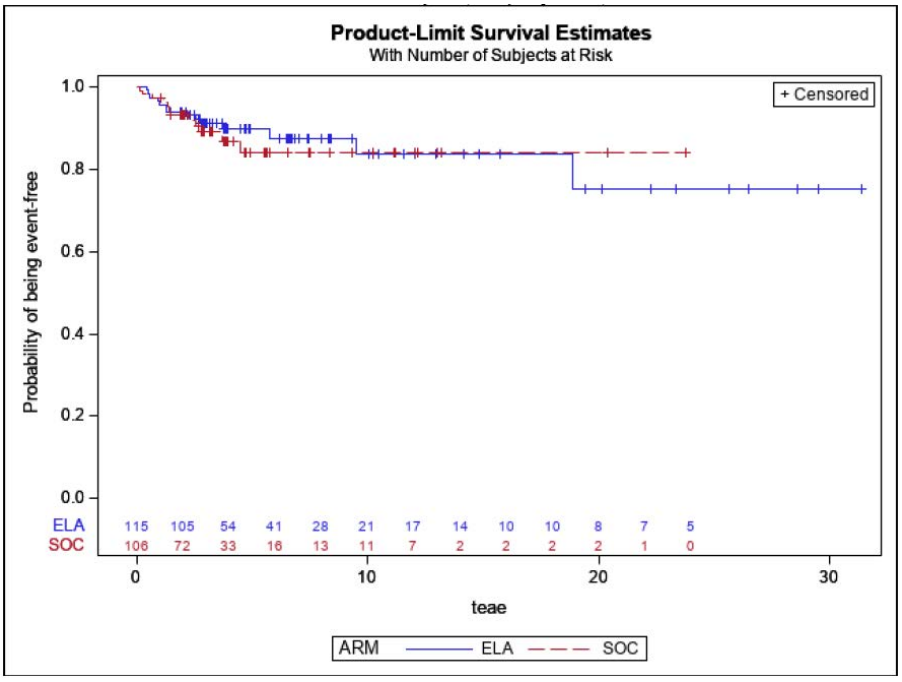

Figure 17: Kaplan-Meier curve, outcome of SAEs

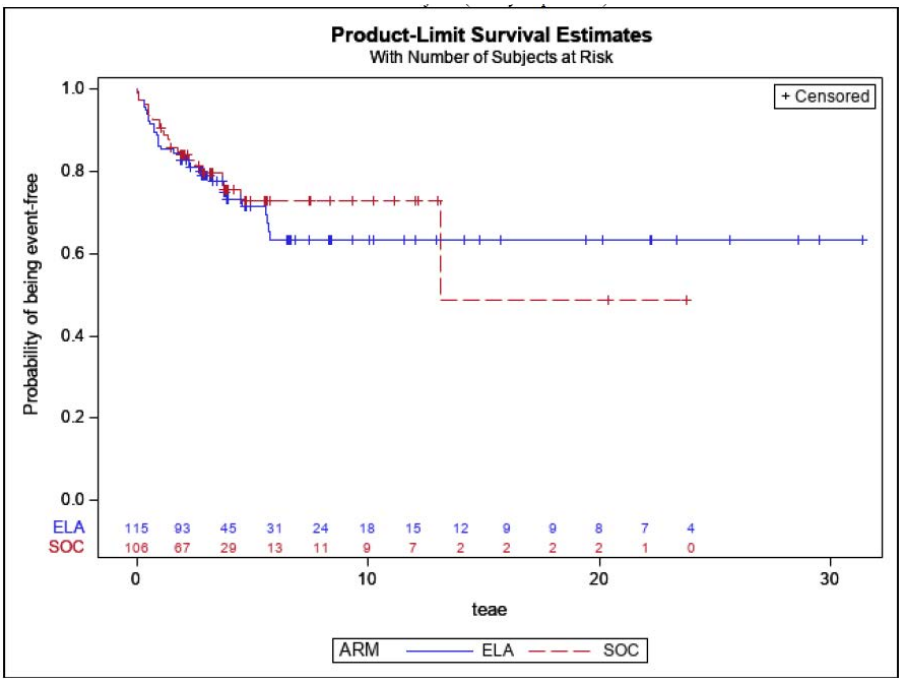

Figure 18: Kaplan-Meier curve, outcome of severe AEs (CTCAE grade ≥ 3)

