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Enzalutamide (prostate cancer) –

Addendum to Commission A21-77[1]

Addendum

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

Annette Christoph

Katrin Nink

Christoph Schürmann

Katharina Wölke

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List of abbreviations

Abbreviation	Meaning
ADT	androgen deprivation therapy
AE	adverse event
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

1. Background

On 12 October 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-77 (Enzalutamid – benefit assessment according to § 35a Social Code Book V) [1].

To assess the benefit of enzalutamide in combination with androgen deprivation therapy (ADT) for the treatment of adult patients with metastatic hormone-sensitive prostate carcinoma (mHSPC), an adjusted indirect comparison of enzalutamide + ADT versus docetaxel + prednisolone + ADT was used on the basis of the randomized controlled trials (RCTs) ARCHES and STAMPEDE. For the ARCHES study, the data from the first data cut-off (14 October 2018) were used.

In the commenting procedure, the company presented new analyses of the ARCHES study's final data cut-off of 28 May 2021 [2]. Therefore, the G-BA commissioned IQWiG with the below assessment of the analyses submitted by the company in the commenting procedure, taking into account the information provided in the dossier [3]:

- Final data cut-off of the ARCHES study, 28 May 2021, for the indirect comparison of data on overall survival, including the subgroup analysis with the attribute of tumour burden, symptomatic skeletal-related events, serious adverse events (SAEs) as well as severe adverse events (AEs)

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

2. Assessment

2.1. Unblinded enzalutamide extension phase (after the first data cut-off) of the ARCHES study

The first data cut-off of the ARCHES study was after 292 events concerning the primary outcome of radiographic progression-free survival (14 October 2018). The ARCHES study was unblinded after the first data cut-off.

With the 3rd amendment to the study protocol (10 December 2018), an open-label enzalutamide extension phase was initiated (open-label period), during which patients in the comparator arm were allowed to receive enzalutamide upon the investigator's discretion while maintaining the existing ADT. This treatment switch was available only to patients who had adhered to the protocol in the double-blind study phase (without disease progression or with disease progression but continued administration of the study drug) and had not received any other prostate cancer treatment after unblinding. These criteria were met by 245 patients in the comparator arm. From this group, 153 patients (28.8% of all patients in the comparator arm) switched to study treatment with enzalutamide while maintaining the existing ADT.

Treatment with enzalutamide + ADT was continued until radiographic disease progression or beyond that time if the investigator deemed continuation to be of clinical benefit. The survey included, among others, AEs, concomitant medications, disease progression data, and quality of life outcomes. The long-term follow-up surveyed survival status, initiation of new treatments for prostate cancer, and the occurrence of symptomatic skeletal-related events.

Patients in either study arm of the double-blind study phase who were not included or chose not to participate in the open-label enzalutamide extension phase discontinued treatment with the study drug and proceeded to follow-up observation.

As described above, in the ARCHES study's enzalutamide extension phase, a relevant percentage of patients in the comparator arm switched to subsequent treatment with the intervention, enzalutamide + ADT.

For patients who had experienced disease progression in the meantime and who fell under the indication of patients with metastatic castration-resistant prostate carcinoma who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated, the treatment switch to enzalutamide + ADT represents an approved transition to the next treatment option [4]. No data are available on the number of patients in the ARCHES comparator arm who had disease progression and switched to enzalutamide treatment or on the extent to which said patients met the conditions stated in the approval for subsequent therapy with enzalutamide.

However, according to the company's estimate provided in the oral hearing, none of the patients in the extension phase exhibited disease progression. No detailed information is available on

the percentage of patients who switched to treatment with enzalutamide + ADT without prior disease progression.

However, the treatment of patients with metastatic hormone-sensitive prostate cancer, i.e. of patients without disease progression in the double-blind study phase, corresponds to the research question of the present benefit assessment. The treatment switch from the comparator to the intervention arm therefore might bias the treatment effect [5].

The resulting uncertainties are taken into account in the assessment of the outcome-specific risk of bias.

2.2. Analysis of the ARCHES study's final data cut-off for the adjusted indirect comparison

2.2.1. Risk of bias

For the ARCHES study's final data cut-off of 28 May 2021, which has now become available, the risk of bias of results must be reassessed. For the results on all-cause mortality, the risk of bias is deemed high due to the potential treatment switch at the time of unblinding. The treatment switch was an option for a subpopulation of the originally randomized patients of the placebo + ADT treatment arm, and a high percentage of patients (28.8%) availed themselves of it. As described in Section 2.1, for these 28.8% of patients, it is safe to assume that the administration of enzalutamide as subsequent therapy is to be viewed as treatment switching as defined by the IQWiG working paper on treatment switching in oncological studies [6].

