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Addendum to Commission A13-33 (enzalutamide)[1]

Addendum

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[2] Due to legal data protection regulations, employees have the right not to be named.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SAE	serious adverse event
WHO	World Health Organization

1 Background

On 23 January 2014 the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for commission A13-33 (benefit assessment of enzalutamide [1]).

In the commenting procedure on the assessment of enzalutamide, on 19 December 2013, the pharmaceutical company (hereinafter abbreviated to "the company") submitted further data to the G-BA [2] that went beyond the information in the dossier [3]. These were data on the AFFIRM study on the comparison of enzalutamide + best supportive care (BSC) versus BSC. This study was already contained in the company's dossier and was included as relevant in the dossier assessment A13-33. For the outcomes on adverse events (AEs), however, the data presented in the dossier were either not evaluable or could only be interpreted in qualitative terms. With the comments, the company subsequently submitted new analyses, which, from the company's point of view, allow to assess the AEs. Moreover, it was unclear in the assessment on the basis of the information presented in the dossier whether the administration of analgesics in the first 13 weeks of the AFFIRM study was optimized for the individual patient in the sense of the appropriate comparator therapy (ACT) BSC. In the comment, the company submitted additional data on the treatment with analgesics in the first 13 weeks of the AFFIRM study, which, from the point of view of the company, prove that the ACT was adequately implemented.

The G-BA commissioned IQWiG with the assessment of these analyses subsequently submitted for the AFFIRM study in the commenting procedure.

In the following Chapter 2 the additional analyses for the AFFIRM study are assessed according to the commission. The extent and probability of added benefit of enzalutamide are then described under consideration of the analyses subsequently submitted.

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

2 Assessment

2.1 Selection of analyses for the benefit assessment

On the one hand, the company presented additional analyses on the administration of analgesics in the AFFIRM study in its comment [2]. These are assessed in the present addendum with regards to the adequate implementation of the ACT BSC in the AFFIRM study.

On the other hand, the company presented analyses on AEs on the basis of the time to first event, as proposed in the assessment A13-33 [1], in its comment. Of these, relevant data were only available for the outcomes "serious AEs (SAEs) and "severe AEs" (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3).

In contrast, the analyses presented for the outcome "treatment discontinuations due to AEs" were not relevant. As described in the dossier assessment A13-33, 2 different operationalizations for this outcome were available in the company's dossier, in each case on the basis of naive proportions. On the one hand, this was an analysis of those patients, in whom the AE was described by the investigator as primary reason for the discontinuation of the treatment. On the other hand, this was an analysis of those patients who had experienced an AE that had led to study discontinuation, irrespective of whether or not this was described by the investigator as primary reason for the discontinuation. Since all treatment discontinuations due to AEs were in fact only recorded with the second operationalization, only this one was included in the dossier assessment A13-33 (for more details, see dossier assessment A13-33, Section 2.7.2.4.3 [1]). With the comment, the company subsequently submitted an analysis on the basis of the time to first event for the outcome "treatment discontinuations due to AEs", but this was only based on the first (irrelevant) operationalization. The company neither justified why it regarded this operationalization to be suitable nor did it subsequently submit an analysis of the other operationalization as additional information. Hence it could also not be assessed whether the results of the 2 analyses differ from each other. The analyses on the outcome "treatment discontinuation due to AE" were not considered in the present addendum. Additionally it should be noted that this would not influence the overall conclusion on added benefit.

2.2 Risk of bias

Table 1 shows the risk of bias at study level (for reasons see dossier assessment A13-33 [1]), as well as the risk of bias of the results on the outcomes "SAEs" and "severe AEs" (CTCAE grade ≥ 3) subsequently submitted by the company.

