IQWiG Reports – Commission No. 21-77

Enzalutamide (prostate cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Enzaludatmid (Prostatakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 August 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADT	androgen deprivation therapy
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GnRH	gonadotropin-releasing hormone
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAB	maximal androgen blockade
mHSPC	metastatic hormone sensitive prostate cancer
NSAA	non-steroidal anti-androgens
PSA	prostate-specific antigen
PSA	prostate-specific antigen
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
rPFS	radiographic progression-free survival
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
WHO PS	World Health Organization Performance Status

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug enzalutamide. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 31 May 2021.

Research question

The aim of this report was to assess the added benefit of enzalutamide in combination with an androgen deprivation therapy (ADT) in comparison with the appropriate comparator therapy (ACT) in adult patients with metastatic hormone sensitive prostate cancer (mHSPC).

The research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of enzalutamide

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

a. Presentation of the respective ACT specified by the G-BA.
b. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists.
c. In the present therapeutic indication, it is assumed that a combination therapy - an additional therapy to conventional androgen deprivation - is a regular option for the patients with regard to possible comorbidities and their general condition.
d. The therapies mentioned represent ACTs for the respective specified subpopulation. The subpopulations result in an intersection. Docetaxel with or without prednisone or prednisolone + ADT as well as abiraterone acetate + prednisone + 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 patient populations in Table 2 defined on the basis of the ACT partly overlap. The intersection of these overlapping patient populations comprised patients with mHSPC with the following disease characteristics:

- Good general condition (according to Eastern Cooperative Oncology Group Performance Status (ECOG PS)/ World Health Organization Performance Status (WHO PS) 0 to 1 or Karnofsky index ≥ 70%)

- High risk prostate cancer
- newly diagnosed prostate cancer

The two listed options of the ACT only apply to the patients of this intersection.

The company deviates from the ACT specified by the G-BA by considering not only the ADT but also the combination of ADT with non-steroidal anti-androgens (NSAA) - in the sense of a maximal androgen blockade (MAB) - to be included in the ACT for each of the two patient populations. In addition, the company expanded the ACT to include the option of conventional ADT alone, possibly in combination with an NSAA, for patients with mHSPC and low tumour load. These expansions of the ACT are not appropriate. The present assessment was conducted in comparison with the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Study pool and study design

In Module 4 A, the company presented both a direct and an adjusted indirect comparison for the assessment of enzalutamide + ADT. The company's study pool comprised the following randomized controlled trials (RCTs):

- Direct comparison
  - ENZAMET study: enzalutamide + ADT vs. docetaxel + NSAA + ADT
- Indirect comparison
  - Intervention:
    - ARCHES study: enzalutamide + ADT vs placebo + ADT
    - ENZAMET study: enzalutamide + ADT vs. NSAA + ADT
  - Comparator therapy:
    - CHAARTED study: docetaxel + ADT ± NSAA vs. ADT ± NSAA
    - STAMPEDE study: docetaxel + prednisolone + ADT vs. ADT

The ENZAMET study presented by the company in both the direct and indirect comparison and the CHAARTED study presented in the indirect comparison are not suitable for the assessment of the added benefit of enzalutamide. On the one hand, this is due to the lack of implementation of the ACT (combination of ADT with NSAA) in the direct comparison or, for the edge of the comparator therapy, in the indirect comparison. Second, there is insufficient similarity of the common comparator (ADT + NSAA in the studies ENZAMET and CHAARTED) compared to the studies ARCHES and STAMPEDE (ADT alone).

From the data submitted by the company, only the studies ARCHES and STAMPEDE were used in the indirect comparison for the assessment of enzalutamide + ADT.

ARCHES study (study with enzalutamide + ADT)

The ARCHES study is a randomized, double-blind, multicentre study comparing enzalutamide in combination with ADT versus treatment with placebo in combination with ADT. The study included adult men with mHSPC.

A total of 1150 patients were randomized in a 1:1 ratio. For the present benefit assessment, the company only presented a subpopulation of patients that exclusively included patients with confirmed metastasis based on an independent central review at baseline. This patient population comprised 536 patients in the enzalutamide + ADT arm and 531 patients in the placebo + ADT arm. All patients in the relevant subpopulation had an ECOG PS of 0 or 1.

Administration of enzalutamide was in compliance with the specifications of the respective Summary of Product Characteristics (SPC). In both study arms, ADT treatment could be surgical or drug-based through the administration of gonadotropin-releasing hormone (GnRH) analogues.

The ARCHES study started in 2016 and is still ongoing.

STAMPEDE study (study with docetaxel + prednisolone + ADT)

STAMPEDE is a randomized, open-label, multi-arm and multi-phase platform trial on the comparison of different systemic drugs (12 arms in total) for advanced or metastatic prostate cancer.

The STAMPEDE study included both patients with distant metastases and patients with locally advanced prostate cancer. All patients in the study had hormone-sensitive prostate cancer regardless of their metastatic status. In accordance with the approval of enzalutamide, only the subpopulation of patients with hormone sensitive prostate cancer and distant metastases was relevant for the present benefit assessment. This subpopulation comprised a total of 1086 patients, 362 patients in the docetaxel + prednisolone + ADT arm and 724 patients in the ADT arm.

Treatment with docetaxel in the intervention arm of the STAMPEDE study corresponds to the recommendations of the SPC for docetaxel in the present therapeutic indication. ADT treatment in both study arms could be surgical or drug-based through the administration of GnRH analogues.

The STAMPEDE study started in 2005 and is still ongoing.

Similarity of the studies for the indirect comparison

The overall consideration shows some differences in the study and patient characteristics between the ARCHES and STAMPEDE studies, none of which, however, fundamentally calls

into question the sufficient similarity for conducting an adjusted indirect comparison via the common comparator placebo + ADT or ADT. However, there are differences at the level of the outcome “skeletal-related events”, so that no adjusted indirect comparison was performed for this outcome.

Risk of bias

The risk of bias across outcomes was rated as low for both studies.

For both studies, there was a low risk of bias for the results on overall survival. There is a high risk of bias for each of the results on the outcomes “SAEs” and “severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)”.

There was one RCT each on both sides of the available adjusted indirect comparison. Hence, the homogeneity was not checked. As there is no study of direct comparison for the comparison of enzalutamide + ADT versus the ACT, the consistency of the results cannot be checked. Therefore, the adjusted indirect comparisons had at most a low certainty of results. Hence, on the basis of the available data, at most hints, e.g. of an added benefit, could be derived from the adjusted indirect comparison.

Results

Mortality

Overall survival

The adjusted indirect comparison showed no statistically significant difference between the treatment groups for the outcome "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.

Morbidity

Symptomatic skeletal-related events

Due to the insufficient similarity of the two studies with regard to the outcomes, there were no usable data for an adjusted indirect comparison for the outcome “symptomatic skeletal-related events”. 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.

Symptoms

For the outcome “symptoms”, the studies ARCHES and STAMPEDE partly used different instruments to record the morbidity.

There were no usable data for an adjusted indirect comparison. 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.

Health status

There were no data for an adjusted indirect comparison for the outcome “health status”. 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.

Health-related quality of life

The studies ARCHES and STAMPEDE partly used different instruments to record the outcome “health-related quality of life”.

There were no usable data for an adjusted indirect comparison. 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. For this outcome, however, both the STAMPEDE study and the adjusted indirect comparison using the common comparator placebo + ADT or ADT each show a very large effect estimation. It is not assumed in the present data situation that the advantage in the adjusted indirect comparison is completely called into question by potential biases. Thus, there is a sufficiently high qualitative certainty of results for the interpretation of the present effect despite the high outcome-specific risk of bias in the studies ARCHES and STAMPEDE. Therefore, in the present situation, the derivation of a hint of greater or lesser harm from enzalutamide + ADT is possible.

The adjusted indirect comparison for the outcome SAE 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 of both studies included in the indirect comparison.

Severe AEs (CTCAE grade ≥ 3)

In the studies ARCHES and STAMPEDE, there is a high risk of bias for the results on the outcome “severe AEs (CTCAE grade ≥ 3)”. Thus, the certainty of results of an effect estimation for the indirect comparison is insufficient for this outcome.

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.

Discontinuation due to AEs

No data are available for an indirect comparison for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from enzalutamide + ADT in comparison with docetaxel + prednisolone + ADT; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Based on the results presented, probability and extent of the added benefit of the drug enzalutamide in comparison with the ACT are assessed as follows:

The overall consideration of the results only shows a positive effect of enzalutamide + ADT in the category “side effects”. The advantage for the outcome “SAE” is not challenged by any disadvantage. Usable data are not available for the outcomes of the categories “morbidity” and “health-related quality of life”, nor for the outcome “discontinuation due to AEs” and for specific AEs.

In summary, there is a hint of a non-quantifiable added benefit of enzalutamide in combination with ADT versus the ACT docetaxel with or without prednisone or prednisolone in combination with ADT for patients with mHSPC and a good general condition.

Table 3 shows a summary of probability and extent of the added benefit of enzalutamide.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Enzalutamide – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
For the treatment of adult men with mHSPC in combination with ADT	▪ Only for patients with distant metastases (M1 stage) and 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. Detailed information on the number of patients with WHO PS 2 is not available. The conclusion on the added benefit thus refers to patients with mHSPC and a 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 approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of enzalutamide in combination with ADT in comparison with the ACT in adult patients with mHSPC.