For the results on the outcomes of SAEs and severe AEs, the risk of bias was deemed high already for the first data cut-off. The reasoning for this categorization provided in dossier assessment A21-77 [1] continues to apply at the final data cut-off; therefore, a high risk of bias is still to be assumed for these outcomes. The high risk of bias is further supported by a relevant percentage of patients in the comparator arm switching treatment after unblinding. For the results of the outcome of symptomatic skeletal-related events, the assessment of risk of bias was foregone since no indirect comparison was conducted due to the lack of similarity (see Section 2.2.3).

2.2.2. Results

The company has presented results on the final data cut-off of the ARCHES study. Data on the course of the study are found in Appendix A of the present addendum.

Table 1 summarizes the results of the comparison of enzalutamide with docetaxel + prednisolone, each in combination with ADT, in consideration of the final data cut-off of the ARCHES study in patients with mHSPC. Kaplan-Meier curves on the presented time-to-event analyses can be found in Appendix B of the present addendum. Results on the effect estimates of the adjusted indirect comparison are provided, as commissioned, as supplementary information in Appendix C of the present addendum for the outcomes of overall survival and

severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) and in Appendix D for the outcome of skeletal-related events.

Table 1: Results (mortality, side effects) – RCT, indirect comparison: enzalutamide + ADT vs. docetaxel + prednisolone + ADT (multipage table)

Outcome category **Outcome** **Comparison** **Study**	**Enzalutamide + ADT or docetaxel + prednisolone + ADT**		**(Placebo +) ADT**		**Group difference**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value**
Mortality					
Overall survival					
Enzalutamide + ADT vs. placebo + ADT					
ARCHES[a]	536	NR 148 (27.6)	531	NR [47.7; NR] 199 (37.5)	0.62 [0.50; 0.77]; < 0.001
Docetaxel + prednisolone + ADT vs. ADT					
STAMPEDE	362	59.1 [51.1; 69.8] 225 (62.2)	724	43.1 [41.0; 47.4] 494 (68.2)	0.81 [0.69; 0.95]; 0.008
Indirect comparison via common comparators[b]:					
Enzalutamide + ADT vs. docetaxel + prednisolone + ADT					_[d]
Side effects					
SAEs					
enzalutamide + ADT vs. placebo + ADT					
ARCHES[a]	534	33.7 [29.9; 36.4] 189 (35.4)	530	29.5 [25.6; 34.2] 143 (27.0)	0.81 [0.64; 1.01]; 0.062
docetaxel + prednisolone + ADT vs. ADT					
STAMPEDE	335	NR 96 (28.7)	724	NR [109.1; NR] 80 (11.0)	9.04 [5.92; 13.79]; < 0.001
Indirect comparison via common comparators[b]:					
Enzalutamide + ADT vs. docetaxel + prednisolone + ADT					0.09 [0.06; 0.14]; < 0.001

Table 1: Results (mortality, side effects) – RCT, indirect comparison: enzalutamide + ADT vs. docetaxel + prednisolone + ADT (multipage table)

Outcome category Outcome Comparison Study	Enzalutamide + ADT or docetaxel + prednisolone + ADT		(Placebo +) ADT		Group difference
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
Severe AEs[c]					
Enzalutamide + ADT vs. placebo + ADT					
ARCHES[a]	534	29.2 [26.2; 33.7] 221 (41.4)	530	25.6 [24.4; 28.6] 184 (34.7)	0.84 [0.69; 1.03]; 0.093
Docetaxel + prednisolone + ADT vs. ADT					
STAMPEDE	335	NR 108 (32.2)	724	NR [102.8; NC] 219 (30.2)	2.39 [1.84; 3.11]; < 0.001
Indirect comparison via common comparators[b]: **Enzalutamide + ADT vs. docetaxel + prednisolone + ADT**					–[d]

a. Final data cut-off from 28 May 2021.
b. Indirect comparison according to Bucher [7].
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. In the absence of the certainty of results required for conducting an adjusted indirect comparison, no indirect comparison has been calculated.

ADT: androgen deprivation therapy; AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least 1) event; NR: not reached; RCT: randomized controlled trial; SAE: serious adverse event

Mortality

Overall survival

For the outcome of overall survival, the STAMPEDE study with a low risk of bias on the outcome level was used on the one side of the adjusted indirect comparison and the ARCHES study with a high risk of bias on the outcome level on the other side. Therefore, the prerequisites for deriving conclusions with sufficient certainty of results on the added benefit from an adjusted indirect comparison were not fulfilled.

For the outcome of overall survival, this resulted in no hint of an added benefit of enzalutamide + ADT in comparison with docetaxel + prednisolone + ADT; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome "SAEs", there is one study with a high outcome-specific risk of bias (ARCHES or STAMPEDE) on both sides of the adjusted indirect comparison. Therefore, the prerequisites for being able to derive conclusions with sufficient certainty of results on the added benefit from an adjusted indirect comparison were initially not fulfilled. After including the ARCHES study's final data cut-off, despite the high risk of bias on the outcome level in the ARCHES and STAMPEDE studies, the very high effect estimator resulted in a sufficient qualitative certainty of results to allow interpreting the identified effect; this had also been the case in the dossier assessment (see dossier assessment A21-77 Section 2.4.2 [1]). In the present situation, it is therefore possible to derive a hint of greater or lesser harm from enzalutamide + ADT.