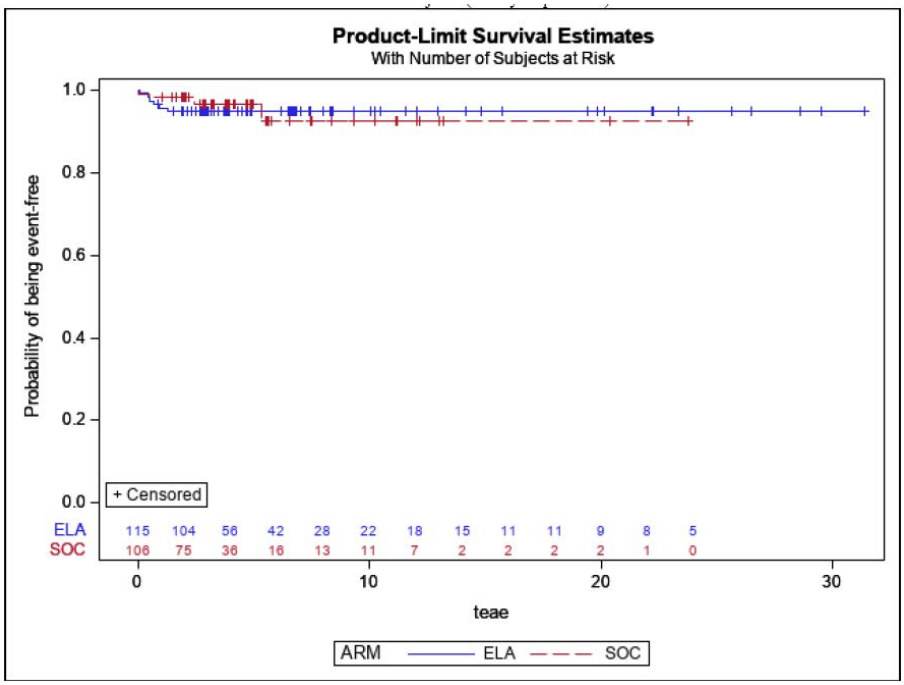

Figure 19: Kaplan-Meier curve, outcome of discontinuation due to AEs

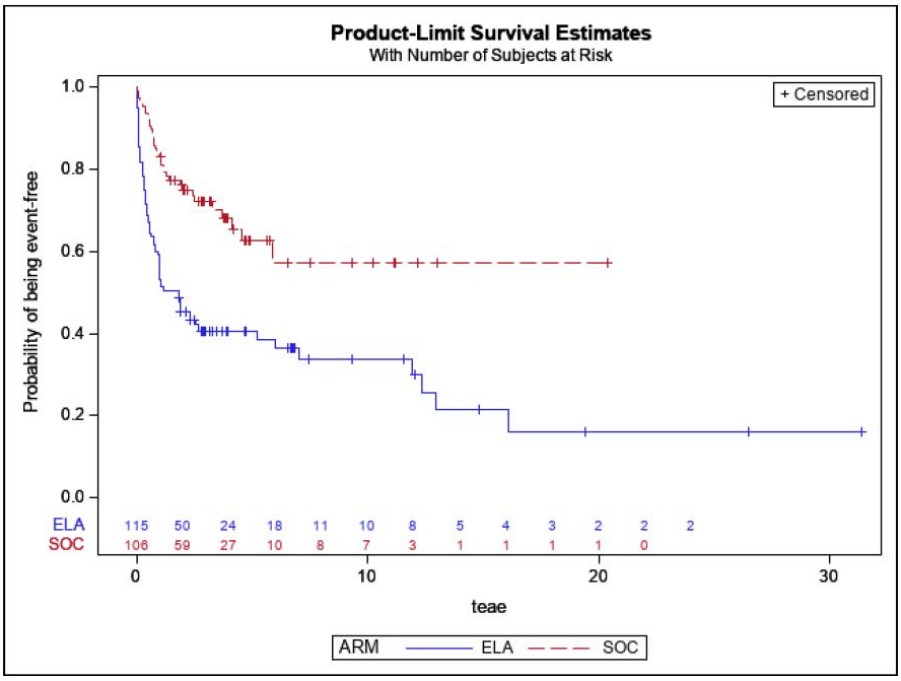

Figure 20: Kaplan-Meier curve, outcome