The research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of enzalutamide

Therapeutic indication	ACT[a]
For the treatment of adult men with mHSPC in combination with ADT	▪ Only for patients with distant metastases (M1 stage) and good general condition (according to ECOG/WHO PS 0 to 1 or Karnofsky index ≥ 70%): conventional ADT[b] in combination with docetaxel[c] with or without prednisone or prednisolone or[d] ▪ only for patients with newly diagnosed high risk mHSPC: conventional ADT in combination with abiraterone acetate and prednisone or prednisolone

a. Presentation of the respective ACT specified by the G-BA.
b. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists.
c. In the present therapeutic indication, it is assumed that a combination therapy - an additional therapy to conventional androgen deprivation - is a regular option for the patients with regard to possible comorbidities and their general condition.
d. The therapies mentioned represent ACTs for the respective specified subpopulation. The subpopulations result in an intersection. Docetaxel with or without 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 patient populations in Table 4 defined on the basis of the ACT partly overlap. The intersection of these overlapping patient populations comprised patients with mHSPC to whom each of the following disease characteristics applied:

- Good general condition (according to ECOG PS/WHO PS 0 to 1 or Karnofsky index ≥ 70%)
- High risk prostate cancer
- newly diagnosed prostate cancer

The two listed options of the ACT only apply to the patients of this intersection.

The company deviates from the ACT specified by the G-BA by considering not only the ADT but also the combination of ADT with NSAA - in the sense of a (MAB) - to be included in the ACT for both patient populations. In addition, the company expanded the ACT to include the option of conventional ADT alone, possibly in combination with an NSAA, for patients with mHSPC and low tumour load. This expansion of the ACT was not appropriate. This is explained in the following Section. The present assessment was conducted in comparison with the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Deviation of the company from the G-BA's ACT

MAB

The company described that patients in the present therapeutic indication could be offered a combination of ADT with an NSAA, in the sense of an MAB, which would then have to be considered in the ACT. Among other things, the company justified this with the fact that the MAB is cited as a therapy option in the German S3 guideline as well as in international guidelines [3,4] and that 6-18% of mHSPC patients receive such an MAB in everyday health care in Germany. The company's justification was not followed. Due to a lack of evidence on the efficacy and the side effect profile, MAB is either completely advised against in the guidelines or only significantly weakened recommendations are made compared to ADT by means of orchiectomy or GnRH analogue [3-6]. The G-BA also commented accordingly in the consultation on the ACT [7]. The effects of the deviation from the ACT on the study pool of the present benefit assessment are described in Section 2.3.

Patients with low tumour load

The company also supplemented the G-BA's ACT with ADT alone, possibly in combination with an NSAA, for patients with mHSPC and low tumour load, which would correspond to a subset of the patient population defined by the G-BA. The company justified this extension by stating that for mHSPC patients with a low tumour load, there was no clear evidence proving the efficacy of the administration of docetaxel in addition to ADT with regard to overall survival. This was also reflected in the recommendations of current guidelines differentiated by tumour load [3], in which the recommendation for docetaxel in patients with low tumour burden is clearly weakened. The company's justification was not followed. It is correct that the updated S3 guideline makes a concrete distinction between patients according to the tumour load. However, treatment of patients with mHSPC in good general condition and low tumour load with ADT alone is not included in the recommendations of the updated S3 guideline [3]. The guideline rather describes that contradictory data are available for patients with low tumour load. While some studies or meta-analyses show no influence of the "metastasis volume" on the effectiveness of early chemo-hormone therapy, other analyses could not prove any advantage for patients with low tumour load. In view of the numerous treatment alternatives now available and the toxicity profile of chemo-hormone therapy compared to combined hormone therapy, the recommendation for low volume metastasis was weakened. In its specification of the ACT, the G-BA also assumes that a combination therapy is a regular option for patients in the present therapeutic area. The company’s approach to expand the ACT to include the option of ADT alone (possibly in combination with NSAA) is therefore not followed and accordingly, the question considered separately by the company in Module 3 B and Module 4 B is not the subject of the present benefit assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on erenumab (status: 1 April 2021)
- bibliographical literature search on enzalutamide (last search on 1 April 2021)
- search in trial registries/trial results databases for studies on enzalutamide (last search on 1 April 2021)
- search on the G-BA website for enzalutamide (last search on 1 April 2021)
- bibliographical literature search on the ACT (last search on 1 April 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 1 April 2021)
- search on the G-BA website for the ACT (last search on 1 April 2021)

To check the completeness of the study pool:

- search in trial registries for studies on enzalutamide (last search on 7 June 2021); for search strategies, see Appendix A of the full dossier assessment
- focused search for systematic reviews on the ACT (last search on 30 June 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

Study pool of the company

In Module 4 A, the company presented both a direct and an adjusted indirect comparison for the assessment of enzalutamide + ADT. The company's study pool comprised the following RCTs:

- Direct comparison
  - ENZAMET study: enzalutamide + ADT vs. docetaxel + NSAA + ADT
- Indirect comparison
  - Intervention:
    - ARCHES study: enzalutamide + ADT vs placebo + ADT
    - ENZAMET study: enzalutamide + ADT vs. NSAA + ADT
  - Comparator therapy:
    - CHAARTED study: docetaxel + ADT ± NSAA vs. ADT ± NSAA
    - STAMPEDE study: docetaxel + prednisolone + ADT vs. ADT

The ENZAMET study presented by the company in both the direct and indirect comparison and the CHAARTED study presented in the indirect comparison are not suitable for the assessment of the added benefit of enzalutamide. On the one hand, this is due to the lack of implementation of the ACT (combination of ADT with NSAA), and on the other hand to the insufficient similarity of the common comparator (ADT alone vs. ADT + NSAA) and is explained below.

ENZAMET study (study with enzalutamide + ADT)

The ENZAMET study [8] is an open-label RCT comparing enzalutamide + ADT with NSAA (bicalutamide, nilutamide, flutamide) + ADT in patients with mHSPC. Concomitant treatment with docetaxel for a maximum of 6 cycles was allowed in both study arms. Whether such concomitant treatment with docetaxel was planned had to be determined prior to randomization. Concomitant administration of prednisone or prednisolone was not intended. The study included adult patients with histologically confirmed prostate cancer or metastatic disease of the prostate cancer with increasing concentration of the prostate-specific antigen (PSA) serum concentration. Patients had to have an ECOG PS ≤ 2 and metastases according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria 1.1.

In the study, a total of 1125 patients were randomly assigned in a 1:1 ratio, 563 patients to the intervention arm and 562 patients to the comparator arm.

Primary outcome was overall survival, further outcomes were clinical or biochemical PFS, outcomes on morbidity and health-related quality of life as well as AEs.

For the direct comparison of enzalutamide, the company used one subpopulation for each treatment arm. In the enzalutamide + ADT arm, it restricted the population to those patients who received no docetaxel treatment (N = 309) and only included those patients in the comparator arm who had received treatment with docetaxel in addition to NSAA + ADT (N = 171).

For the indirect comparison of enzalutamide, the company used the subpopulation of both treatment arms who did not receive concomitant treatment with docetaxel (N = 309 in the intervention arm and N = 313 in the comparator arm).

Direct comparison: missing implementation of the ACT

In the present therapeutic indication, the G-BA has specified conventional ADT in combination with docetaxel as an option of the ACT. The combination with NSAA is explicitly not covered by the ADT (see explanations in Section 2.2). Therefore, treatment with NSAA + ADT used in the comparator arm of the ENZAMET study does not represent the ACT specified by the G-BA, and the ENZAMET study is not suitable for the benefit assessment.

Moreover, for the comparison presented, the company used different subpopulations per study arm and thus disjunctive strata between the treatment groups of the ENZAMET study. Thus, it is no longer a randomized comparison of the treatments. This approach is not appropriate.

Indirect comparison: Similarity in the common comparator not given

Furthermore, the company included the ENZAMET study in the indirect comparison on the intervention side, the comparator arm (ADT + NSAA) represents the common comparator. However, the common comparator ADT alone resulted from the other included studies relevant in the indirect comparison (ARCHES and STAMPEDE, for the CHAARTED study see below). As described in Section 2.2 on the ACT, treatment with ADT alone must clearly be demarcated from a combination of ATD with NSAA, in the sense of a MAB, Sufficient similarity of the comparator arms of the studies with regard to the common comparator can thus not be assumed. Hence, the ENZAMET study is not used for the indirect comparison, which deviates from the company's approach.

Study CHAARTED (study with docetaxel + ADT, included by the company for the indirect comparison)

The study CHAARTED [9-12] is an open-label RCT on the comparison of docetaxel + ADT with treatment with ADT in patients with mHSPC. An additional combination of the conventional ADT with NSAA (e.g. bicalutamide or flutamide) in the sense of an MAB was allowed. Concomitant administration of prednisone or prednisolone was not intended in the study. The study included adult patients with pathologically confirmed prostate cancer or diagnosis of prostate cancer via an increased PSA level, patients with radiological evidence of distant metastases and an ECOG PS of ≤ 2.

A total of 790 patients were randomized in a ratio of 1:1; 397 patients to the intervention arm docetaxel + ADT ± NSAA and 393 patients to the comparator arm ADT ± NSAA.

