IQWiG Reports – Commission No. A18-80

Enzalutamide (prostate cancer) –

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

Extract

[1] Translation of the executive summary of the dossier assessment *Enzalutamid (Prostatakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 26 February 2019). Please note: This document was translated by an external translator and 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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Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) 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 19 November 2018.

Research question

The aim of the present report is to assess the added benefit of enzalutamide compared with the appropriate comparator therapy (ACT) of a wait-and-see approach while continuing the existing conventional androgen deprivation therapy (ADT) in patients with non-metastatic castration-resistant high-risk prostate cancer (high-risk nmCRPC).

Table 2 presents the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2[2]: Research question of the benefit assessment for enzalutamide

Indication	**ACT[a]**
Non-metastatic castration-resistant high-risk prostate cancer	Wait-and-see approach while continuing the existing conventional ADT[b]
a: Presentation of the ACT specified by the G-BA. b: Surgical castration or drug-based castration through therapy with GnRH agonists or GnRH antagonists. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone	

The company followed the G-BA's specification of the ACT.

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

Results

The PROSPER study was included for assessing any added benefit of enzalutamide in patients with non-metastatic castration-resistant high-risk prostate cancer (high-risk nmCRPC).

Study design

The PROSPER study is a randomized, double-blind, placebo-controlled, parallel-group study comparing enzalutamide in combination with ADT versus treatment with ADT and additional

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

use of placebo. Included were adult patients with high-risk nmCRPC. A total of 1401 patients were included and randomized to the two arms at a 2:1 ratio.

Patients were treated according to the specifications set forth in the Summary of Product Characteristics (SPC) for enzalutamide for the therapeutic indication being reviewed here. Patients in the study had to continue the ADT in addition to their study medication. The ADT was either drug-based castration through a gonadotropin-releasing hormone (GnRH) agonist/antagonist or previous bilateral orchiectomy. Patients were treated until disease progression, initiation of chemotherapy, use of androgen receptor inhibitors or other investigational substances, or treatment discontinuation as decided by the physician or patient.

The study's primary outcome was metastasis-free survival (MFS); patient-relevant secondary outcomes included mortality, pain, health status, health-related quality of life, and adverse events.

Risk of bias

The risk of bias at study level was rated as low. Except for the two outcomes of overall survival and discontinuation due to adverse events (AEs), the risk of bias at the outcome level was rated as high.

Results

Mortality

Overall survival

No statistically significant difference between treatment arms was found for the outcome of overall survival. Consequently, there is no hint of added benefit of enzalutamide + ADT in comparison with the wait-and-see approach + ADT; an added benefit is therefore not proven.

Morbidity

Worst pain

The outcome of worst pain was analysed using item 3 of the Brief Pain Inventory – Short Form (BPI-SF). No statistically significant difference between the treatment arms was found for time to first deterioration. Consequently, with respect to the outcome of worst pain, there is no hint of added benefit of enzalutamide in comparison with the wait-and-see approach + ADT; an added benefit is therefore not proven.

Interference due to pain

The outcome of interference due to pain was surveyed by means of BPI-SF items 9a–g. No statistically significant difference between treatment arms was found for this outcome. Consequently, with respect to the outcome of interference due to pain, there is no hint of added benefit of enzalutamide + ADT in comparison with the wait-and-see approach + ADT; an added benefit is therefore not proven.

Health status (Visual Analog Scale [VAS] of the European Quality of Life – 5 Dimensions [EQ-5D])

No statistically significant difference between treatment arms was found on the basis of mean value comparisons for the health status outcome, as measured using the EQ-5D VAS. Consequently, there is no hint of added benefit of enzalutamide + ADT in comparison with the wait-and-see approach + ADT; an added benefit is therefore not proven.

Health-related quality of life

The outcome of health-related quality of life was surveyed using the FACT-P. No statistically significant difference between the treatment arms was found for time to first deterioration. Consequently, with respect to the outcome of health-related quality of life, there is no hint of added benefit of enzalutamide + ADT in comparison with the wait-and-see approach + ADT; an added benefit is therefore not proven.

