



**Enzalutamide** (Reassessment after the Deadline: Non-metastatic Castration-resistant Prostate Cancer)

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valid until: unlimited

**Therapeutic indication (according to the marketing authorisation of 23 October 2018):**

Xtandi is indicated for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC).

**1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy**

Adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC)

**Appropriate comparator therapy:**

A wait-and-see approach while maintaining the existing conventional androgen deprivation therapy (ADT).

**Extent and probability of the additional benefit of enzalutamide compared with the wait-and-see approach while maintaining the existing conventional androgen deprivation therapy (ADT):**

Indication of a minor additional benefit.

## Study results according to endpoints:<sup>1</sup>

Adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC)

PROSPER study: Enzalutamide + ADT vs placebo + ADT

Study design: randomised, double-blind, two-armed, Phase III

Data cut-offs: 1st data cut-off of 28 June 2017; 3rd data cut-off of 15 October 2019

### Mortality

Endpoint	Enzalutamide + ADT		Placebo + ADT		Intervention vs control
	N	Median survival time in months [95% CI] <i>Patients with event n (%)</i>	N	Median survival time in months [95% CI] <i>Patients with event n (%)</i>	Hazard Ratio [95% CI] p value Absolute difference (AD) <sup>a</sup>
<b>Overall survival</b>					
3rd data cut-off	933	67.0 [64.0; n.a.] 288 (30.9)	468	56.3 [54.4; 63.0] 178 (38.0)	0.73 [0.61; 0.88] 0.001 AD = 10.7 months

### Morbidity

Endpoint	Enzalutamide + ADT		Placebo + ADT		Intervention vs control
	N	Median time to event in months [95% CI] <i>Patients with event n (%)</i>	N	Median time to event in months [95% CI] <i>Patients with event n (%)</i>	Hazard Ratio [95% CI] p value Absolute difference (AD) <sup>a</sup>
<b>Metastasis-free survival (MFS)<sup>2</sup></b>					
1st data cut-off	933	36.6 [33,1; n.c.] 219 (23.5)	468	14.7 [14.2; 15.6] 228 (48.7)	0.29 [0.24; 0.35] < 0.001 AD = 21.9 months
<b>Time to start of cytotoxic chemotherapy<sup>3</sup></b>					
3rd data cut-off	933	58.3 [52.6; 66.0]	468	41.6 [37.3; 46.4]	0.62 [0.52; 0.72]

<sup>1</sup> Data from the dossier assessment of the IQWiG (A20-46) unless otherwise indicated.

<sup>2</sup> Data from the addendum (A19-34) of the IQWiG on the dossier assessment (A18-80)

<sup>3</sup> Data from the dossier on enzalutamide (Module 4A) dated 14 May 2020

Endpoint	Enzalutamide + ADT		Placebo + ADT		Intervention vs control
	N	Median time to event in months [95% CI] <i>Patients with event n (%)</i>	N	Median time to event in months [95% CI] <i>Patients with event n (%)</i>	Hazard Ratio [95% CI] p value Absolute difference (AD) <sup>a</sup>
		372 (39.9)		242 (51.7)	p < 0.0001 AD = 16.7 months
<b>Worst pain (BPI-SF Item 3)<sup>b</sup></b>					
1st data cut-off	839	18.5 [18.3; 22.1] 390 (41.8)	415	18.5 [14.8; 25.8] 165 (35.3)	0.98 [0.82; 1.18] 0.838
<b>Health status (EQ-5D VAS)<sup>4</sup></b>					
MID 7 1st data cut-off	836	11.1 [7.8; 11.2] 515 (55.2)	414	7.5 [7.4; 11.0] 250 (53.4)	0.83 [0.71; 0.97] 0.019 AD = 3.6 months
MID 10 1st data cut-off	836	14.6 [11.1; 14.8] 473 (50.7)	414	11.0 [7.5; 11.1] 235 (50.2)	0.79 [0.67; 0.93] 0.004 AD = 3.6 months

Endpoint	Enzalutamide + ADT		Placebo + ADT		Intervention vs control
	N	Values at the start of study MV (SE)  Change at week 97 MV (SE)	N	Values at the start of study MV (SE)  Change at week 97 MV (SE)	Mean difference [95% CI]  p value
<b>Pain intensity (BPI-SF items 3– 6; presented additionally)</b>					
1st data cut-off	839	no data available  0.49 (0.1)	415	no data available  0.55 (0.16)	-0.06 [-0.40; 0.29] no data available
<b>Impairment due to pain (BPI-SF item 9a–g)</b>					
1st data cut-off	839	no data available  0.65 (0.1)	415	no data available  0.85 (0.16)	-0.20 [-0.53; 0.13] no data available

<sup>4</sup> Data from the addendum (A19-34) of the IQWiG on the dossier assessment (A18-80)

Health status (EQ-5D VAS) (presented additionally)					
1st data cut-off	836	no data available -4.57 (0.91)	414	no data available -5.29 (1.47)	0.72 [-2.30; 3.75] 0.639