"Overall survival" was defined as primary outcome. Further outcomes were "time to clinical progression", "time to castration-resistant prostate cancer", "morbidity" as well as the "change of health-related quality of life" and "AEs".

Missing implementation of the ACT

In both study arms of the CHAARTED study, treatment with a combination of conventional ADT with NSAA in the sense of an MAB was possible and was used in about 42% of the patients [12]. As already described for the ENZAMET study, this does not correspond to the ACT specified by the G-BA. Therefore, the therapy used in the CHAARTED study does not represent the ACT for a relevant proportion of the subpopulation. Subgroup analyses for the subpopulation who did not receive MAB are not available. Deviating from the company's approach, the CHAARTED study is therefore not included in the assessment.

Summary

From the data submitted by the company, only the studies ARCHES and STAMPEDE were used in the indirect comparison for the assessment of enzalutamide + ADT.

2.3.1 Studies included

The studies listed in the following Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, indirect comparison: enzalutamide + ADT vs. docetaxel + prednisolone + ADT

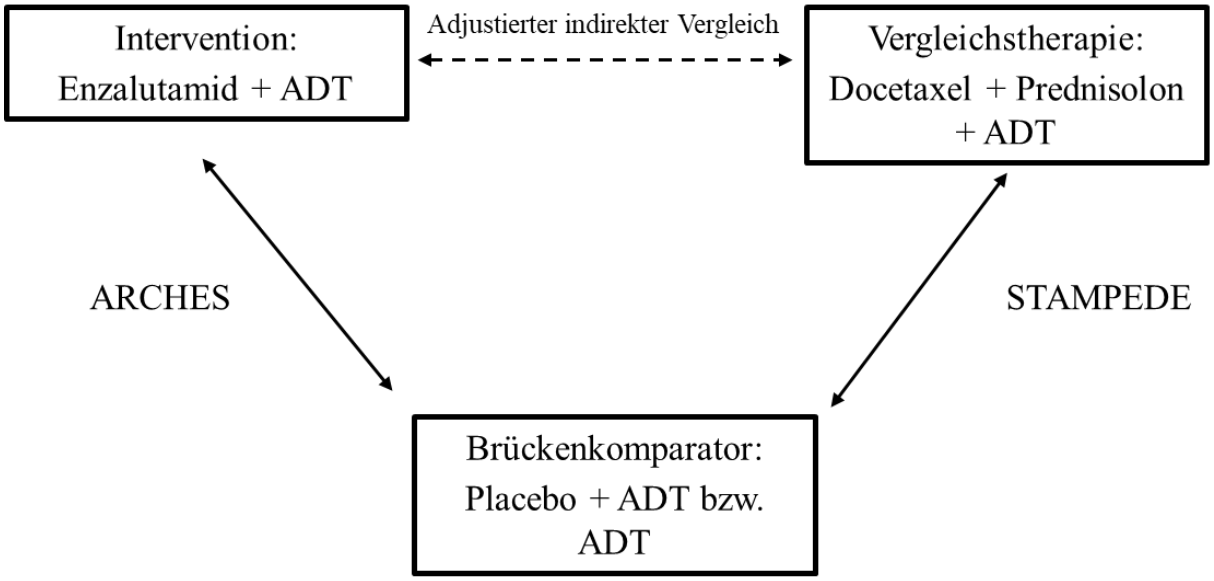
Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Enzalutamide + ADT vs. placebo + ADT						
9785-CL-0335 (ARCHES[d])	Yes	Yes	No	No[e]	Yes [13,14]	Yes [15-17]
docetaxel + prednisolone + ADT vs. ADT						
STAMPEDE	No	No	Yes	No	Yes [18-20]	Yes [21-27]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to with this abbreviated form.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool for the benefit assessment did not concur with that of the company (see Section 2.3).

Figure 1 shows a schematic representation of the indirect comparison.



Adjustierter indirekter Vergleich:	adjusted indirect comparison
Vergleichstherapie:	comparator therapy
Brückenkomparator:	common comparator#

Figure 1: Study pool for the indirect comparison between enzalutamide + ADT and docetaxel + prednisolone + ADT

2.3.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, indirect comparison: enzalutamide + ADT vs. docetaxel + prednisolone + ADT (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Enzalutamide + ADT vs. placebo + ADT						
ARCHES	RCT, double-blind, parallel	Adult patients with metastatic[b] HSPC, with ECOG PS 0 or 1	Enzalutamide + ADT (N = 574) placebo + ADT (N = 576) relevant subpopulation thereof[c]: Enzalutamide + ADT (N = 536) placebo + ADT (n = 531)	Screening: 28 days treatment: until occurrence of intolerable AEs, radiographic disease progression, start of a new cancer treatment, discontinuation of the ADT and a testosterone level > 50 ng/dL, lost to follow-up or withdrawal of consent observation: outcome-specific, at most until death, final survival time analysis, end of study, withdrawal of consent	204 study centres in: Argentina, Australia, Belgium, Canada, Chile, Denmark, Finland, France, Germany, Israel, Italy, Japan, Korea, Netherlands, New Zealand, Poland, Romania, Russia, Slovak Republic, Spain, Sweden, Taiwan, United Kingdom, USA 03/2016–ongoing data cut-offs: 14 October 2018 31 January 2019	Primary: rPFS secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, indirect comparison: enzalutamide + ADT vs. docetaxel + prednisolone + ADT (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Docetaxel + prednisolone + ADT vs. ADT						
STAMPEDE	RCT, open-label, parallel	Adult patients with prostate cancer for whom long-term ADT is intended, with WHO PS 0 to 2: ▪ with newly diagnosed, metastatic or lymph node-positive disease, or ▪ with high risk, locally advanced, non-metastatic disease with intended radiotherapy, or ▪ with recurrent, locally advanced or metastatic disease, pretreated with radiotherapy or surgery	Arms relevant for the assessment[d]: docetaxel + prednisolone + ADT (N = 592) ADT (N = 1184) relevant subpopulation thereof[e]: docetaxel + prednisolone + ADT (N = 362) ADT (n = 724)	Screening: up to 8 weeks treatment: until disease progression, unacceptable toxicity, withdrawal of consent, initiation of a new anticancer treatment or decision by the physician ▪ docetaxel: at most 6 cycles ▪ ADT: ND observation: until death, withdrawal of consent	A total of 116 centres in Great Britain and Switzerland[f] overall study: 09/2005–ongoing relevant study arms: ND data cut-off (overall survival): 13 July 2018	primary: overall survival, survival without treatment failure Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Patients with brain metastases or spread only to the pelvic lymph nodes were excluded.
c. Patients with confirmed metastasis based on an independent central review upon screening at baseline.
d. In the STAMPEDE study, one comparator arm (arm A) and different intervention arms were investigated. The comparison between arm A (ADT) and arm C (docetaxel + ADT) is relevant for the present assessment.
e. Patients with metastatic (M1) prostate cancer.
f. Information on how many centres included patients in the 2 relevant study arms is not available.

ADT: androgen deprivation therapy; AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; n: relevant subpopulation; N: number of randomized patients; ND: not data; RCT: randomized controlled trial; rPFS: radiographic progression-free survival

Table 7: Characteristics of the interventions – RCT, indirect comparison: enzalutamide + ADT vs. docetaxel + prednisolone + ADT (multipage table)

Study	Intervention/comparator therapy	Common comparator
Enzalutamide + ADT vs. placebo + ADT		
ARCHES	Enzalutamide 160 mg/day (4 x 40 mg capsules) + ADT[a]	Placebo 4 capsules daily + ADT[a]
	Treatment adjustment: ▪ enzalutamide/placebo: treatment interruption and dose adjustment allowed in case of toxicity grade ≥ 3 or symptoms of a posterior reversible encephalopathy syndrome (PRES) ▪ ADT: no adjustment; if ADT was discontinued and the testosterone level was > 50 ng/dL, treatment had to be terminated	
	Permitted pretreatment ▪ ≤ 3 months ADT[a, b] (± concomitant anti-androgenic medication) prior to randomization ▪ palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease ≥ 4 weeks prior to randomization ▪ docetaxel: ≤ 6 cycles, ≤ 2 months prior to randomization[b] and ≤ 6 months ADT[a,b] (± concomitant anti-androgenic medication) prior to randomization ▪ neoadjuvant/adjuvant ADT: > 9 months before randomization **prohibited prior and concomitant treatment** ▪ ≤ 4 weeks before randomization and during the study: ▫ 5α reductase inhibitors (finasteride, dutasteride) ▫ oestrogen, cyproterone acetate or androgen treatment ▫ systemic glucocorticoid therapy with ≥ 10 mg/day prednisone or equivalent for the treatment of the prostate cancer ▫ phytopharmaceutical treatment with known anti-prostate cancer activity and/or known effect of lowering PSA levels ▪ major surgeries ≤ 4 weeks before randomization ▪ test substances (e.g. enzalutamide) which inhibit the androgen receptor or the androgen synthesis ▪ biological agents with antitumour effect against prostate cancer during the study	
	Permitted concomitant treatment ▪ bisphosphonates and denosumab, at a stable dosage (2 weeks) before randomization and during the study or for the treatment of osteoporosis ▪ pain therapy ▪ palliative radiotherapy ▪ palliative surgical interventions for the treatment of skeletal-related events ▪ hormone therapy for the treatment of side effects of the GnRH analogues ▪ flutamide, bicalutamide or nilutamide for the treatment of the flare reaction[c] in the treatment with GnRH agonists	