The adjusted indirect comparison for the outcome of SAEs showed a statistically significant difference in favour of enzalutamide + ADT in comparison with docetaxel + prednisolone + ADT. This resulted in a hint of lesser harm from enzalutamide + ADT. However, the extent of the effect cannot be quantified due to the high risk of bias in both studies included in the indirect comparison.

Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)

For the results on the outcome "severe AEs (CTCAE grade ≥ 3)", the ARCHES and STAMPEDE studies had a high risk of bias (see dossier assessment A21-77 Section 2.4.2 [1]). Hence, an effect estimator for the indirect comparison does not offer sufficient certainty of results, even when taking into account the ARCHES study's final data cut-off.

This resulted in no hint of greater or lesser harm from enzalutamide + ADT in comparison with docetaxel + prednisolone + ADT for the outcome "severe AEs (CTCAE grade ≥ 3)"; greater or lesser harm is therefore not proven.

2.2.3. Symptomatic skeletal-related events

IQWiG was also commissioned to assess the indirect comparison for the outcome of symptomatic skeletal-related events using the ARCHES final data cut-off. As was the case in dossier assessment A21-77, due to the insufficient similarity between the two studies for this outcome, no data usable for an adjusted indirect comparison are available (see dossier assessment A21-77, Section 2.4.1 [1]). The company's comments do not include any information which would lead to a different evaluation of similarity. The results are presented, as commissioned, in Appendix D.

2.2.4. Subgroups

In the dossier assessment, it was impossible to evaluate the subgroup results on the basis of the available data (see dossier assessment A21-77 Section 2.4.4 [1]). With its comments, the company presented subgroup analyses for the indirect comparison regarding the attribute of tumour load (low versus high) for the outcome of overall survival.

In the present assessment, the attribute of tumour load (low versus high) is considered a potential effect modifier. For the outcome of overall survival, no adjusted indirect comparison was carried out due to the insufficient certainty of results. Nevertheless, the subgroup analyses presented by the company have been evaluated as commissioned.

For the present subgroup analysis, taking into account the ARCHES study's final data cut-off, the indirect comparison regarding the outcome of overall survival shows no relevant effect modification with a statistically significant and relevant effect.

2.3. Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion on the added benefit of enzalutamide drawn in dossier assessment A21-77.

Table 2 below shows the result of the benefit assessment of enzalutamide taking into account dossier assessment A21-77 and the present addendum.

Table 2: Enzalutamide – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
For the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with ADT	▪ only for patients with distant metastasis (M1 stage) who are in good general condition (according to ECOG/WHO PS 0 to 1 or Karnofsky index ≥ 70%): conventional ADT[d] in combination with docetaxel[e] with or without prednisone or prednisolone or[f] ▪ only for patients with newly diagnosed high risk mHSPC: conventional ADT in combination with abiraterone acetate and prednisone or prednisolone	Hint of non-quantifiable added benefit[b, c]

a. Presentation of the respective ACT specified by the G-BA.
b. The ARCHES study included patients with an ECOG PS of 0 or 1. In the STAMPEDE study, the inclusion of patients with WHO PS 2 was allowed. However, the majority of patients had a WHO PS of 0. No detailed data on the number of patients with WHO-PS 2 are available (see dossier assessment A21-77 Table 9 [1]). The conclusion on the added benefit thus refers to patients with mHSPC who are in good general condition (according to ECOG/WHO PS 0 to 1).
c. Patients with brain metastases were excluded from the studies ARCHES and STAMPEDE. It remains unclear whether the observed results can be transferred to patients with brain metastases.
d. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists.
e. In the present therapeutic indication, it is assumed that a combination therapy - additional therapy to conventional androgen deprivation - is a regular option for the patients with regard to possible comorbidities and their general condition.
f. The therapies mentioned represent ACTs for the respective cited subpopulation. The subpopulations result in an intersection. Docetaxel + prednisone or prednisolone + ADT as well as abiraterone acetate + prednisone or prednisolone + ADT present alternative ACTs ("or disjunction") only for this intersection.

ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; WHO PS: World Health Organization Performance Status

The G-BA decides on the added benefit.

3. References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Enzalutamid (Prostatakarzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 02.09.2021]. URL: https://www.iqwig.de/download/a21-77_enzalutamid_nutzenbewertung-35a-sgb-v_v1-0.pdf.