Adverse events

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

No statistically significant difference between treatment arms was found for any of the outcomes of SAEs, severe AEs (CTCAE grade ≥ 3), and discontinuation due to AEs. Consequently, none of these outcomes result in a hint of greater or lesser harm from enzalutamide + ADT in comparison with the wait-and-see approach + ADT; greater or lesser harm is therefore not proven.

Renal and urinary disorders (system organ class [SOC], severe AEs CTCAE grade ≥ 3), urinary tract infections (preferred term [PT], AEs)

A statistically significant difference in favour of enzalutamide + ADT compared with placebo + ADT was found for each of the outcomes of renal and urinary disorders (SOC, severe AEs CTCAE grade ≥ 3) and urinary tract infections (PT, AEs). This results in a hint of lesser harm from enzalutamide + ADT versus the wait-and-see approach + ADT for the outcome of renal and urinary disorders (SOC, severe AEs CTCAE grade ≥ 3).

For the outcome of urinary tract infections, an effect modification by the Gleason score attribute was found. Consequently, for patients with a Gleason score ≤ 7, there is a hint a lesser harm from enzalutamide + ADT. Conversely, for patients with a Gleason score ≥ 8, there is no hint of greater or lesser harm from enzalutamide + ADT compared to the wait-and-see approach + ADT; greater or lesser harm is therefore not proven for these patients.

Nervous system disorders (SOC, severe AEs CTCAE grade ≥ 3), fatigue (PT, severe AEs CTCAE grade ≥ 3), decreased appetite (PT, AEs), vascular disorders (SOC, AEs), fall (PT, AEs)

A statistically significant difference to the disadvantage of enzalutamide + ADT versus the wait-and-see approach + ADT was found for each of the following outcomes: nervous system

disorders (SOC, severe AEs CTCAE grade ≥ 3), fatigue (PT, severe AEs CTCAE grade ≥ 3), decreased appetite (PT, AEs), vascular disorders (SOC, AEs), and fall (PT, AEs). Consequently, there is a hint of greater harm from enzalutamide + ADT versus placebo for the outcomes: nervous system disorders (SOC, severe AEs CTCAE grade ≥ 3), fatigue (PT, severe AEs CTCAE grade ≥ 3), decreased appetite (PT, AEs), and vascular disorders (SOC, AEs).

For the outcome regarding falls, an effect modification by the attribute of age was found. Consequently, for patients ≥ 75 years of age, there is a hint a greater harm from enzalutamide + ADT. Conversely, for patients < 75 years of age, there is no hint of greater or lesser harm from enzalutamide + ADT versus the wait-and-see approach + ADT; greater or lesser harm is therefore not proven for these patients.

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

On the basis of the results presented, the probability and extent of added benefit of the drug enzalutamide in comparison with the ACT is assessed as follows:

A high-level review of the results reveals both positive and negative effects for enzalutamide (in some cases only in subgroups) in the adverse events category. It is questionable in this regard whether the positive effects revealed by the comparison of enzalutamide with placebo for the outcomes of renal and urinary disorders and urinary tract infections are in fact attributable to the outcome category of adverse events or rather mark the progression of the underlying disease. A clear distinction is not possible on the basis of the available information. Irrespective thereof, on high-level review, the positive and negative effects of enzalutamide play a lesser role.

In summary, for patients with high-risk nmCRPC, there is no hint of an added benefit of enzalutamide + ADT versus the ACT of the wait-and-see approach while continuing the existing, conventional ADT; an added benefit is not proven.

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

[3] 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

Indication	**ACT**[a]	**Probability and extent of added benefit**
Non-metastatic castration-resistant high-risk prostate cancer	Wait-and-see approach while continuing the existing conventional ADT[b]	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. b: Surgical castration or drug-based castration through therapy with GnRH agonists or GnRH antagonists. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone		

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

Note:

An addendum (A19-34) to dossier assessment A18-80 has been published.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10 July 2017 [Accessed: 4 June 2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-80-enzalutamide-prostate-cancer-benefit-assessment-according-to-35a-social-code-book-v.11102.html.