Table 7: Characteristics of the interventions – RCT, indirect comparison: enzalutamide + ADT vs. docetaxel + prednisolone + ADT (multipage table)

Study	Intervention/comparator therapy	Common comparator
Docetaxel + prednisolone + ADT vs. ADT		
STAMPEDE	Docetaxel 75 mg/m² BSA IV on day 1 of a cycle (for a maximum of 6 21-day cycles) + ADT[a, d] + prednisolone 5 mg twice daily + dexamethasone both before and after the infusion	ADT[a, d]
	Treatment adjustment: ▪ ADT: ND ▪ docetaxel: 2 dose reductions to 45 mg/m² BSA due to toxicity allowed	
	Permitted pretreatment ▪ previous ADT up to 3 months[a], with or without simultaneous administration of anti-androgens (these had to have started 14 weeks before randomization) **non-permitted pretreatment** ▪ chemotherapy, surgery within 4 weeks before study inclusion ▪ long-term hormonal therapy ▪ systemic therapy (except for the therapies listed below) **permitted concomitant treatment** ▪ any treatment deemed appropriate by the investigator (such as NSAIDs, bisphosphonates, vitamins) ▪ anti-androgens for the treatment of the flare reaction[d] in the treatment with GnRH agonists	

a. Surgical castration (bilateral orchiectomy) or medical castration using treatment with GnRH analogues.
b. Without evidence for disease progression or increasing PSA levels.
c. Short-term sharp increase of the testosterone concentration in the blood through administration of GnRH agonists.
d. In case of an ADT before the start of the study, this should have been initiated at most 12 weeks before randomization.

ADT: androgen deprivation therapy; BSA: body surface area; GnRH: gonadotropin-releasing hormone; NSAID: nonsteroidal anti-inflammatory drug; PRES: posterior reversible encephalopathy syndrome, PSA: prostate-specific antigen; RCT: randomized controlled trial

Study design

ARCHES study (study with enzalutamide + ADT)

The ARCHES study is a randomized, double-blind, multicentre study comparing enzalutamide in combination with ADT versus treatment with placebo in combination with ADT. The study included adult men with mHSPC. Patients had to have a general condition corresponding to an ECOG PS of 0 or 1. Patients with brain metastases or leptomeningeal metastases were excluded.

A total of 1150 patients were randomized in a 1:1 ratio. Of these, 574 patients were included in the intervention arm and 576 patients in the comparator arm. The company only used a subpopulation from the total population of these two study arms for the present benefit

assessment (see description of the relevant patient population). Stratification was based on previous docetaxel therapy (none vs. 1-5 cycles vs. 6 cycles) and tumour load (low vs. high). High tumour load was defined as the presence of visceral metastases or 4 or more bone metastases, at least 1 of which had to be in a bony structure beyond the spine and the pelvic bone.

Administration of enzalutamide was in compliance with the specifications of the SPC [28]. In both study arms, ADT treatment could be surgical or drug-based through the administration of GnRH analogues. Up to 6 cycles of prior docetaxel therapy were allowed if completed 2 months prior to study entry. If ADT was already performed at study entry, it had to have started a maximum of 3 months before study entry, or 6 months in the case of previous docetaxel treatment.

Treatment was continued in both study arms until the occurrence of unacceptable toxicity, radiological or biochemical progression, initiation of a new anticancer therapy, or discontinuation at the patient's request.

Primary outcome was “radiographic progression-free survival (rPFS)”. Further patient-relevant outcomes were “overall survival”, outcomes on morbidity, health-related quality of life and AEs.

The ARCHES study started in 2016 and is still ongoing. Recruitment of patients took place from March 2016 to October 2018. After the interim analysis at the present data cut-off (14 October 2018), the study was unblinded and patients in the placebo + ADT arm were allowed to switch to enzalutamide + ADT. At the present data cut-off (14 October 2018), 8% of the patients in the enzalutamide + ADT arm and 23% of the patients in the placebo + ADT arm were already receiving subsequent systemic therapy. Most patients received chemotherapy or treatment with an anti-androgen (see Table 28 of the full dossier assessment).

Relevant patient population of the ARCHES study

The ARCHES study included patients with mHSPC. For the present benefit assessment, the company only presented a subpopulation of patients that exclusively included patients with confirmed metastasis based on an independent central review at baseline. With 536 patients in the enzalutamide + ADT arm and 531 patients in the placebo + ADT arm, this subpopulation comprised 93% of the total population included in the ARCHES study. All patients in the relevant subpopulation had an ECOG PS of 0 or 1.

Overall, the subpopulation of the ARCHES study presented by the company sufficiently represents the target population of the present assessment and is included in the present benefit assessment (referred to as "relevant subpopulation” in the present assessment).

STAMPEDE (study with docetaxel + prednisolone + ADT)

STAMPEDE is a randomized, open-label, multi-arm and multi-phase platform trial on the comparison of different systemic drugs (12 arms in total) for advanced or metastatic prostate cancer.

The STAMPEDE study included adult men with hormone-sensitive prostate cancer for whom long-term treatment with ADT was planned and whose clinical picture corresponded to one of the following 3 criteria:

1) newly diagnosed disease with presence of distant metastases or lymph node metastases
2) newly diagnosed disease with high risk, locally advanced prostate cancer without distant metastases or lymph node metastases
3) recurrent locally advanced or metastatic disease after prior radiotherapy and/or surgery.

Patients with brain metastases were excluded.

Only the comparison between the docetaxel + prednisolone + ADT arm (study arm C) and the ADT arm (study arm A) is relevant for the present benefit assessment. These study arms included a total of 1776 patients, 592 patients in the docetaxel + prednisolone + ADT arm and 1184 patients in the ADT arm. However, from the total population of these two study arms, only a subpopulation is relevant for the present benefit assessment (see the detailed description of the relevant patient population below).

Treatment with docetaxel in the intervention arm of the STAMPEDE study corresponds to the specifications of the SPC for docetaxel in the present therapeutic indication [29]. ADT treatment in both study arms could be surgical or drug-based through the administration of GnRH analogues. If ADT had already been performed at baseline, it had to have started at least 14 days and no more than 3 months prior to the start of the study.

Treatment with ADT in the relevant study arms was continued according to the protocol for at least 2 years or until the first radiological, clinical or biochemical progression occurred. Treatment with docetaxel was performed for a maximum of 6 cycles, or until disease progression, unacceptable toxicity, withdrawal of consent, initiation of a new anticancer therapy or discontinuation of treatment at the physician’s decision.

Primary outcome for the study arms of the STAMPEDE study relevant for the present assessment was “overall survival”. Further patient-relevant outcomes were outcomes on morbidity, health-related quality of life and AEs.

The STAMPEDE study started in 2005 and is still ongoing. Patients were recruited for different lengths of time for the individual study arms. For the docetaxel + prednisolone + ADT arm, patients were recruited between October 2005 and March 2013. For the present data cut-off (13

July 2018), also in the ADT arm, only patients who had been recruited during this period were analysed.

Relevant patient population of the STAMPEDE study

The STAMPEDE study included both patients with distant metastases and patients with locally advanced prostate cancer. All patients in the study had hormone-sensitive prostate cancer regardless of their metastatic status. In accordance with the approval of enzalutamide, only the subpopulation of patients with hormone sensitive prostate cancer and distant metastases was relevant for the present benefit assessment.

The company presented a subpopulation of the STAMPEDE study that only comprised patients with distant metastases. This subpopulation comprised a total of 1086 patients, 362 patients in the docetaxel + prednisolone + ADT arm and 724 patients in the ADT arm.

The majority of patients in the relevant subpopulation had a WHO PS of 0 (75% or 72%). The remaining patients were reported to have a WHO PS of 1 to 2, which means that not all of these patients would be part of the relevant subpopulation. Assuming that the remaining patients cannot be completely assigned to a WHO PS 2, the subpopulation of the STAMPEDE study presented by the company sufficiently represents the target population of the present assessment and is included in the present benefit assessment (referred to as the relevant subpopulation in the present assessment).

A large proportion of patients in the relevant subpopulation had already received subsequent systemic therapy by the time of the present data cut-off (docetaxel + prednisolone + ADT arm: 68%, ADT arm: 80%). However, it cannot be inferred from the available data whether the information on the subsequent therapy refers only to therapies for prostate cancer or also to concomitant therapies such as e.g. bisphosphonates (see Table 29 of the full dossier assessment). In the docetaxel + prednisolone + ADT arm, abiraterone and/or antiandrogens were predominantly used as subsequent therapy. In the ADT arm, docetaxel and/or antiandrogens were predominantly used as subsequent therapy. However, even in the docetaxel + prednisolone + ADT arm, 14% of the patients continued to receive docetaxel as subsequent therapy (see Table 29 of the full dossier assessment).