Table 1: Risk of bias at study and outcome level – RCT, direct comparison: enzalutamide + BSC vs. placebo + BSC

Study	Study level	Outcomes	
		Serious adverse events	Severe adverse events (CTCAE grade ≥ 3)
AFFIRM	Low	High[a]	High[a]
a: High risk of bias due to possible informative censoring and high proportion of censored observations. BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; RCT: randomized controlled trial; vs.: versus			

The risk of bias at study level was low. The company subsequently submitted survival time analyses (Cox regression) for the outcomes on AEs. AEs were recorded up to 30 days after the end of treatment. The study treatment was continued until the withdrawal of consent, the occurrence of safety concerns or the occurrence of disease progression. The main reason for treatment discontinuation was disease progression. In the AFFIRM study, 441 (55.1%) patients in the enzalutamide arm, and 296 (74.2%) patients in the placebo arm discontinued treatment due to disease progression. Patients without event until treatment discontinuation were censored at the time point of the last evaluable observation. Due to the possible association between disease progression and AEs, there were probably informative censorings, which occurred at different frequencies because disease progression occurred less frequently and later in the enzalutamide arm. The results for the outcomes on AEs were therefore rated overall as potentially highly biased. Since strength and direction of the association between disease progression and AEs were unclear, however, no conclusion could be drawn on the direction of the bias.

2.3 Results

Implementation of the appropriate comparator therapy in the AFFIRM study

It was described in the dossier assessment A13-33 that it remained unclear from the information presented in the dossier whether the BSC treatment was adequately implemented in the AFFIRM study. This mainly referred to the restrictions in pain therapy in the first 13 weeks after the start of the treatment described in the study protocol. Hence it was unclear from the information available in the dossier whether the AFFIRM study sufficiently represented the research question of the benefit assessment of enzalutamide + BSC versus BSC. Because of this, the probability of an added benefit for the study was reduced overall by one level, so that at the most “hints”, e.g. of an added benefit, could be derived on the basis of the study.

With the comment, the company subsequently submitted analyses on the patients' concomitant use of analgesics in the first 13 weeks after the start of the treatment. The analgesics most commonly administered in the study are presented in the following Table 2.

Table 2: Most common (≥ 10% in at least one treatment arm) concomitant treatments with analgesics in the AFFIRM study in the first 13 weeks after the start of the treatment

Study Analgesic	**Enzalutamide + BSC** **N = 800**	**Placebo + BSC** **N = 399**
	Patients with concomitant administration of analgesics **n (%)**	**Patients with concomitant administration of analgesics** **n (%)**
AFFIRM		
Total analgesics	603 (75.4)	318 (79.7)
paracetamol	350 (43.8)	181 (45.4)
oxycodone hydrochloride	108 (13.5)	73 (18.3)
morphine sulfate	91 (11.4)	56 (14.0)
fentanyl	82 (10.3)	63 (15.8)
oxycodone	55 (6.9)	45 (11.3)
panadeine co (codeine phosphate, paracetamol)	52 (6.5)	47 (11.8)
BSC: best supportive care		

It could be observed from the data subsequently submitted in the comment that the overall proportion of patients who had concomitant administration of analgesics was higher in the placebo arm of the AFFIRM study also in the first 13 weeks. With regards to individual analgesics, this particularly referred to highly potent analgesics according to step 3 of the World Health Organization's (WHO) pain relief ladder. This was rated as sufficient evidence that individual pain therapy in the sense of BSC was also conducted in the first 13 weeks.

Overall, on the basis of the data of the AFFIRM study subsequently submitted with the company's comment, the ACT was considered to be adequately implemented. Hence the derivation of indications, e.g. of an added benefit, is possible on the basis of the results of the AFFIRM study.

Adverse events

The results on the comparison of enzalutamide + BSC with BSC for the analyses on AEs subsequently submitted with the comment are summarized in Table 3. The Kaplan-Meier curves on these outcomes can be found in Appendix B.