of gastrointestinal disorders (SOC, AEs)

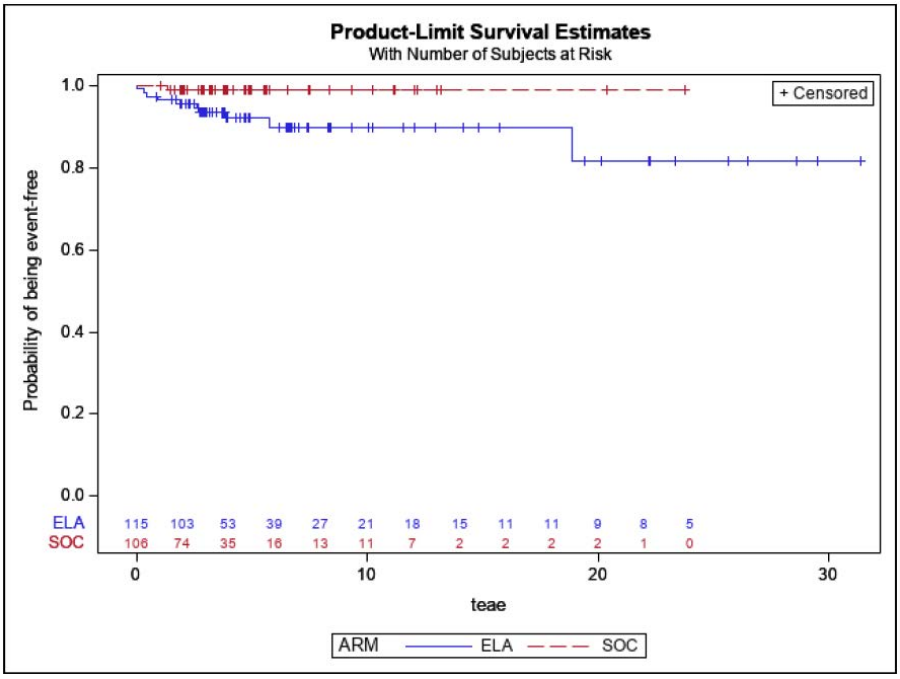

Figure 21: Kaplan-Meier curve, outcome of musculoskeletal and connective tissue disorders (SOC, severe AEs)