Planned duration of follow-up observation

Table 8 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, indirect comparison: enzalutamide + ADT vs. docetaxel + prednisolone + ADT

Study **outcome category** **outcome**	**Planned follow-up observation**
Enzalutamide + ADT vs. placebo + ADT	
ARCHES	
Mortality	
Overall survival	Until death, lost to follow-up, final survival time analysis or end of study
Morbidity	
Skeletal-related events, symptoms (EORTC QLQ-PR25, FACT-P), health status (EQ-5D VAS)	Until disease progression, achievement of the planned number of events of the final PFS analysis, or initiation of a new antineoplastic treatment
Health-related quality of life (EORTC QLQ-PR25)	Until disease progression, achievement of the planned number of events of the final PFS analysis, or initiation of a new antineoplastic treatment
Side effects	
All outcomes in the AE category	30 days after discontinuation of the study medication or until the initiation of a new antineoplastic treatment
Docetaxel + prednisolone + ADT vs. ADT	
STAMPEDE	
Mortality	
Overall survival	Until death
Morbidity	
Skeletal-related events	Until death
Symptoms (EORTC QLQ-C30, EORTC QLQ-PR25),	ND
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-PR25)	ND
Side effects	
All outcomes in the AE category	Up to 30 days after the last dose of the study medication
ADT: androgen deprivation therapy; AE: adverse event; EORTC: European Organization for Research and Treatment of Cancer; PFS: progression-free survival; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PR25: Quality of Life Questionnaire Prostate Cancer with 25 items; RCT: randomized controlled trial; VAS: visual analogue scale	

With the exception of the outcome "symptomatic skeletal-related events" in the STAMPEDE study, the observation times for the outcomes on morbidity, health-related quality of life and side effects (if corresponding data are available) are systematically shortened in both the ARCHES and the STAMPEDE study, as they were only recorded for the period of treatment with the study medication (for side effects plus 30 days). To be able to draw a reliable conclusion about the entire study period or the time until death of the patients, however, it would be necessary for these outcomes to be recorded over the entire period of time, as was the case for “survival”.

Data cut-offs

Study ARCHES

For the ARCHES study, a final analysis of the primary outcome "rPFS" was planned to be performed when 262 events (radiographic progression or death) had occurred. At this point in time, a prespecified interim analysis of the outcome "overall survival" and an analysis of all other outcomes should also be performed. The present data cut-off (14 October 2018) took place after 292 rPFS events had occurred. At this data cut-off, data on the patient-relevant outcomes were available for the relevant subpopulation. This data cut-off was used for the benefit assessment. This concurs with the company's approach.

Study STAMPEDE

For the STAMPEDE study, the company submitted an analysis on the planned data cut-off of 13 July 2018 for the assessment of the added benefit for the relevant subpopulation. Other data cut-offs for the relevant comparison were not published. Data for all patient-relevant outcomes are available for this data cut-off. This data cut-off was used for the benefit assessment. This concurs with the company's approach.

Study population

Table 9 shows the characteristics of the patients in the studies included.

Table 9: Characteristics of the study populations – RCT, indirect comparison: enzalutamide + ADT vs. docetaxel + prednisolone + ADT (multipage table)

Study characteristic category	ARCHES		STAMPEDE	
	enzalutamide + ADT	placebo + ADT	docetaxel + prednisolone + ADT	ADT
	N[a] = 536	N[a] = 531	N[a] = 362	N[a] = 724
Age [years], median [Q1; Q3]	70 [46; 92][b]	70 [42; 92][b]	65 [60; 70]	65 [60; 71]
Family origin, n (%)				
White	437 (82)	423 (80)	ND	ND
Black	7 (1)	8 (2)	ND	ND
Asian	72 (13)	75 (14)	ND	ND
Other	2 (< 1)	3 (1)	ND	ND
Unknown	18 (3)	22 (4)	ND	ND
Region, n (%)				
North America/Europe	81 (15)	75 (14)	0 (0)	0 (0)
Europe	318 (59)	314 (59)	362 (100)	724 (100)
Rest of the world	137 (26)	142 (27)	0 (0)	0 (0)
ECOG PS/WHO PS, n (%)				
0	421 (79)	405 (76)	270 (75)[c]	521 (72)[c]
1 (ARCHES) or 1-2 (STAMPEDE)	114 (21)	126 (24)	92 (25)[c]	203 (28)[c]
Gleason score, n (%)				
< 8	150 (28)	165 (31)	65 (18)	158 (22)
≥ 8	371 (71)	350 (66)	253 (70)	480 (66)
Unknown	15 (3)[d]	16 (3)[d]	44 (12)	86 (12)
Tumour load, n (%)				
Low	194 (36)	175 (33)	124 (34)	238 (33)
High	342 (64)	356 (67)	148 (41)	320 (44)
Unknown	0 (0)	0 (0)	90 (25)	166 (23)
Time from initial diagnosis to randomization [months], median [Q1; Q3]	3 [0; 268][b]	3 [0; 259][b]	2.4 [2; 3]	2.3 [2; 3]
Distant metastases at initial diagnosis, n (%)	402 (70)[e]	365 (63)[e]	347 (96)	690 (95)
Distant metastases at baseline, n (%)	536 (100)[f]	531 (100)[f]	362 (100)[g]	724 (100)[g]
Location of the metastases at baseline, n (%)				
Bones	485 (90)	486 (92)	307 (85)	634 (88)
Bones alone	268 (50)	245 (46)	ND	ND
Soft tissue	51 (10)	45 (8)	ND	ND
Bones and soft tissue	217 (40)	241 (45)	ND	ND
Lymph nodes	2 (< 1)	3 (1)	102 (28)	221 (31)

Table 9: Characteristics of the study populations – RCT, indirect comparison: enzalutamide + ADT vs. docetaxel + prednisolone + ADT (multipage table)

Study characteristic category	ARCHES		STAMPEDE	
	enzalutamide + ADT	placebo + ADT	docetaxel + prednisolone + ADT	ADT
	N[a] = 536	N[a] = 531	N[a] = 362	N[a] = 724
Prior therapy, n (%)				
Prostatectomy or radiotherapy				
Radical prostatectomy	61 (11)	76 (14)	ND	ND
Bilateral orchiectomy	44 (8)	27 (5)	ND	ND
Radiotherapy	86 (16)	86 (16)	ND	ND
Prostatectomy + radiotherapy	ND	ND	ND	ND
Prior therapy with an ATD, n (%)			0 (0)	0 (0)
None	39 (7.3)	55 (10.4)	362 (100)[h]	221 (100)[h]
≤ 3 months	390 (72.8)	369 (69.5)	–	–
> 3 months	107 (20.0)	107 (20.2)	–	–
Previous docetaxel therapy, n (%)				
No	445 (83)	438 (82)	Pretreatment with chemotherapy was not allowed.	
Yes	91 (17)[d]	93 (18)[d]		
Treatment discontinuation, n (%)	128 (24)	234 (44)	ND[i]	ND
Study discontinuation, n (%)	59 (10)[e]	86 (15)[e]	ND	ND

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. [Min; Max].
c. Data for WHO PS 0 or 1 to 2.
d. Institute's calculation.
e. Data for the total population: enzalutamide + ADT (N = 574), placebo + ADT (N = 576), information for the subpopulation is not available.
f. Only patients with confirmed metastasis based on an independent central review upon screening at baseline were included in the analysed subpopulation.
g. Only patients in the metastatic stage were included in the analysed subpopulation.
h. All patients started ADT at study inclusion.
i. 29 patients in the docetaxel arm did not start the treatment.

ADT: androgen deprivation therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; GnRH: gonadotropin-releasing hormone; mHSPC: metastatic hormone sensitive prostate cancer; n: number of patients in the category; N: number of randomized patients; ND: not data; RCT: randomized controlled trial; SD: standard deviation; WHO PS: World Health Organization Performance Status

The characteristics of the patients were largely balanced between the arms of the individual studies. The mean age of the patients in both studies was 70 or 65 years, all of them had distant metastases at baseline and the majority of the patients had a Gleason score ≥ 8 and a good general condition (ECOG PS or WHO PS von 0). Differences between the studies were found in the proportion of patients with high or unknown tumour load and, where applicable, patients with ECOG/WHO PS 2. Furthermore, differences were shown in the pretreatment with ADT and docetaxel. These aspects are discussed in Section 2.3.3 on the examination of similarity.

Treatment duration and observation period

Table 10 shows the mean and median treatment duration of the patients and the mean and median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, indirect comparison: enzalutamide + ADT vs. docetaxel + prednisolone + ADT

Study **duration of the study phase** **outcome category**	**Enzalutamide + ADT** **or** **docetaxel + prednisolone + ADT**	**(Placebo +) ADT**
Enzalutamide + ADT vs. placebo + ADT		
ARCHES	N = 536[a]	N = 531[a]
Treatment duration [months]		
Median [min; max]	13.1 [0; 27]	11.5 [0; 25]
Mean (SD)	13.2 (5.1)	11.7 (5.2)
Observation period [months]		
Overall survival		
Median [Q1; Q3]	14.3 [1; 30]	13.5 [0; 29]
Mean (SD)	14.5 (4.5)	13.9 (4.6)
Morbidity		
Symptomatic skeletal-related events, symptoms (EORTC QLQ-PR25, FACT-P), health status (EQ-5D VAS)	ND	ND
Health-related quality of life (EORTC QLQ-PR25)	ND	ND
Side effects		
Median [min; max]	13.2 [1; 27]	11.6 [1; 25]
Mean (SD)	13.4 (4.9)	12.0 (5.0)
Docetaxel + prednisolone + ADT vs. ADT		
STAMPEDE	N = 362	N = 724
Treatment duration [months]	ND	ND
Observation period [months]		
Overall survival		
Median [Q1; Q3]	76.4 [ND]	78.2 [ND]
Mean (SD)	ND	ND
Morbidity		
Symptomatic skeletal-related events		
Median [Q1; Q3]	76.4 [ND]	78.2 [ND]
Mean (SD)	ND	ND
Symptoms (EORTC QLQ-C30, EORTC QLQ-PR25)	ND	ND
Health-related quality of life (EORTC C30, EORTC QLQ-PR25)	ND	ND
Side effects	ND	ND

a. Data in the table are partly based on slightly different patient numbers (± 2) in the respective treatment groups.