Table 3: Results on AEs – RCT, direct comparison: enzalutamide + BSC vs. placebo + BSC

Study Outcome	Enzalutamide + BSC		Placebo + BSC		Enzalutamide + BSC vs. placebo + BSC
	N	Median time to event in months [95% CI]	N	Median time to event in months [95% CI]	HR[a] [95% CI]; p-value
AFFIRM					
Adverse events					
Severe AEs (CTCAE grade ≥ 3)	800	12.6 [10.5; 17.3]	399	4.2 [3.4; 5.1]	0.55 [0.46; 0.66]; p < 0.001[b]
SAEs	800	NA [17.3; NA]	399	7.8 [6.2; 11.1]	0.51 [0.42; 0.63]; p < 0.001[b]

a: The company cited the effect measure for the analyses subsequently submitted in the text of the comment in each case as relative risk. However, this was designated as hazard ratio in the figures of the Kaplan-Meier curves provided. In each case, the numbers in the text correspond to the ones in the figures.
b: P-value from log-rank test.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of randomized patients; NA: not achieved; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Serious adverse events, severe adverse events (CTCAE grade ≥ 3)

Both with regards to SAEs and to severe AEs (CTCAE grade ≥ 3), a statistically significant difference in favour of enzalutamide + BSC was shown on the basis of the time to first event. The risk of bias was rated as high for both outcomes. The direction of the possible bias was unclear. This provides a hint of lesser harm of enzalutamide + BSC compared with BSC for each of the outcomes "SAEs" and "severe AEs" (CTCAE grade ≥ 3). The results subsequently submitted by the company in the commenting procedure and assessed in the present addendum were used for SAEs and severe AEs. The results presented in the dossier assessment A13-33 were used for all remaining outcomes [1].

2.4 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the General Methods of IQWiG [4].

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

2.4.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 of the dossier assessment A13-33 [1] and in Section 2.3 of the present addendum resulted in an indication of an effect modification for each of the subgroup characteristics "age" (< 65, ≥ 65 years) and "visceral metastases" (yes versus no) at the start of the study for the outcomes "time to first skeletal-related complication" and

"overall survival". On the basis of these results, the extent of the added benefit in each case was assessed at outcome level. In the overall assessment, it was then investigated whether different conclusions on the extent of added benefit arise for the individual patient groups.

The following Table 4 is an update of Table 14 of the assessment A13-33, which was supplemented with the results considered in the present addendum.

Table 4: Extent of added benefit at outcome level: enzalutamide + BSC versus BSC

Outcome category **outcome** effect modifier subgroup	**Enzalutamide + BSC vs. placebo + BSC** **median time to event or proportion of events or MD[a]** **effect estimates [95% CI]** **p-value** **probability[b]**	**Derivation of extent[c]**
Mortality		
Overall survival	Median: 18.4 vs. 13.6 months HR: 0.63 [0.53; 0.75] p < 0.001 probability: "indication"	Outcome category: survival time $CI_u < 0.85$ added benefit, extent: "major"[d]
Visceral metastases		
yes	Median: 13.4 vs. 9.5 months HR: 0.78 [0.56; 1.09] p = 0.148 probability: "hint"	Outcome category: survival time added benefit, extent: "non-quantifiable"
no	Median: NA vs. 14.2 months HR: 0.57 [0.46; 0.70] p < 0.001 probability: "indication"	Outcome category: survival time $CI_u < 0.85$ added benefit, extent: "major"
Morbidity		
Time to first skeletal-related complication	Median: 16.7 vs.13.3 months HR: 0.69 [0.57; 0.84] p < 0.001 probability: "indication"	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"[d]
Age (years)		
< 65	Median: 14.4 vs. 8.6 months HR: 0.60 [0.44; 0.83] p = 0.002 probability: "indication"	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
≥ 65	Median: 18.7 vs. 15.0 months HR: 0.77 [0.60; 0.99] p = 0.04 probability: "indication"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Time to pain progression[e]	25% quantile[f]: 11.0. vs. 4.6 months HR: 0.56 [0.41; 0.78] p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications[g] $CI_u < 0.80$ added benefit, extent: "considerable"