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Appendix A ARCHES – Information on the course of the study

Table 3: Information on the course of the study – RCT, direct comparison: enzalutamide + ADT vs. placebo + ADT

Study **Duration of the study phase** **Outcome category**	**Enzalutamide + ADT**	**Placebo + ADT[a]**	**(Placebo + ADT) with treatment switch to enzalutamide + ADT after unblinding**
ARCHES	N = 536[b]	N = 531[b]	N = 153
Treatment duration [months]			
Median [min; max]	39.2 [0; 58]	13.8 [0; 28]	24.0 [0; 28]
Mean (SD)	31.5 (16.7)	13.2 (6.1)	21.0 (7.28)
Observation period [months]			
Overall survival			
Median [Q1; Q3]	42.7 [1; 61]	39.0 [0; 61]	24.2 [1; 28]
Mean (SD)	37.7 (13.6)	33.0 (14.7)	22.6 (5.5)
Morbidity			
Symptomatic skeletal-related events			
Median [Q1; Q3]	38.4 [0; 58]	16.4 [0; 53]	22.2 [0; 28][c]
Mean (SD)	31.3 (15.5)	21.0 (14.7)	19.6 (7.0)[c]
Side effects [months[d]]			
Median [min; max]	40.8 [0; 60]	14.4 [0; 48]	24 [0; 24]
Mean (SD)	32.4 (16.6)	15.6 (7.2)	20.4 (7.2)

a. It remains unclear whether the information includes the data from the follow-up observation after the treatment switch.
b. Data in the table are partly based on slightly different patient numbers (± 2) in the respective treatment groups.
c. Data based on 143 patients.
d. IQWiG calculation from data in years.

ADT: androgen deprivation therapy; max: maximum; min: minimum; N: number of randomized patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

Appendix B Kaplan-Meier curves

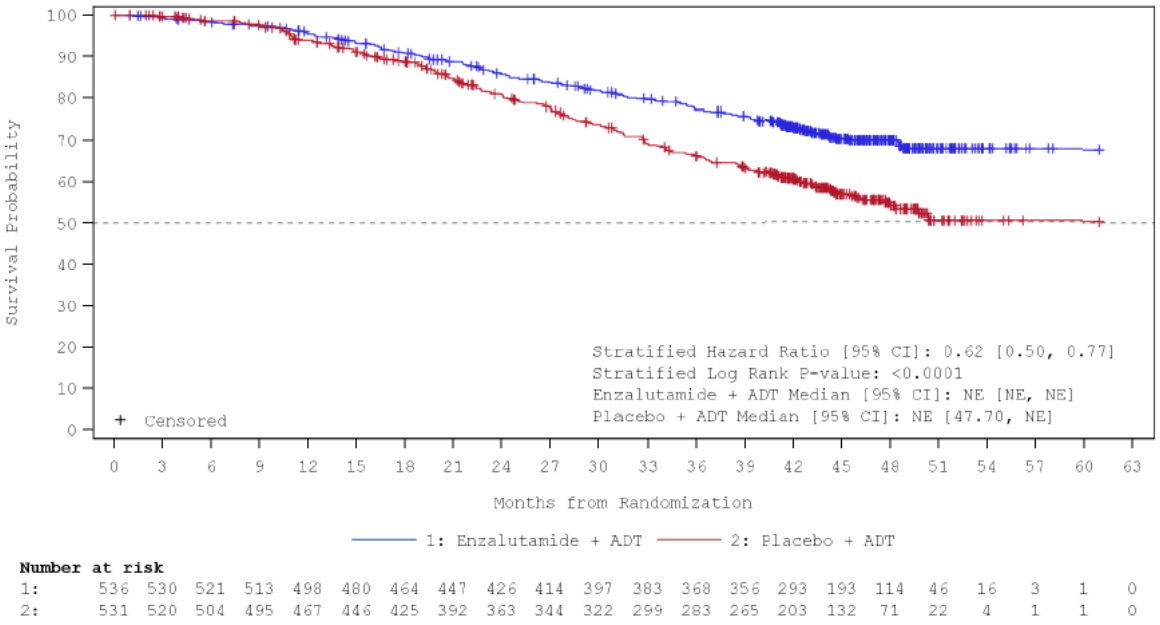

Figure 1: Kaplan-Meier curves for the outcome of overall survival – RCT, direct comparison: enzalutamide + ADT vs. placebo + ADT, ARCHES study (data cut-off: 28 May 2021)

