# Darolutamide (prostate cancer)

## Addendum to Project A23-21 (dossier assessment)[1]

**ADDENDUM**

Project: A23-81 Version: 1.0 Status: 24 August 2023

[1] Translation of addendum A23-81 *Darolutamid (Prostatakarzinom) – Addendum zum Projekt A23-21 (Dossierbewertung)*. 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 |
|---|---|
| ADT | androgen deprivation therapy |
| DRS-P | Disease-Related Symptoms Subscale – Physical |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| mHSPC | metastatic hormone-sensitive prostate cancer |
| NFPSI-17 | National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index – 17-item version |
| SGB | Sozialgesetzbuch (Social Code Book) |

# 1 Background

On 8 August 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-21 (Darolutamide – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the analyses subsequently submitted by the pharmaceutical company (hereinafter referred to as "the company") in the commenting procedure, taking into account the information provided in the dossier [2]:

- analyses on the Disease-Related Symptoms Subscale – Physical [DRS-P] of the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index – 17-item version [NFPSI-17])

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

# 2 Assessment

The double-blind randomized parallel-group study ARASENS, which compared darolutamide in combination with docetaxel and androgen deprivation therapy (ADT) (hereinafter referred to as "darolutamide + docetaxel + ADT") with placebo + docetaxel + ADT, was used for the benefit assessment of darolutamide in patients with metastatic hormone-sensitive prostate cancer (mHSPC). A detailed description of the study can be found in dossier assessment A23-21 [1].

In compliance with the commission, the analyses on the outcome of symptoms (DRS-P subscale of the NFPSI-17) of the ARASENS study subsequently submitted by the company in the commenting procedure [3] are assessed below.

## 2.1 Analyses on the outcome of symptoms (DRS-P subscale of the NFPSI-17)

In its dossier, the company had presented responder analyses for the time to first deterioration by ≥ 3 points (scale range 0 to 40) for the outcome of symptoms (DRS-P subscale of the NFPSI-17). It was noted in the dossier assessment, that, as explained in the Institute's *General Methods* [4], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified (in post-hoc analyses exactly 15% of the scale range). In response to this, the company presented analyses for the time to first deterioration by ≥ 6 points for this outcome in the commenting procedure. This response criterion corresponds to 15% of the scale range of the instrument (scale range 0 to 40).

### 2.1.1 Risk of bias

The risk of bias of the results for the outcome of symptoms (DRS-P subscale of the NFPSI-17) is assessed as high due to incomplete observations for potentially informative reasons with different treatment durations between treatment arms.

### 2.1.2 Results

The results for the outcome of symptoms (DRS-P subscale of the NFPSI-17) from the ARASENS study comparing darolutamide + docetaxel + ADT with placebo + docetaxel + ADT in patients with mHSPC are shown in Table 1.

The Kaplan-Meier curves on the time-to-event analysis are presented in Appendix A.

Table 1: Results (morbidity) – RCT, direct comparison: darolutamide + docetaxel + ADT versus placebo + docetaxel + ADT

| Study<br>Outcome category<br>Outcome | Darolutamide + docetaxel + ADT | | Placebo + docetaxel + ADT | | Darolutamide + docetaxel + ADT vs. placebo + docetaxel + ADT |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value |
| **ARASENS** | | | | | |
| **Morbidity** | | | | | |
| Symptoms (DRS-P subscale of the NFPSI-17)[a] | 651 | 13.9 [13.1; 19.3]<br>386 (59.3) | 654 | 13.8 [11.0; 16.4]<br>370 (56.6) | 0.902 [0.78; 1.04]; 0.156[b] |

a. Time to first deterioration. A score decrease by ≥ 6 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 40).
b. Effect and CI: Cox proportional hazards model; p-value: log-rank test. Each stratified by the extent of disease at baseline (only non-regional lymph node metastases versus bone metastases with or without lymph node metastases and without visceral metastases versus visceral metastases with or without lymph node metastases or with or without bone metastases) and ALP value (< ULN versus ≥ ULN).

ADT: androgen deprivation therapy; ALP: alkaline phosphatase; CI: confidence interval; DRS-P: Disease-Related Symptoms Subscale – Physical; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NFPSI-17: National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index – 17-item version; RCT: randomized controlled trial; ULN: upper limit of normal

## Morbidity

### *Symptoms (DRS-P subscale of the NFPSI-17)*

No statistically significant difference between treatment groups was found for the outcome of symptoms (DRS-P subscale of the NFPSI-17). There is no hint of an added benefit of darolutamide + docetaxel + ADT in comparison with docetaxel + ADT; an added benefit is therefore not proven.

### *Subgroups and effect modifiers*

The company has not submitted any subgroup analyses on the subsequently submitted analyses. In the present situation, the missing subgroup analyses are not assumed to impact the overall conclusion on added benefit.

## 2.2 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of darolutamide + docetaxel + ADT from dossier assessment A23-21.

The following Table 2 shows the result of the benefit assessment of darolutamide + docetaxel + ADT under consideration of dossier assessment A23-21 and the present addendum.