(continued)

Table 4: Extent of added benefit at outcome level: enzalutamide + BSC versus BSC (continued)

Outcome category **outcome** effect modifier subgroup	**Enzalutamide + BSC vs. placebo + BSC** **median time to event or proportion of events or MD[a]** **effect estimates [95% CI]** **p-value** **probability[b]**	**Derivation of extent[c]**
Morbidity, continued		
Change in pain intensity[h]	MD: -0.99 [-1.29; -0.69] SMD: -0.48 [-0.62; -0.34][i] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications[j] added benefit, extent: "non-quantifiable"
Paralyses and paralysis-related urinary incontinence	No evaluable results available	Lesser benefit/added benefit not proven
Health-related quality of life		
FACT-P	No evaluable results available	Lesser benefit/added benefit not proven
EQ-5D	No evaluable results available	Lesser benefit/added benefit not proven
Adverse events		
SAEs	Median: NA vs. 7.8 months HR: 0.51 [0.42; 0.63] $p < 0.001$ probability: "hint"	Outcome category: serious/severe AEs $CI_u < 0.75$ lesser harm, extent: "major"
Treatment discontinuations due to AEs	Qualitative interpretation on the basis of the naive proportions of patients with AEs[k]	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	Median: 12.6 vs. 4.2 months HR: 0.55 [0.46; 0.66] $p < 0.001$ probability: "hint"	Outcome category: serious/severe AEs $CI_u < 0.75$ lesser harm, extent: "major"
Seizures	No evaluable results available	Greater/lesser harm not proven

(continued)

Table 4: Extent of added benefit at outcome level: enzalutamide + BSC versus BSC (continued)

a: Mean difference week 13 minus baseline value.
b: Probability given, if statistically significant differences are present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: Despite the indication of effect modification, the results for the total population are shown because they are relevant in the derivation of added benefit in respect of the subgroup characteristics "age" and "presence of visceral metastases".
e: Recorded on the basis of the following question from the FACT-P: "I have pain", which was answered by the patients using a 5-point scale from 0 to 4 points (0 = no pain to 4 = very much pain).
f: The 25% quantile is the time at which 25% of the patients have an event (Kaplan-Meier estimator). The median time to the event or the associated CI could not be estimated, because at the analysis time point less than 50% of patients in the enzalutamide arm had had an event.
g: The outcome category (non-serious/non-severe symptoms/late complications) was determined on the basis of the change in pain intensity. This assessment concurs with that of the company.
h: Recorded on the basis of question 3 of the BPI-SF: assessment of the worst pain within the last 24 hours on an 11-point scale from 0 (no pain) to 10 (worst pain imaginable).
i: Standardized effect without definition of the standardization.
j: The outcome category (non-serious/non-severe symptoms/late complications) was determined from the mean pain score at week 13. This assessment concurs with that of the company.
k: The naive proportions of the patients with events are presented in Appendix A, Table 22, of assessment A13-33 [1].

AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; MD: mean difference; NA: not achieved; SAE: serious adverse event; SMD: standardized mean difference; vs.: versus

The results showed that for the characteristic "visceral metastases" a relevant effect modification was present for the outcome "overall survival". The same applied to the characteristic "age" for the outcome "time to first skeletal-related complication". In both cases, consideration of the individual subgroups produced a different extent of added benefit at outcome level. Both for patients with and without visceral metastases as well as for the 2 age groups, the conclusions on added benefit are therefore considered separately at first.

2.4.2 Overall conclusion on added benefit

The derivation of the overall conclusion on added benefit is presented below. This is done separately for the 2 relevant subgroup characteristics "visceral metastases" and "age".

2.4.2.1 Subgroup characteristic "visceral metastases"

The summary of results that determined the overall conclusion on added benefit is shown in Table 5. The subgroup effects by the characteristic "visceral metastases" were initially disregarded, in that only those effects were shown in which no indication or proof of an effect modification by the characteristic "visceral metastases" was provided. Thereafter, it was investigated whether different conclusions for patients with or without visceral metastases arose if the results on overall survival were taken into account.