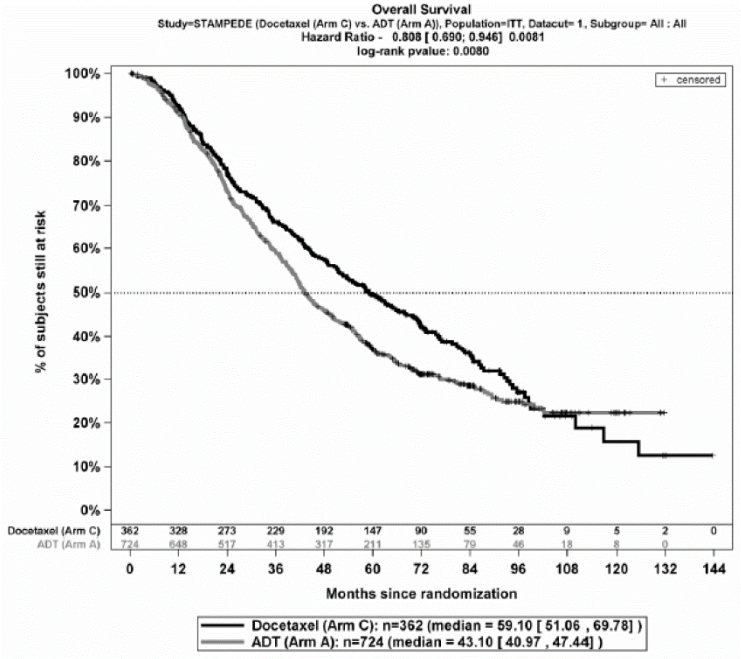

Figure 2: Kaplan-Meier curves for the outcome of overall survival – RCT, direct comparison: docetaxel + prednisolone + ADT vs. ADT, STAMPEDE study (data cut-off from 13 July 2018)

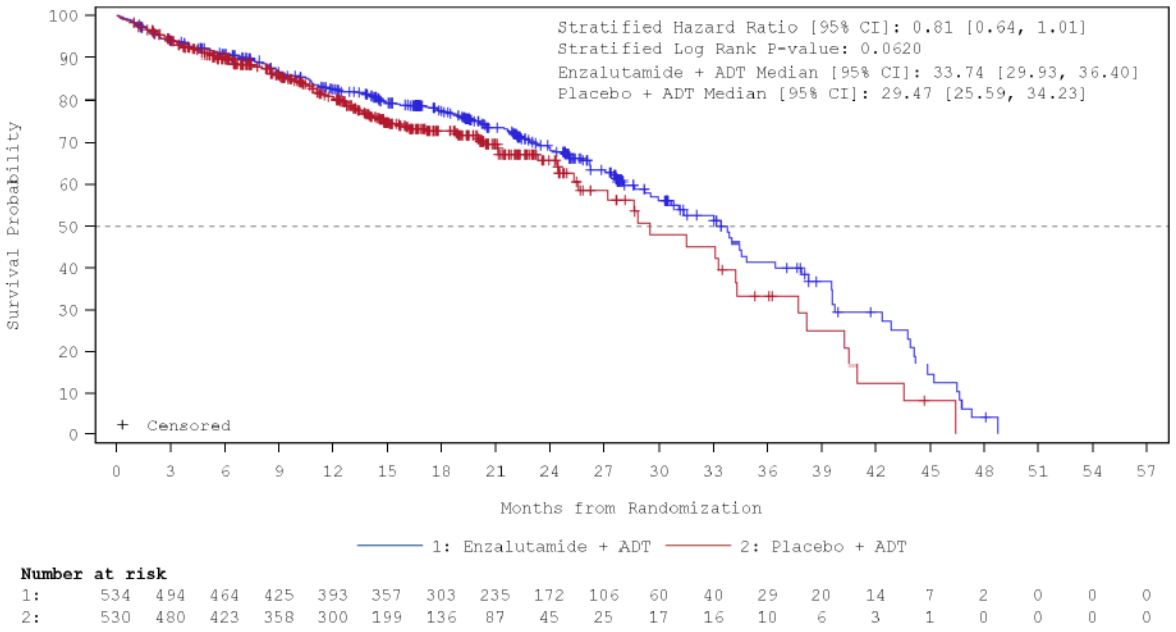

Figure 3: Kaplan-Meier curves for the outcome of SAEs – RCT, direct comparison: enzalutamide + ADT vs. placebo + ADT, ARCHES study (data cut-off: 28 May 2021)