ADT: androgen deprivation therapy; EORTC: European Organization for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PR25: Quality of Life Questionnaire Prostate Cancer with 25 items; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

Within the ARCHES study, there are no relevant differences between the treatment arms in the median and mean treatment duration and the median observation period for the outcome "overall survival" and the outcomes on side effects. Information on the observation periods of the outcomes on morbidity and health-related quality of life is lacking. Data on the treatment duration are missing for the STAMPEDE study. The median observation periods for the outcomes "overall survival" and "symptomatic skeletal-related events" do not differ relevantly between the treatment arms. Data on the observation period for further outcomes are not available.

There are clear differences in the observation periods between the individual studies. However, this has no consequences for the indirect comparison of the two studies. Assuming proportional hazards, the observation period does not affect the point estimation of the effect in the case of the analysis method chosen here for the indirect comparison (Cox proportional hazards model). Since this model assumption seems to be acceptable, the adjusted indirect comparison can be carried out and assessed despite the differences in the observation periods between the studies.

2.3.3 Similarity of the studies for the indirect comparison

Several aspects concerning the similarity of the studies arise from the study characteristics described in the previous Section 2.3.2. These are discussed in more detail below.

Similarity of study conduct

Study design

Both included studies are multicentre RCTs. While the ARCHES study is a double-blind study, the STAMPEDE study is unblinded. The lack of blinding usually leads to a high risk of bias of the corresponding results for subjectively recorded outcomes. However, since in the present data constellation an adjusted indirect comparison is not performed for any such outcomes, the lack of blinding has no effect in this respect (see Section 2.4.2).

Moreover, the periods of study conduct differ. The STAMPEDE already study started in 2005, whereas the ARCHES study did not start before 2016. Possible effects of this are described below.

Concomitant therapies

There may be differences in the concomitant therapies due to different time periods of study conduct. The use of pharmacological prevention and treatment of skeletal-related events was allowed in both studies. In the ARCHES study, drugs from the bisphosphonate group or the drug denosumab were permitted for the prophylaxis and treatment of skeletal-related events or for the treatment of osteoporosis, if a stable dose was continued. In the STAMPEDE study, all necessary drugs were permitted. However, the drug denosumab was only approved in 2010 and was not available to the included patients during the first 5 years of the STAMPEDE study. Information on the concomitant therapies performed in the STAMPEDE study is not available. Therefore, it cannot be assessed to what extent there were further differences in concomitant

treatment beyond the described availability of denosumab. Overall, it is not known how many patients received concomitant treatment to prevent or treat skeletal-related events and which drugs were used for it. Although the difference described does not call into question the fundamental similarity of the studies, it is taken into account for the individual outcomes, especially when interpreting the results of the outcome "symptomatic skeletal-related events" (see Section 2.4.3).

Subsequent therapies

The data on subsequent therapies in the individual studies ARCHES and STAMPEDE presented in Table 28 and Table 29 of the full dossier assessment are not comparable per se due to the clear differences in the observation periods and different categorization of the subsequent therapies. However, it can be inferred from the data that similar therapies were basically available and used in both studies, predominantly hormone therapy (e.g. abiraterone, enzalutamide) and/or chemotherapy (mainly with docetaxel). Overall, the used drugs largely reflect the recommendations of the S3 Guideline on Early Detection, Diagnostics and Therapy of Prostate Cancer [3]. Some drugs such as enzalutamide or abiraterone were only available later in the course of the STAMPEDE study due to different time periods of study conduct. Overall, the sufficient similarity of the two studies with regard to the subsequent therapies for conducting an adjusted indirect comparison is not fundamentally questioned.

Similarity of the patient population

Patient characteristics

The demographic and clinical characteristics of the included patients, such as age, family origin and Gleason score, are sufficiently comparable between the studies ARCHES and STAMPEDE.

Smaller differences between the studies were shown in the ECOG PS and WHO PS. Here, in contrast to the ARCHES study, patients with a WHO PS 2 were also allowed per inclusion criterion in the STAMPEDE study. The number of patients with an WHO PS 2 is unknown. However, since approx. 3 quarters of the patients in both studies were in good general condition with an ECOG PS/WHO PS of 0, it is assumed that the study populations were sufficiently similar with regard to these aspects.

All patients included in the adjusted indirect comparison had distant metastases at baseline. However, there are differences between the studies in the proportion of patients with low or high tumour loads. In the STAMPEDE study, the tumour load was unknown in almost 25% of the patients, the proportion of patients with low tumour load was at least approx. 35%, and the proportion with high tumour load was at least approx. 40%. Due to the proportion of patients with unknown tumour load, the similarity of the study populations cannot be conclusively assessed. However, the similarity of the studies is not fundamentally questioned.

Pretreatment

Pretreatment with ADT

There are differences in the pretreatment with ADT between the studies ARCHES and STAMPEDE. In the ARCHES study, the majority of patients had pretreatment with ADT (> 90percentage), although for most patients (about 70%), this pretreatment had started ≤ 3 months before the start of the study. In the STAMPEDE study, preference was given to include patients whose ADT had not been initiated prior to randomization; in the relevant subpopulation of the STAMPEDE study, ADT for the treatment of mHSPC was initiated in all patients only after randomization. A comparatively short pretreatment with ADT of ≤ 3 months in the ARCHES study compared to the total treatment duration in both studies (see Table 10), is not expected to have a significant impact, in particular because an ADT is used permanently. Overall, it is not assumed that the patients of the ARCHES study therefore differed significantly from the patients of the relevant subpopulation of the STAMPEDE study at the time of randomization, for example with regard to their disease severity or their risk profile.

Docetaxel pretreatment

Another difference in the pretreatment between the studies was that pretreatment with docetaxel (≤ 6 cycles) was allowed in the ARCHES study. Pretreatment with the chemotherapy was not allowed in the STAMPEDE study. However, as approx. 83% of the patients in the ARCHES study had not received pretreatment with docetaxel prior to study inclusion, it is assumed that the similarity of the study populations does not have to be fundamentally questioned.

Similarity of the common comparator

Treatment in the common comparator arm was placebo + ADT in the ARCHES study, and ADT in STAMPEDE. In both studies, this could be done surgically or with medication by administering GnRH analogues (GnRH agonists or antagonists). In both studies, short-term administration of antiandrogens was considered appropriate when GnRH agonists were used. The use of first-generation anti-androgens for ≥ 7 days in addition to GnRH agonists to control the increase in testosterone in patients with bone metastases is also recommended according to the clinical practice guideline for prostate cancer of the National Comprehensive Cancer Network (NCCN) [4]. In the STAMPEDE study, prolonged treatment with oral antiandrogens was also possible. At study inclusion, long-term administration of antiandrogens was planned for about 15% of the patients in the total population; long-term administration of bicalutamide or MAB for individual patients was planned for the relevant subpopulation [23]. It is unknown how many patients in the relevant subpopulation were actually treated with anti-androgens and how long this treatment lasted.

This difference as well as the described differences in the pretreatment with ADT (see section on the similarity of pretreatments with ADT above) do not fundamentally call into question the similarity of the common comparator.

Summary on the comparability of the studies

The overall consideration shows some differences in the study and patient characteristics between the ARCHES and STAMPEDE studies, none of which, however, fundamentally calls into question the sufficient similarity for conducting an adjusted indirect comparison via the common comparator placebo + ADT or ADT. These described uncertainties were taken into account in the interpretation of the results.

This concurs with the assessment of the company insofar, as it considers the studies ARCHES and STAMPEDE to be sufficiently similar for carrying out an adjusted indirect comparison. However, the company also considers the ENZAMET and CHAARTED studies to be relevant for the assessment (see Section 2.3).

2.3.4 Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, indirect comparison: enzalutamide + ADT vs. docetaxel + prednisolone + ADT

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			
Enzalutamide + ADT vs. placebo + ADT							
ARCHES	Yes	Yes	Yes	Yes	Yes	Yes	Low
Docetaxel + prednisolone + ADT vs. ADT							
STAMPEDE	Yes	Yes	No	No	Yes	Yes	Low
ADT: androgen deprivation therapy; RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for both studies. This concurs with the company's assessment.

Transferability of the study results to the German health care context

Since the included studies were planned as multinational, multicentre RCTs, transferability to the German healthcare context can be assumed from the company's point of view. Moreover, there were no hints suggesting why the characteristics of the patients in Germany would differ from those of the study populations.

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

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptomatic skeletal-related events
  - symptoms
  - health status (visual analogue scale [VAS] of the European Quality of Life-5 Dimensions [EQ-5D])
- Health-related quality of life
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - further specific AEs, if any

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

Table 12 shows for which outcomes data were available in the included studies (yes/no) and whether an indirect comparison is possible based on the available data (yes/no).