Table 5: Positive and negative effects from the assessment of enzalutamide + BSC compared with BSC on the basis of outcomes in which there was no effect modification by the characteristic “visceral metastases”

Positive effects	**Negative effects**
Indication of an added benefit – extent: “considerable” (serious late complications: time to first skeletal-related complication)	—
Indication of an added benefit – extent: “considerable” (non-serious/non-severe symptoms/time to pain progression)	
Hint of an added benefit – extent: “non-quantifiable” (non-serious/non-severe symptoms: change in pain intensity)	
Hint of lesser harm – extent: “major” (serious/severe AEs: severe AEs [CTCAE grade ≥ 3])	
Hint of a lesser harm – extent: “major” (SAEs)	
AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event	

Overall, only positive effects of different probability remain at outcome level on the basis of the available and evaluable results. These were shown in the outcome categories “mortality”, “serious/severe symptoms/late complications”, “serious/severe AEs” and “non-serious/non-severe symptoms/late complications”. For the outcomes “SAEs” and “severe AEs” (CTCAE grade ≥ 3), the extent is “major” with the probability “hint”. Overall, without consideration of the results that showed an indication of an effect modification by the characteristic “visceral metastases”, there is first of all a hint of a major added benefit of enzalutamide + BSC compared with BSC.

For patients with visceral metastases, there is also a hint of a non-quantifiable added benefit for the outcome “overall survival”. This did not lead to a change of the overall conclusion (hint of a major added benefit). For patients without visceral metastases, there is also an indication of a considerable added benefit for the outcome “overall survival”. This also changes the overall conclusion on added benefit for these patients to an indication of a major added benefit.

In summary, for patients with metastatic castration-resistant prostate cancer and visceral metastases, whose disease has progressed on or after docetaxel chemotherapy, there is a hint of a major added benefit of enzalutamide + BSC compared with the ACT BSC. For patients with metastatic castration-resistant prostate cancer without visceral metastases, whose disease has progressed on or after docetaxel chemotherapy, there is an indication of a major added benefit of enzalutamide + BSC compared with the ACT BSC.

2.4.2.2 Subgroup characteristic "age" (< 65 years versus ≥ 65 years)

The summary of results that determined the overall conclusion on added benefit is shown in Table 6. The subgroup effects by the characteristic "age" were initially disregarded, in that only those effects in which no indication or proof of an effect modification by the characteristic "age" were shown. Thereafter, it was investigated whether different conclusions for the 2 age groups arose if the results on time to first skeletal-related complication were taken into account.

Table 6: Positive and negative effects from the assessment of enzalutamide + BSC compared with BSC on the basis of outcomes in which there was no effect modification by age

Positive effects	**Negative effects**
Indication or hint of an added benefit – extent "major" (survival time: all-cause mortality)	—
Indication of an added benefit – extent: "considerable" (non-serious/non-severe symptoms/time to pain progression)	
Hint of an added benefit – extent: "non-quantifiable" (non-serious/non-severe symptoms: change in pain intensity)	
Hint of lesser harm – extent: "major" (serious/severe AEs: severe AEs [CTCAE grade ≥ 3])	
Hint of a lesser harm – extent: "major" (SAEs)	
AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event	

Overall, only positive effects of different probability remain at outcome level on the basis of the available and evaluable results. These were shown in the outcome categories "mortality", "serious/severe symptoms/late complications", "serious/severe AEs" and "non-serious/non-severe symptoms/late complications". The indication of a major added benefit in terms of overall survival is decisive for the derivation of the overall conclusion on added benefit. Overall, without consideration of the results in which an indication of an effect modification by the characteristic "age" was produced, there is first of all an indication or hint of a major added benefit of enzalutamide + BSC compared with BSC.