Table 2: Darolutamide + docetaxel + ADT – probability and extent of added benefit

| **Therapeutic indication** | **ACT**[a] | **Probability and extent of added benefit** |
|---|---|---|
| Adult men with mHSPC | ▪ Conventional ADT[b] in combination with apalutamide[c]<br>or<br>▪ Conventional ADT[b] in combination with enzalutamide[c]<br>or<br>▪ Conventional ADT[b] in combination with abiraterone acetate and prednisone or prednisolone (only for patients with newly diagnosed high-risk mHSPC)<br>or<br>▪ **Conventional ADT[b] in combination with docetaxel[c] with or without prednisone or prednisolone** | Indication of major added benefit[d] |

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. The present ACT was determined under the assumption that patients are in first-line therapy for the metastatic stage.
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, with regard to possible comorbidities and general health, patients are typically eligible for combination therapy – i.e. treatment in addition to conventional ADT.
d. The ARASENS study included only patients with an ECOG PS ≤ 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

ADT: androgen deprivation therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; mHSPC: metastatic hormone-sensitive prostate cancer

The G-BA decides on the added benefit.

## 3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Darolutamid (Prostatakarzinom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2023 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a23-21_darolutamid_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Bayer Vital. Darolutamid (Nubeqa); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2023 [Accessed: 26.07.2023]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/934/#dossier.

3. Bayer Vital. Stellungnahme zum IQWiG-Bericht Nr. 1584: Darolutamid (Prostatakarzinom) - Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/934/#beschluesse in the document "Zusammenfassende Dokumentation"].

4. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.1 [online]. 2022 [Accessed: 27.01.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf.

## Appendix A Kaplan-Meier curves

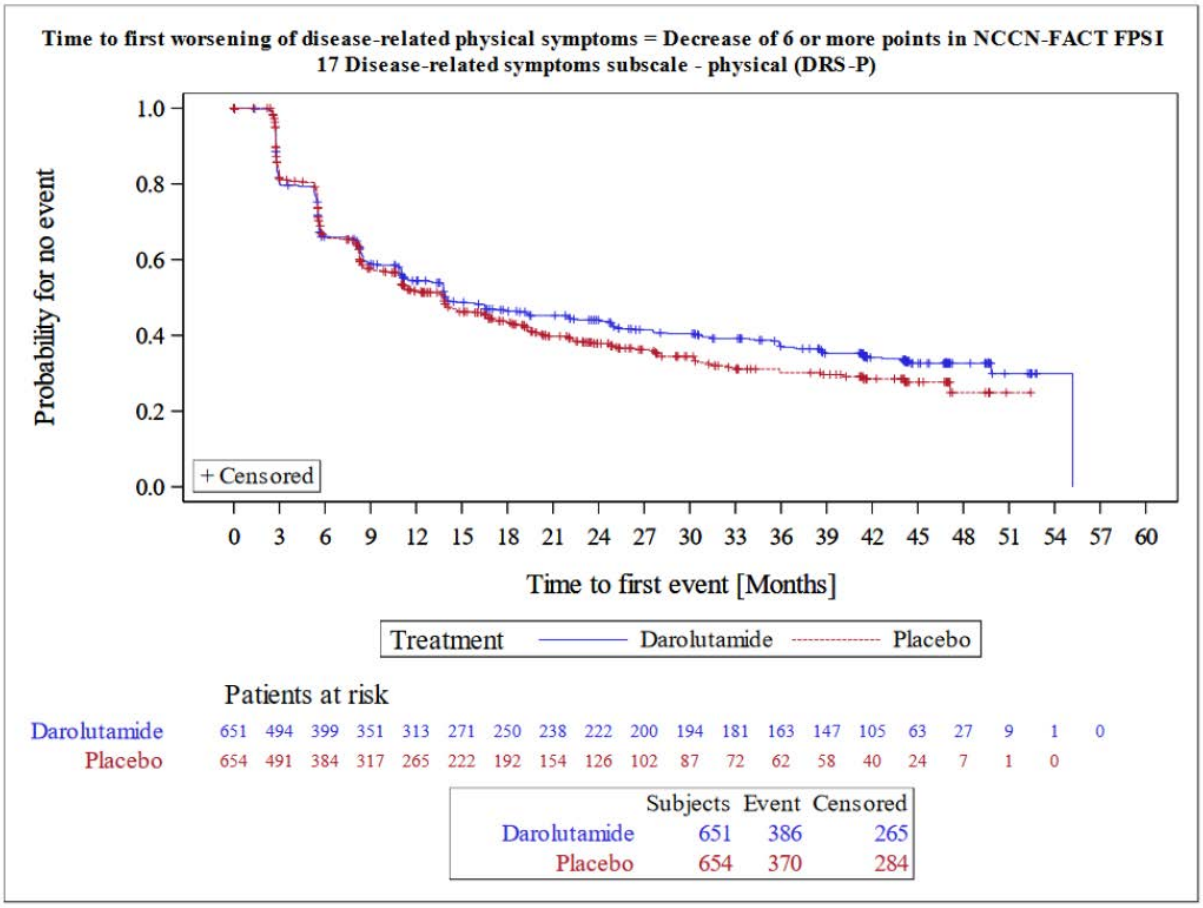


Figure 1: Kaplan-Meier curves on the outcome of symptoms (DRS P subscale of the NFPSI 17, first deterioration by ≥ 6 points; data cut-off: 25 October 2021)