Table 12: Matrix of outcomes – RCT, indirect comparison: enzalutamide + ADT vs. docetaxel + prednisolone + ADT

Study	Outcomes								
	Overall survival	Symptoms	Symptomatic skeletal-related events	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[a]	Discontinuation due to AEs	Specific AEs
Enzalutamide + ADT vs. placebo + ADT									
ARCHES	Yes	Yes[b]	Yes[c]	No[d]	Yes[e]	Yes	Yes	No[d]	No[f]
Docetaxel + prednisolone + ADT vs. ADT									
STAMPEDE	Yes	Yes[g]	Yes[c]	No[h]	Yes[g]	Yes	Yes	No[h]	No[f]
Indirect comparison possible	Yes	No[i]	No[j]	No	No[i]	Yes[k]	No[f]	No	No[f]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Recorded using the BPI-SF (pain). e. The results on the EORTC QLQ-PR25 are not usable (see below).
c. Operationalized as radiotherapy of the bone, bone surgery, pathologic bone fracture or spinal cord compression.
d. The outcome was recorded in the ARCHES study, but the company presented no data on the outcome in Module 4.
e. Recorded using the FACT-P. The results on the EORTC QLQ-PR25 are not usable (see below).
f. Requirement for the certainty of results to perform an adjusted indirect comparison is not met. Therefore, no specific AEs were selected.
g. Recorded with the EORTC QLQ-C30 and the EORTC QLQ-PR25
h. Outcome not recorded.
i. Usable data on all instruments used for the recording of outcomes in this category are available from a maximum of 1 study; hence, an indirect comparison is not possible.
j. In the present assessment, an indirect comparison was not conducted for the outcome due to insufficient similarity.
k. Despite a high risk of bias, an indirect comparison was presented for the outcome SAE due to the special size of the effect.

ADT: androgen deprivation therapy; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FACT-P: Functional Assessment of Cancer Therapy-Prostate; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PR25: Quality of Life Questionnaire Prostate Cancer with 25 items; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Morbidity and health-related quality of life

- For the outcome "symptomatic skeletal-related events", the studies ARCHES and STAMPEDE show markedly different rates of patients with event in the respective common comparator arm at all time points recorded, which calls into question the

outcome-related similarity of both studies. For example, when considering the time point of 24 months, the common comparator arm of the ARCHES study shows a symptomatic skeletal-related event in approx. 19% and the STAMPEDE study in approx. 38% of the patients (see Appendix C; each rate estimated on the basis of the available Kaplan-Meier curves). In both studies, prophylactic medication for skeletal-related events was principally permitted, but no information is available in how many patients and with which drugs concomitant treatment for skeletal-related events was actually used (see also Section 2.3.3). Therefore, the studies are not sufficiently similar for this outcome, so that the available data could not be used and an indirect comparison was not carried out.

- In the ARCHES study, symptoms and health-related quality of life were assessed with the EORTC QLQ-PR25 questionnaire, among others. According to the authors of the EORTC QLQ-PR25, this questionnaire is only valid in conjunction with the core questionnaire (QLQ-C30) [30]. This was not recorded in the ARCHES study. When only the QLQ-PR-25 is presented in isolation, the content validity is not given, for example, with regard to the completeness of symptoms and/or functional restrictions. For this reason, the results of the EORTC QLQ-PR25 are considered unusable for the ARCHES study.

Side effects

- No choice of specific AEs was made as the requirement for the certainty of results to conduct an adjusted indirect comparison for the side effect outcomes was not met.

2.4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, indirect comparison: enzalutamide + ADT vs. docetaxel + prednisolone + ADT

Study	Study level	Outcomes								
		Overall survival	Symptoms	Symptomatic skeletal-related events	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[a]	Discontinuation due to AEs	Specific AEs
Enzalutamide + ADT vs. placebo + ADT										
ARCHES	N	N	–[b]	–[b]	–[b]	–[b]	H[c]	H[c]	–[d]	–[e]
Docetaxel + prednisolone + ADT vs. ADT										
STAMPEDE	N	N	–[b]	–[b]	–[b]	–[b]	H[f]	H[f]	–[d]	–[e]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Indirect comparison cannot be performed (see Section 2.4.1).
c. Presumably high proportion of incomplete observations for potentially informative reasons: high proportions regarding progression-related discontinuation of the study medication (enzalutamide + ADT: 24% vs. placebo + ADT: 42%) and follow-up observation of AEs only up to 30 days after administration of the last study medication.
d. No data available.
e. The requirement for the certainty of results to perform an adjusted indirect comparison is not met. Therefore, no specific AEs were selected.
f. High proportion of incomplete observations, especially in the docetaxel ± prednisolone + ADT treatment arm: AEs were observed up to a maximum of 7 months after the start of treatment.

ADT: androgen deprivation therapy; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; H: high, L: low; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

No indirect comparison can be performed for outcomes that were not recorded in at least 1 of the 2 studies of the indirect comparison, that were not used due to insufficient content validity or that did not show sufficient similarity. Hence, the risk of bias was not assessed for these outcomes.

Study ARCHES

For the ARCHES study, the risk of bias of the results on "overall survival" was rated as low, which concurs with the company's assessment. For the outcomes "SAEs" and "severe AEs (CTCAE grade ≥ 3)", each observed up to 30 days after treatment discontinuation, there is a high risk of bias due to possibly high proportions of patients with incomplete observation that are differential between treatment arms. This deviates from the assessment of the company, which rated the risk of bias of the results on SAEs and severe AEs (CTCAE grade ≥ 3) as low.

Study STAMPEDE

In the STAMPEDE study, the risk of bias of the results on "overall survival" was rated as low, which concurs with the company's assessment. The risk of bias of the outcomes "SAEs" and "severe AEs (CTCAE grade ≥ 3)" was assessed as high due to incomplete observations at clearly different observation periods between the treatment arms. These are mainly due to the fact that, according to the approval, treatment with docetaxel in the intervention arm was limited to a maximum of 6 cycles, while treatment with ADT in the comparator arm was performed until progression or treatment discontinuation for other reasons. Follow-up of patients in the docetaxel + prednisolone + ADT arm was based on the duration of docetaxel treatment, so that patients in the docetaxel + prednisolone + ADT arm were followed up for a much shorter time overall, at most for 6 to 7 months from randomization for AEs (see Appendix B of the full dossier assessment). The effect estimation presented by the company, the hazard ratio from a Cox proportional hazards model, is appropriate in the present data constellation and is used.

This assessment deviates from that of the company, which rated the risk of bias of the results for the outcomes on SAEs and severe AEs (CTCAE grade ≥ 3) as low.

Results that show a high risk of bias in one of the two studies do not provide the certainty of results necessary to conduct an adjusted indirect comparison. At first, there is thus no sufficient certainty of results for an adjusted indirect comparison for any of the outcomes of the side effects category for which usable data are available in the individual studies. For the outcome "SAE", however, there is a sufficiently high qualitative certainty of results for the interpretation of the present effect due to the special size of the effect (see Section 2.4.3).

2.4.3 Results

Table 14 summarizes the results on the comparison of enzalutamide with docetaxel with prednisolone each in combination with conventional ADT in patients with mHSPC. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Kaplan-Meier curves on the presented event time analyses can be found in Appendix B of the present dossier assessment. Results on common AEs are presented in Appendix D.

Table 14: 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					
All-cause mortality					
Enzalutamide + ADT vs. placebo + ADT					
ARCHES	536	NA 39 (7.3)	531	NA 45 (8.5)	0.79 [0.51; 1.22]; 0.284
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 using common comparators[a]:					
Enzalutamide + ADT vs. docetaxel + prednisolone + ADT					0.98 [0.61; 1.55]; 0.916[b]
Morbidity					
Symptomatic skeletal-related events	No indirect comparison due to insufficient similarity				
Symptoms	No (usable) data for the indirect comparison[c]				
Health status (EQ-5D VAS)	No (usable) data for the indirect comparison[d]				
Health-related quality of life	No (usable) data for the indirect comparison[c]				
Side effects					
AEs (supplementary information)					
Enzalutamide + ADT vs. placebo + ADT					
ARCHES	534	1.0 [1.0; 1.4] 457 (85.6)	530	1.6 [1.1; 2.1] 457 (86.2)	–
Docetaxel + prednisolone + ADT vs. ADT					
STAMPEDE	335	0.8 [0.7; 1.1] 327 (97.6)	724	1.5 [1.5; 1.5] 693 (95.7)	–

Table 14: 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**
SAEs					
Enzalutamide + ADT vs. placebo + ADT					
ARCHES	534	NA [22.7; NC] 100 (18.7)	530	NA 106 (20.0)	0.83 [0.63; 1.09]; 0.182
Docetaxel + prednisolone + ADT vs. ADT					
STAMPEDE	335	NA 96 (28.7)	724	NA [109.1; NA] 80 (11.0)	9.04 [5.92; 13.79]; < 0.001
Indirect comparison using common comparators[a]:					
Enzalutamide + ADT vs. docetaxel + prednisolone + ADT					0.09 [0.06; 0.15]; < 0.001
Severe AEs[e]					
Enzalutamide + ADT vs. placebo + ADT					
ARCHES	534	NA [22.0; NC] 132 (24.7)	530	NA 140 (26.4)	0.87 [0.68; 1.10]; 0.250
Docetaxel + prednisolone + ADT vs. ADT					
STAMPEDE	335	NA 108 (32.2)	724	NA [102.8; NC] 219 (30.2)	2.39 [1.84; 3.11]; < 0.001
Indirect comparison using common comparators[a]:					
Enzalutamide + ADT vs. docetaxel + prednisolone + ADT					_[f]
Discontinuation due to AEs	No (usable) data for the indirect comparison[d]				

a. Indirect comparison according to Bucher [31].
b. Institute's calculation.
c. Usable data on all instruments used for the recording of outcomes in this category are available from a maximum of 1 study; hence, an indirect comparison is not possible (see Section 2.4.1).
d. The outcome was only recorded in the ARCHES study, but the company presented no data on the outcome in Module 4.
e. Severe AEs are operationalized as CTCAE grade ≥ 3.
g. An indirect comparison was not calculated as the requirement for the certainty of results to perform an adjusted indirect comparison was not met (see Section 2.4.1).