For patients < 65 years there is also an indication of a considerable added benefit and for patients ≥ 65 years an indication of a minor added benefit, in each case for the outcome "time to first skeletal-related complication". In neither case does this have any effect on the overall result (indication or hint of a major added benefit).

Overall the characteristic "age" has no influence on the overall conclusion on added benefit.

2.4.3 Extent and probability of added benefit – summary

For patients with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel chemotherapy, in the 2 subgroups of patients with and without visceral metastases there is an added benefit of enzalutamide + BSC compared with the ACT BSC as shown in Table 7.

Table 7: Patient groups, ACT and extent and probability of added benefit of enzalutamide for patients with metastatic castration-resistant prostate cancer, whose disease has progressed on or after docetaxel chemotherapy

Patient group	**ACT**	**Extent and probability of added benefit**
Patients with visceral metastases	BSC[a]	Hint of a major added benefit
Patients without visceral metastases	BSC[a]	Indication of a major added benefit
a: BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care		

3 References

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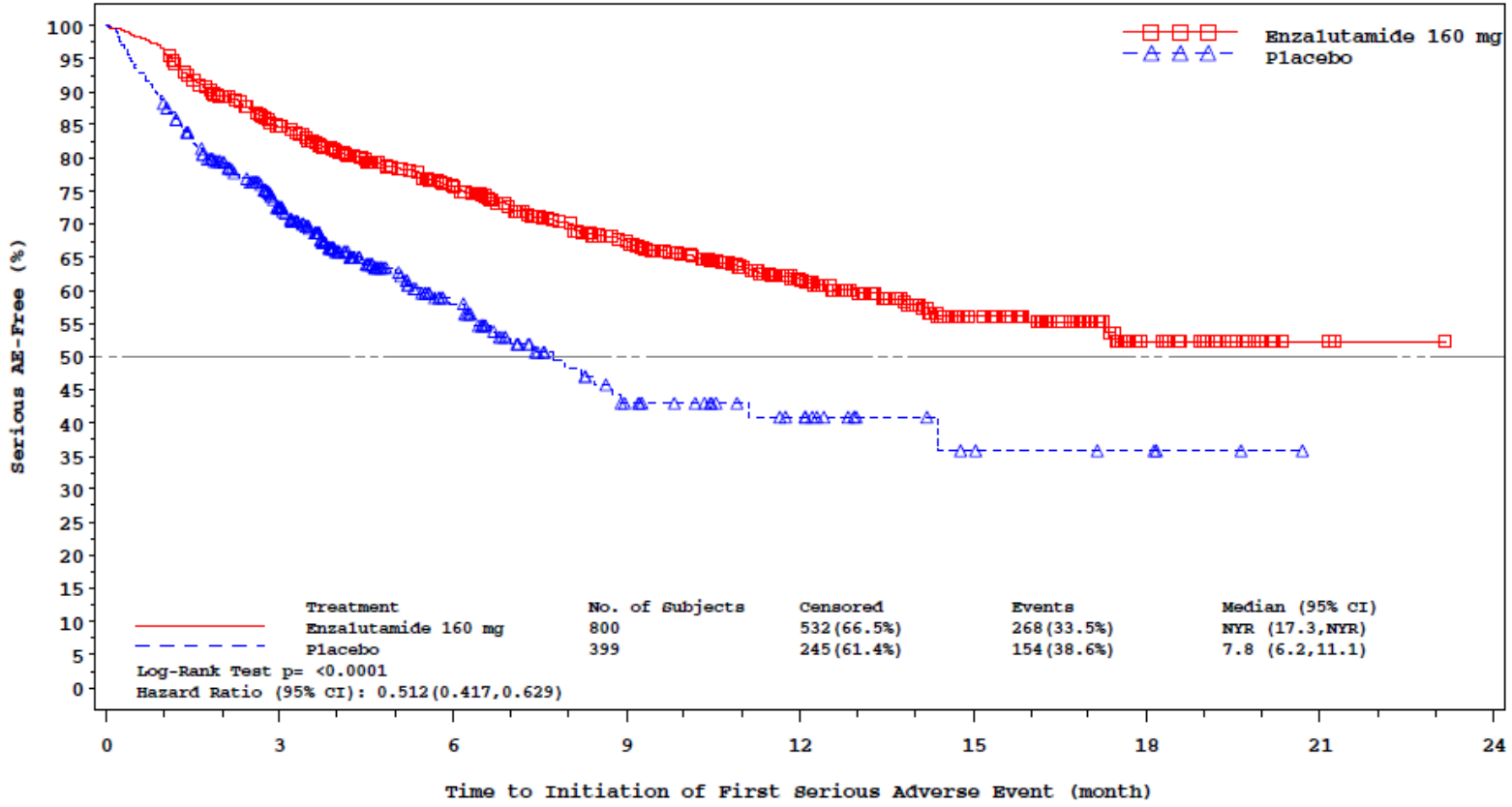
Appendix A– Additional tables on adverse events