B.5 Subgroup analyses

Mortality

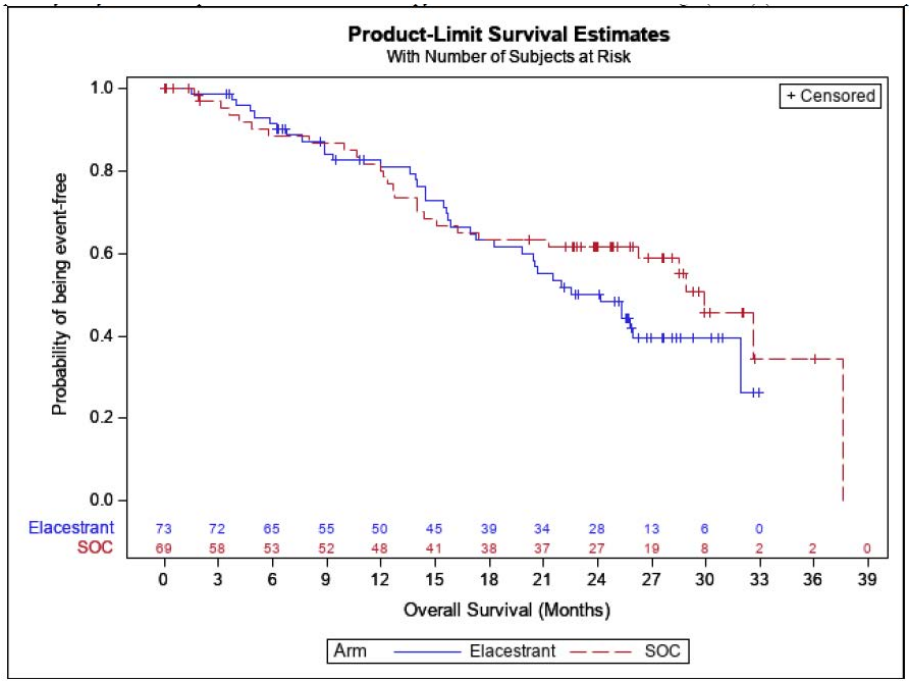

Figure 22: Kaplan-Meier curve, outcome of overall survival, subgroup "1 prior line of endocrine therapy in advanced/metastatic stage"

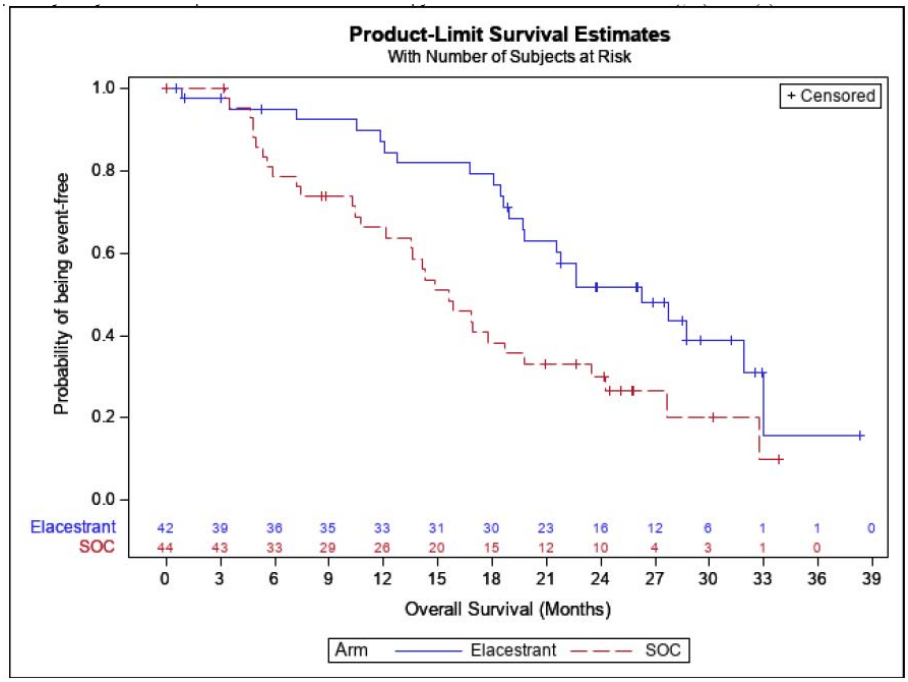

Figure 23: Kaplan-Meier curve, outcome of overall survival, subgroup "2 previous lines of endocrine therapy in advanced/metastatic stage"