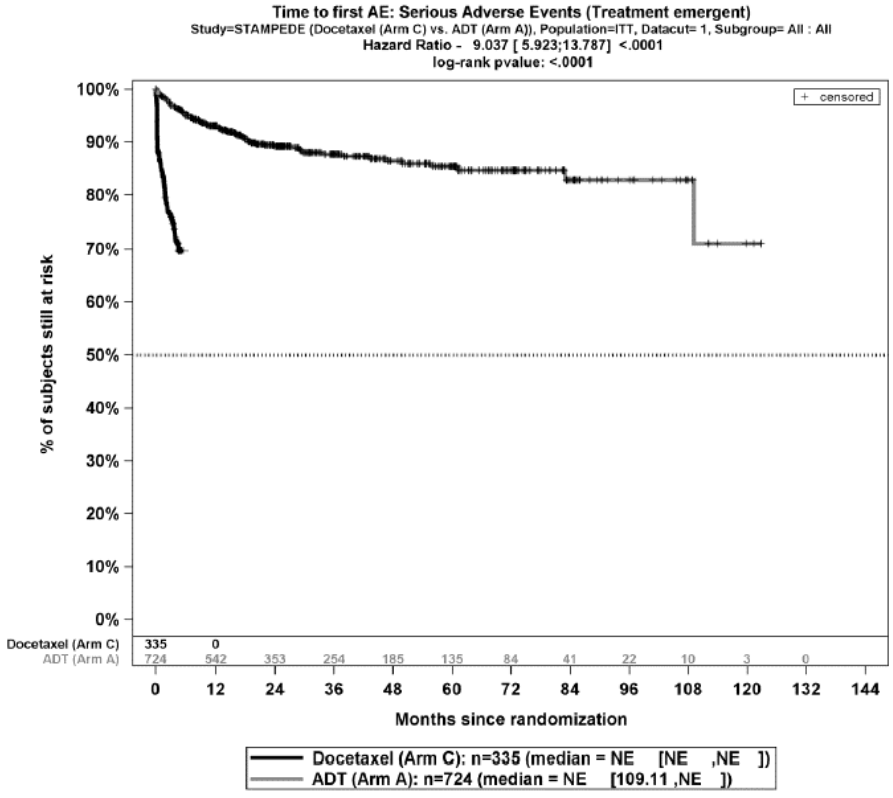

Figure 4: Kaplan-Meier curves for the outcome of SAEs – RCT, direct comparison: docetaxel + prednisolone + ADT vs. ADT, STAMPEDE study (data cut-off: 13 July 2018)

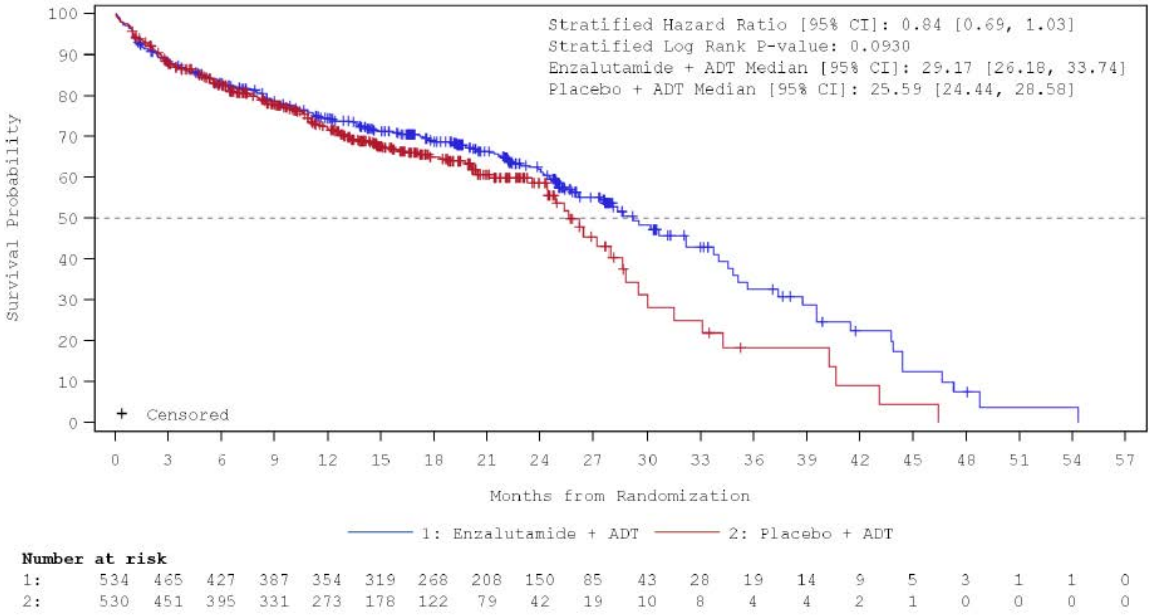

Figure 5: Kaplan-Meier curves for the outcome of severe AEs (CTCAE ≥ 3) – RCT, direct comparison: enzalutamide + ADT vs. placebo + ADT, ARCHES study (data cut-off: 28 May 2021)