Table 8: Most common (≥ 1% patients with ≥ 1 event in at least 1 treatment arm) SAEs – RCT, direct comparison: enzalutamide + BSC vs. placebo + BSC

Study PT	Enzalutamide + BSC N = 800	Placebo + BSC N = 399
	patients with at least one event n (%)	patients with at least one event n (%)
AFFIRM		
Overall rate	268 (33.5)	154 (38.6)
spinal cord compression	48 (6.0)	15 (3.8)
anaemia	21 (2.6)	12 (3.0)
general physical health deterioration	17 (2.1)	8 (2.0)
haematuria	12 (1.5)	5 (1.3)
pneumonia	12 (1.5)	5 (1.3)
bone pain	12 (1.5)	4 (1.0)
metastatic pain	12 (1.5)	3 (0.8)
pathological fracture	12 (1.5)	2 (0.5)
back pain	11 (1.4)	7 (1.8)
cancer pain	8 (1.0)	5 (1.3)
urinary tract infection	7 (0.9)	5 (1.3)
urinary retention	3 (0.4)	8 (2.0)
pulmonary embolism	3 (0.4)	4 (1.0)
vomiting	2 (0.3)	8 (2.0)
pyrexia	2 (0.3)	5 (1.3)
nerve root compression	1 (0.1)	4 (1.0)
bone metastases	1 (0.1)	5 (1.3)