Morbidity

Symptoms

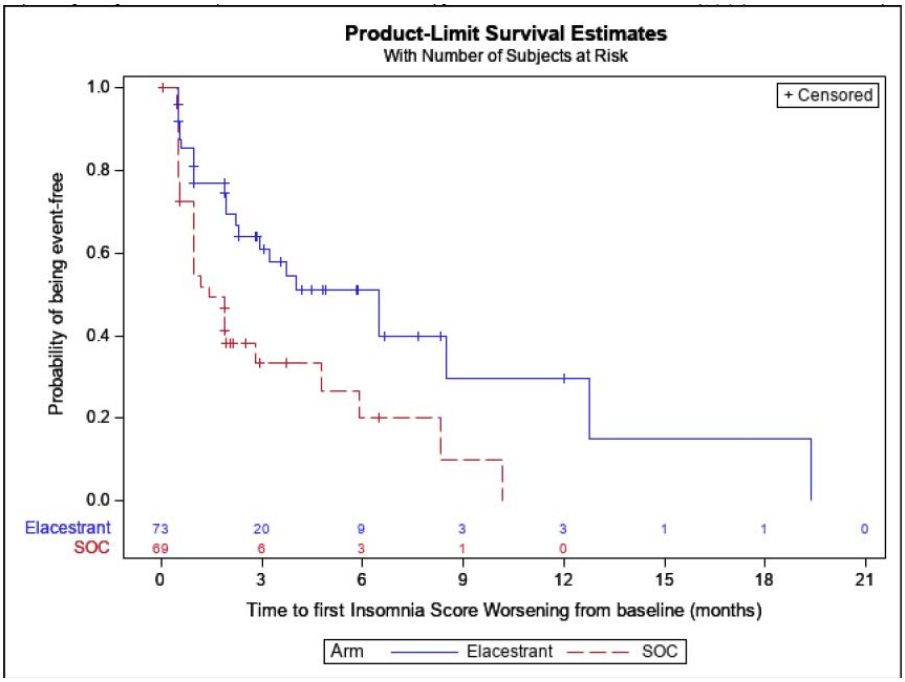

Figure 24: Kaplan-Meier curve, outcome of insomnia (EORTC QLQ-C30, first deterioration by ≥ 10 points), subgroup "1 prior line of endocrine therapy in advanced/metastatic stage"

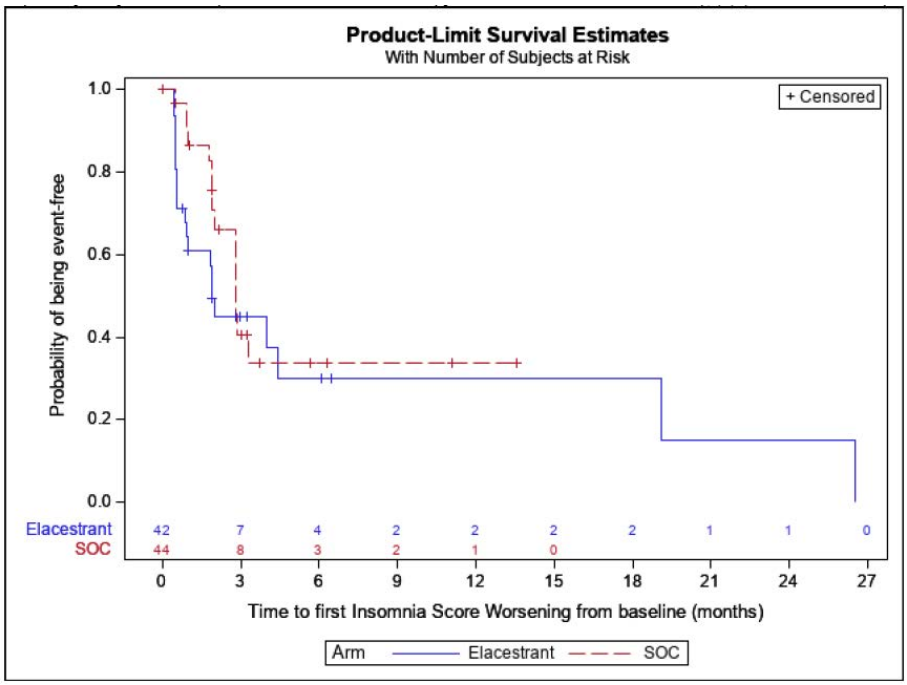

Figure 25: Kaplan-Meier curve, outcome of insomnia (EORTC QLQ-C30, first deterioration by ≥ 10 points), subgroup "2 previous lines of endocrine therapy in advanced/metastatic stage"