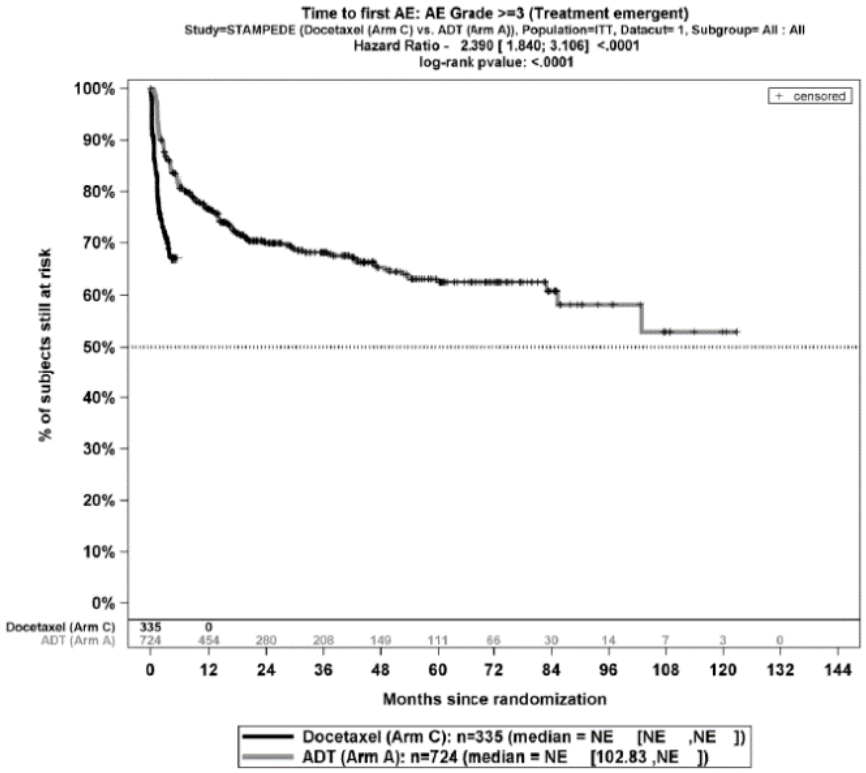

Figure 6: Kaplan-Meier curves for the outcome of severe AEs (CTCAE ≥ 3) – RCT, direct comparison: docetaxel + prednisolone + ADT vs. ADT; STAMPEDE study (data cut-off from 13 July 2018)

Appendix C Results on mortality and side effects – supplementary presentation

Table 4: Results (mortality, side effects) – RCT, indirect comparison: enzalutamide + ADT vs. docetaxel + prednisolone + ADT

Outcome category Outcome Comparison Study	Enzalutamide + ADT or docetaxel + prednisolone + ADT		(Placebo +) ADT		Group difference
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
Mortality					
Overall survival					
Enzalutamide + ADT vs. placebo + ADT					
ARCHES[a]	536	NR 148 (27.6)	531	NR [47.7; NR] 199 (37.5)	0.62 [0.50; 0.77]; < 0.001
Docetaxel + prednisolone + ADT vs. ADT					
STAMPEDE	362	59.1 [51.1; 69.8] 225 (62.2)	724	43.1 [41.0; 47.4] 494 (68.2)	0.81 [0.69; 0.95]; 0.008
Indirect comparison via common comparators[b]:					
Enzalutamide + ADT vs. docetaxel + prednisolone + ADT					0.76 [0.59; 0.998]; 0.048
Side effects					
Severe AEs[c]					
Enzalutamide + ADT vs. placebo + ADT					
ARCHES[a]	534	29.2 [26.2; 33.7] 221 (41.4)	530	25.6 [24.4; 28.6] 184 (34.7)	0.84 [0.69; 1.03]; 0.093
Docetaxel + prednisolone + ADT vs. ADT					
STAMPEDE	335	NR 108 (32.2)	724	NR [102.8; NC] 219 (30.2)	2.39 [1.84; 3.11]; < 0.001
Indirect comparison via common comparators[b]:					
Enzalutamide + ADT vs. docetaxel + prednisolone + ADT					0.35 [0.25; 0.49]; < 0.001

a. Final data cut-off from 28 May 2021.
b. Indirect comparison according to Bucher [7].
c. Severe AEs are operationalized as CTCAE grade ≥ 3.

ADT: androgen deprivation therapy; AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least 1) event; NR: not reached; RCT: randomized controlled trial

Appendix D Results on the outcome of symptomatic skeletal-related events – supplementary presentation

Table 5: Results (morbidity) – RCT, indirect comparison: enzalutamide + ADT vs. docetaxel + prednisolone + ADT

Outcome category Outcome Comparison Study	Enzalutamide + ADT or docetaxel + prednisolone + ADT		(Placebo +) ADT		Group difference
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
Morbidity					
Symptomatic skeletal-related events					
Enzalutamide + ADT vs. placebo + ADT					
ARCHES[a]	536	NR 79 (14.7)	531	NR 108 (20.3)	0.46 [0.34; 0.62]; < 0.001
Docetaxel + prednisolone + ADT vs. ADT					
STAMPEDE	362	95.8 [76.4; NR] 132 (36.5)	724	49.7 [36.9; 68.4] 357 (49.3)	0.63 [0.51; 0.76]; < 0.001
Indirect comparison via common comparators[b]:					
Enzalutamide + ADT vs. docetaxel + prednisolone + ADT					0.73 [0.51; 1.04]; 0.085[c]

a. Final data cut-off from 28 May 2021.
b. Indirect comparison according to Bucher [7].
c. Supplementary presentation as commissioned; insufficient similarity between the two studies regarding the outcome (see dossier assessment A21-77 Section 2.4.1 [1])

ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least 1) event; NR: not reached; RCT: randomized controlled trial