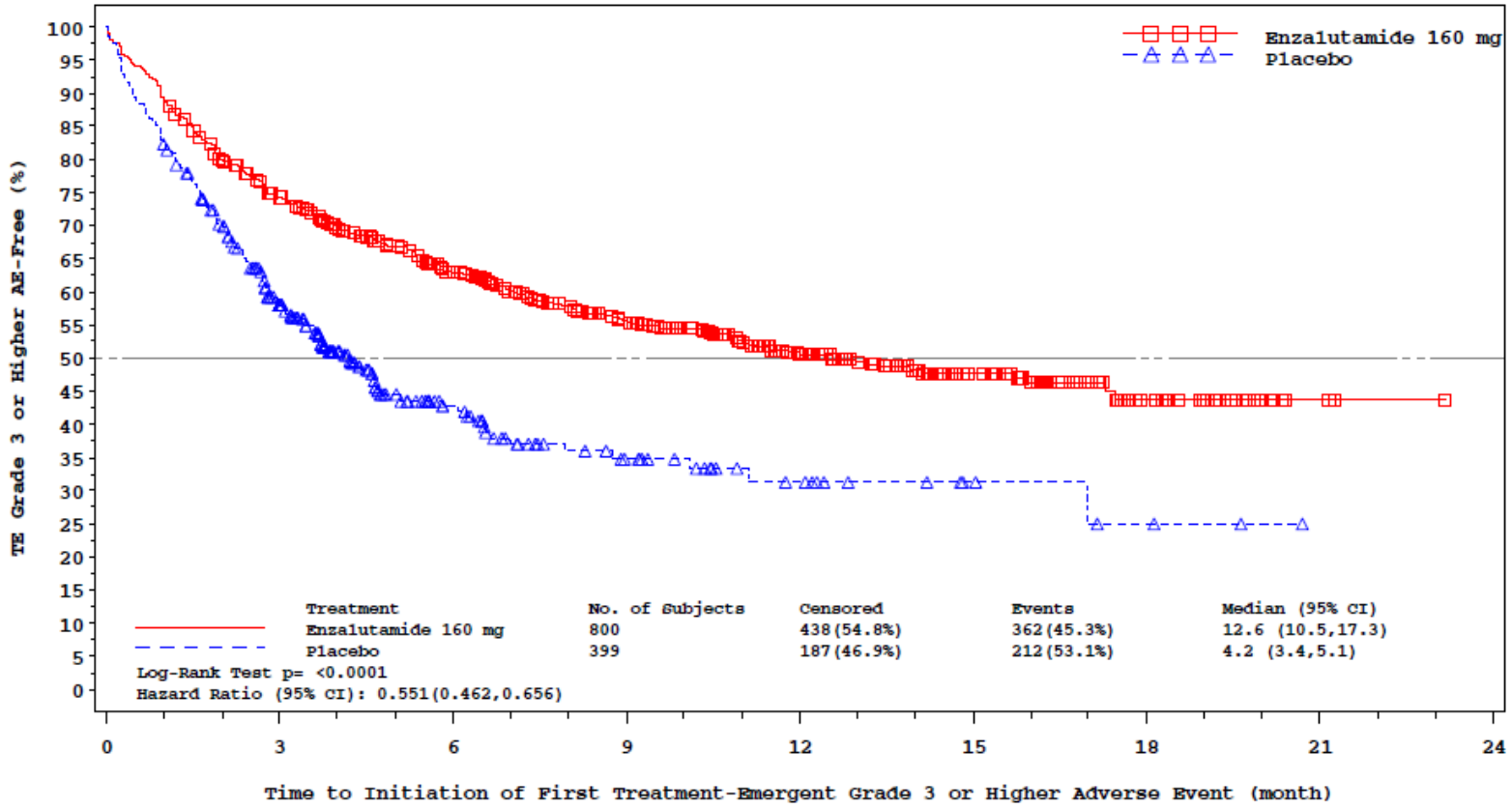
In descending order according to frequency in the enzalutamide arm.
BSC: best supportive care; N: number of randomized patients; n: number of patients with event; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Appendix B – Figures on survival time analyses (Kaplan-Meier curves)



Enzalutamide 160 mg									
Event/Cum. Events	0/0	120/120	62/182	46/228	24/252	13/265	3/268	0/268	0/268
Patients at Risk	800	640	467	344	182	75	25	3	0
Placebo									
Event/Cum. Events	0/0	106/106	32/138	14/152	1/153	1/154	0/154	0/154	0/154
Patients at Risk	399	236	74	30	17	6	4	0	0

Figure 1: Kaplan-Meier curve (AEs: time to first SAE) – RCT, direct comparison: enzalutamide + BSC vs. placebo + BSC



Enzalutamide 160 mg									
Event/Cum. Events	0/0	205/205	80/285	44/329	22/351	7/358	4/362	0/362	0/362
Patients at Risk	800	573	410	306	165	73	26	3	0
Placebo									
Event/Cum. Events	0/0	163/163	37/200	9/209	2/211	0/211	1/212	0/212	0/212
Patients at Risk	399	194	59	28	14	6	3	0	0

Figure 2: Kaplan-Meier curve (AEs: time to first severe AE [CTCAE grade ≥ 3]) – RCT, direct comparison: enzalutamide + BSC vs. placebo + BSC