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 one) event; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

There was one RCT each on both sides of the available adjusted indirect comparison. Hence, the homogeneity was not checked. As there is no study of direct comparison for the comparison of enzalutamide + ADT versus the ACT, the consistency of the results cannot be checked. Therefore, the adjusted indirect comparisons had at most a low certainty of results. Hence, at most hints, e.g. of an added benefit, can be derived on the basis of the data available from the adjusted indirect comparison.

Mortality

Overall survival

The adjusted indirect comparison showed no statistically significant difference between enzalutamide + ADT and docetaxel + prednisolone + ADT for the outcome "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.

This deviates from the assessment of the company, which, on the basis of the direct and adjusted indirect comparison submitted by it, including further studies for overall survival, derived an indication of an added benefit for patients with low tumour load.

Morbidity

Symptomatic skeletal-related events

Due to the insufficient similarity of the two studies with regard to the outcomes, there are no usable data for an adjusted indirect comparison for the outcome "symptomatic skeletal-related events" (see Section 2.4.1). 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.

This concurs with the assessment of the company insofar as the company also derived no hint of an added benefit for the outcome "symptomatic skeletal-related events" from the results of the adjusted indirect comparison submitted by it.

Symptoms

The studies ARCHES and STAMPEDE partly used different instruments for the outcome "symptoms" to record the morbidity (see Section 2.4.1).

There are no usable data for an adjusted indirect comparison (see Section 2.4.1). 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.

This concurs with the assessment of the company insofar as the company also derived no hint of an added benefit for the outcomes on symptoms from the results of the indirect comparisons submitted by it.

Health status

There were no data for an adjusted indirect comparison for the outcome “health status”. 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.

This concurs with the assessment of the company, which also did not use the outcome “health status” for the assessment.

Health-related quality of life

The studies ARCHES and STAMPEDE partly used different instruments to record the outcome “health-related quality of life” (see Section 2.4.1).

There are no usable data for an adjusted indirect comparison (see Section 2.4.1). 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.

This concurs with the assessment of the company insofar as the company also derived no hint of an added benefit for the outcomes on health-related quality of life from the results of the indirect adjusted comparisons submitted by it.

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. The prerequisites for the derivation of conclusions with sufficient certainty of results on the added benefit from an adjusted indirect comparison were therefore initially not fulfilled. For this outcome, however, both the STAMPEDE study and the adjusted indirect comparison using the common comparator placebo + ADT or ADT each show a very large effect estimation. It is not assumed in the present data situation that the advantage in the adjusted indirect comparison is completely called into question by potential bias (Section 2.4.2). Thus, there is a sufficiently high qualitative certainty of results for the interpretation of the present effect despite the high outcome-specific risk of bias in the studies ARCHES and STAMPEDE. Furthermore, the aspects of similarity of the studies described above (Section 2.3.3) do not call into question the conduct of an adjusted indirect comparison. Therefore, in the present situation, the derivation of a hint of greater or lesser harm from enzalutamide + ADT is possible.

The adjusted indirect comparison for the outcome SAE 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.

This deviates from the assessment of the company, which derived an indication of an added benefit with the extent “major” for the SAE outcomes.

Severe AEs (CTCAE grade ≥ 3)

For the results on the outcome “severe AEs (CTCAE grade ≥ 3)”, there is a high risk of bias in the studies ARCHES and STAMPEDE (see Section 2.4.2). Thus, the certainty of results of an effect estimation for the indirect comparison is insufficient for this outcome.

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.

This deviates from the assessment of the company, which used the outcome “severe AEs (CTCAE grade ≥ 3)” and, together with the outcome “SAEs”, derived an indication of an added benefit with the extent “major”.

Discontinuation due to AEs

No data are available for an indirect comparison for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from enzalutamide + ADT in comparison with docetaxel + prednisolone + ADT; greater or lesser harm is therefore not proven.

This concurs with the approach of the company, which did not use the outcome "discontinuation due to AEs” for the assessment either.

2.4.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered in the present assessment:

- Age (< 65 vs. ≥ 65 years in ARCHES or < 70 vs. ≥ 70 years in STAMPEDE)
- Tumour load (low vs. high)

In the ARCHES study, the above-mentioned characteristics “age” and “tumour load” were established a priori as potential effect modifiers. In the STAMPEDE study, the characteristic “age” was predefined, while the characteristic “tumour load” was introduced through a modification of the statistical analysis plan of the study.

The company stated that, on the basis of the published data, only selective subgroup analyses can be conducted, taking into account individual studies. As far as possible, the company presented meta-analyses of the studies ARCHES and ENZAMET or STAMPEDE and CHAARTED for the subgroup characteristic “tumour load” for the outcome “overall survival”. Moreover, Module 4A of the dossier contains published results of the STAMPEDE study on the outcome “overall survival” for the subgroup characteristic “tumour load”. It is unclear why the company used no corresponding published analyses also for the characteristic “age” [21].

In Module 4A of the dossier, the company presented no usable data on subgroup analyses for the ARCHES study alone.

Thus, an assessment of the subgroup results is not possible on the basis of the available data.

2.5 Probability and extent of added benefit

Probability and extent of the 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 [1].

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.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 15).

Table 15: Extent of added benefit at outcome level: enzalutamide + ADT vs. docetaxel + prednisolone + ADT

Outcome category **outcome**	**Enzalutamide + ADT** **vs. docetaxel + prednisolone + ADT** **median time to event (months)** **effect estimation [95% CI]; p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	NA vs. 59.1 HR: 0.98 [0.61; 1.55]; p = 0.916	Lesser benefit/added benefit not proven
Morbidity		
Symptomatic skeletal-related events	No indirect comparison due to insufficient similarity	Lesser benefit/added benefit not proven
Symptoms	No (usable) data[c]	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No (usable) data[d]	Lesser benefit/added benefit not proven
Health-related quality of life		
	No (usable) data[c]	Lesser benefit/added benefit not proven
Side effects		
SAEs	NA vs. NA HR: 0.09 [0.06; 0.15]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects lesser harm, extent: "non-quantifiable"[e]
Severe AEs (CTCAE grade ≥ 3)	No (usable) data[f]	Greater/lesser harm not proven
Discontinuation due to AEs	No (usable) data[d]	Greater/lesser harm not proven
Specific AEs	No (usable) data[f]	Greater/lesser harm not proven

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Usable data on all instruments used for the recording of outcomes in this category are available from a maximum of 1 study; hence, an indirect comparison is not possible (see Section 2.4.1).
d. The outcome was recorded only in the ARCHES study.
e. The size of the effect cannot be quantified due to the present data constellation (see Section 2.4.3).
f. Requirement for the certainty of results to perform an adjusted indirect comparison is not met (see Section 2.4.3).

ADT: androgen deprivation therapy; AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; SAE: serious adverse event; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 16 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of enzalutamide + ADT in comparison with docetaxel + prednisolone + ADT

Positive effects	**Negative effects**
Serious/severe side effects ▪ overall SAE rate: hint of lesser harm – extent: "non-quantifiable"	-
Data usable for the indirect comparison are not available for the outcomes of the categories “morbidity” and “health-related quality of life”, nor for the outcome “discontinuation due to AEs” and for specific AEs.	
ADT: androgen deprivation therapy; AE: adverse event; SAE: serious adverse event	

The overall consideration of the results only shows a positive effect of enzalutamide + ADT in the category “side effects”. The advantage for the outcome “SAE” is not challenged by any disadvantage. Usable data are not available for the outcomes of the categories “morbidity” and “health-related quality of life”, nor for the outcome “discontinuation due to AEs” and for specific AEs.

In summary, there is a hint of a non-quantifiable added benefit of enzalutamide in combination with ADT versus the ACT docetaxel with or without prednisone or prednisolone in combination with ADT for patients with mHSPC and a good general condition.

The result of the assessment of the added benefit of enzalutamide in comparison with the ACT is summarized in Table 17.

Table 17: Enzalutamide – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
For the treatment of adult men with mHSPC in combination with ADT	▪ Only for patients with distant metastasis (M1 stage) and 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. Detailed information on the number of patients with WHO PS 2 is not available (see Table 9). The conclusion on the added benefit thus refers to patients with mHSPC and a 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 + 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 assessment described above deviates from that of the company, which derived an indication of major added benefit.

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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

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