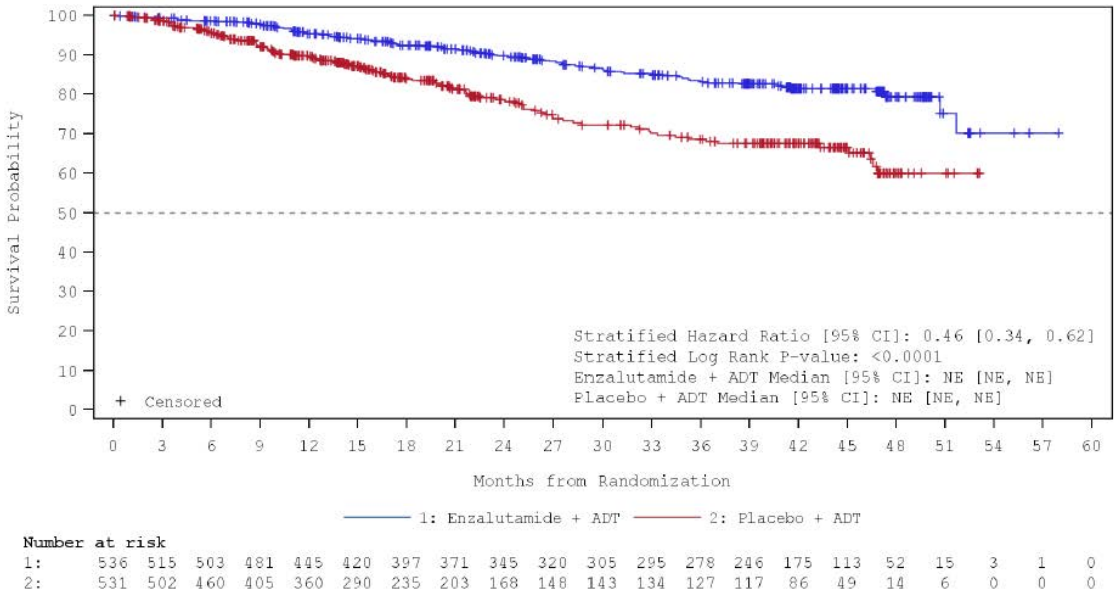

Figure 7: Kaplan-Meier curves for the outcome of symptomatic skeletal-related events – RCT, direct comparison: enzalutamide + ADT vs. placebo + ADT, ARCHES study (data cut-off: 28 May 2021)

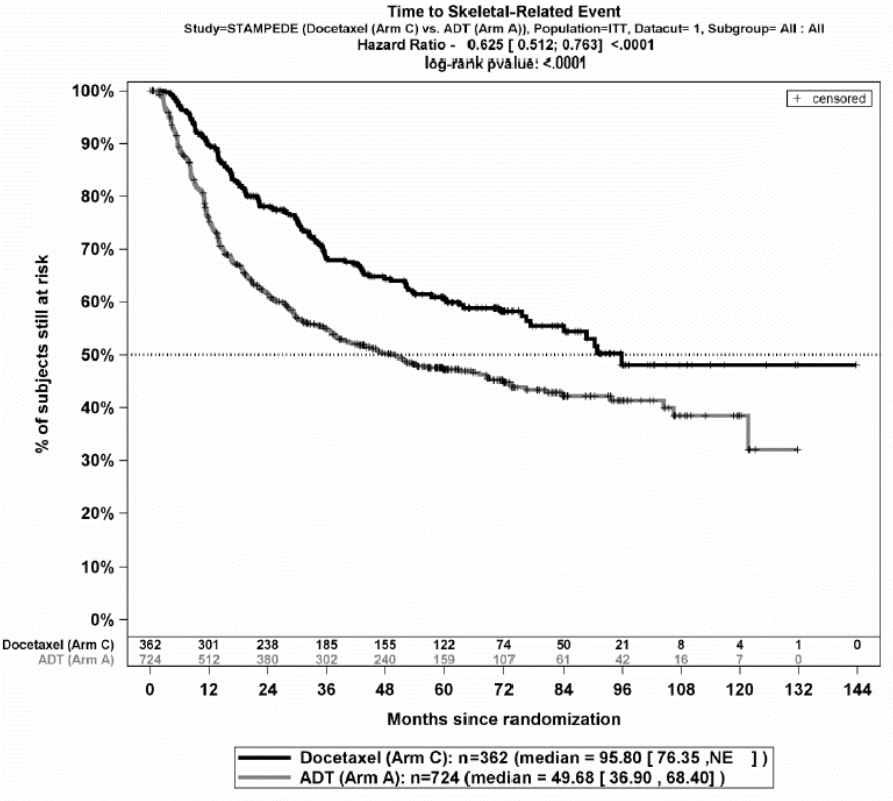

Figure 8: Kaplan-Meier curves for the outcome of symptomatic skeletal-related events – RCT, direct comparison: docetaxel + prednisolone + ADT vs. ADT, STAMPEDE study (data cut-off: 13 July 2018)