### Health-related quality of life

Endpoint	Enzalutamide + ADT		Placebo + ADT		Intervention vs control
	N	Median time to event in months [95% CI] <i>Patients with event n (%)</i>	N	Median time to event in months [95% CI] <i>Patients with event n (%)</i>	Hazard Ratio [95% CI] p value Absolute difference (AD) <sup>a</sup>
<b>FACT-P total score<sup>c</sup></b>					
1st data cut-off	839	11.1 [11.0; 14.7] 499 (53.5)	415	11.1 [11.1; 14.7] 226 (48.3)	0.97 [0.82; 1.14] 0.700
<b>FACT-P sub-scales (presented additionally)</b>					
Physical well-being (PWB) <sup>d</sup> 1st data cut-off	839	7.9 [7.5; 11.1] 538 (57.7)	415	11.5 [11.1; 14.8] 206 (44.0)	1.28 [1.08; 1.50] 0.004 <sup>5</sup>
Social well-being (SWB) <sup>d</sup> 1st data cut-off	839	18.4 [14.8; 22.2] 398 (42.7)	415	14.8 [11.1; 18.6] 187 (40.0)	0.88 [0.73; 1.05] 0.153 <sup>5</sup>
Emotional well-being (EWB) <sup>d</sup> 1st data cut-off	839	25.8 [22.0; 29.4] 359 (38.5)	415	18.4 [14.7; 18.6] 173 (37.0)	0.84 [0.70; 1.01] 0.070 <sup>5</sup>
Functional well-being (FWB) <sup>d</sup> 1st data cut-off	839	11.0 [7.5; 11.1] 534 (57.2)	415	11.1 [10.7; 14.6] 229 (48.9)	1.07 [0.91; 1.25] 0.419 <sup>5</sup>
Prostate cancer sub-scale (PCS) <sup>d</sup> 1st data cut-off	839	7.8 [7.5; 11.1] 549 (58.8)	415	7.7 [7.4; 11.1] 264 (56.4)	0.85 [0.73; 0.99] 0.036 <sup>5</sup>

<sup>5</sup> Data from the addendum (A19-34) of the IQWiG on the dossier assessment (A18-80)

## Side effects

Endpoint	Enzalutamide + ADT		Placebo + ADT		Intervention vs control
	N	Median time to event in months [95% CI] <i>Patients with event n (%)</i>	N	Median time to event in months [95% CI] <i>Patients with event n (%)</i>	Hazard Ratio [95% CI] p value Absolute difference (AD) <sup>a</sup>
<b>Adverse events (presented additionally)<sup>e</sup></b>					
3rd data cut-off	930	1.0 [0.9; 1.3] 873 (93.9)	465	2.8 [1.9; 3.5] 379 (81.5)	-
<b>Serious adverse events (SAE)<sup>e</sup></b>					
3rd data cut-off	930	53.6 [47.5; n.a.] 345 (37.1)	465	n.a. [n.a.; n.a.] 97 (20.9)	0.94 [0.74; 1.19] 0.610
<b>Severe adverse events (CTCAE grade <math>\geq 3</math>)<sup>e</sup></b>					
3rd data cut-off	930	40.8 [37.3; 46.9] 424 (45.6)	465	40.5 [31.9; n.a.] 124 (26.7)	1.05 [0.85; 1.29] 0.637
<b>Therapy discontinuations because of adverse events<sup>e</sup></b>					
3rd data cut-off	930	n.a. [n.a.; n.a.] 133 (14.3)	465	n.a. [n.a.; n.a.] 37 (8.0)	1.01 [0.69; 1.48] 0.946
<b>Specific adverse events<sup>f</sup></b>					
Psychiatric disorders (SOC, AEs) 3rd data cut-off	930	n.a. [n.a.; n.a.] 148 (15.9)	465	n.a. [n.a.; n.a.] 26 (5.6)	2.17 [1.42; 3.31] < 0.001
General disorders and administration site conditions (SOC, severe AEs) 3rd data cut-off	930	n.a. [n.a.; n.a.] 75 (8.1)	465	n.a. [n.a.; n.a.] 10 (2.2)	2.21 [1.13; 4.32] 0.018
Nervous system disorders (SOC, severe AEs) 3rd data cut-off	930	n.a. [n.a.; n.a.] 61 (6.6)	465	n.a. [n.a.; n.a.] 8 (1.7)	2.16 [1.02; 4.59] 0.04

Endpoint	Enzalutamide + ADT		Placebo + ADT		Intervention vs control
	N	Median time to event in months [95% CI] <i>Patients with event n (%)</i>	N	Median time to event in months [95% CI] <i>Patients with event n (%)</i>	Hazard Ratio [95% CI] p value Absolute difference (AD) <sup>a</sup>
Renal and urinary disorders (SOC, severe AEs) 3rd data cut-off	930	n.a. [n.a.; n.a.] 81 (8.7)	465	n.a. [n.a.; n.a.]; 46 (9.9)	0.43 [0.29; 0.63] < 0.001
Hypertension (SMQ <sup>g</sup> , severe AEs) 3rd data cut-off	930	n.a. [n.a.; n.a.] 54 (5.8)	465	n.a. [n.a.; n.a.] 11 (2.4)	1.99 [1.03; 3.82] 0.036

<sup>a</sup> Absolute difference (AD) given only in the case of a statistically significant difference; own calculation

<sup>b</sup> Time to first deterioration by  $\geq 2$  points

<sup>c</sup> Time to first deterioration by  $\geq 10$  points

<sup>d</sup> Time to first deterioration by  $\geq 3$  points

<sup>e</sup> Without events that are considered to be a progression of the underlying disease

<sup>f</sup> Selection according to the methodology of the IQWiG; selection using events based on frequency and differences between treatment arms and taking into account patient relevance.

<sup>g</sup> Based on the information provided in Module 4 A, it is assumed that the SMQ hypertension includes PTs of severity CTCAE  $\geq 3$

Abbreviations used:  
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; DC = data cut-off; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; SMQ = standardised MedDRA query; SOC = system organ class; vs = versus

### Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	↔	No difference relevant for the benefit assessment
Health-related quality of life	↔	No difference relevant for the benefit assessment
Side effects	↔	No difference relevant for the benefit assessment; advantage and disadvantage in individual specific AE

Explanations:  
 ↑: statistically significant and relevant positive effect with low/unclear reliability of data  
 ↓: statistically significant and relevant negative effect with low/unclear reliability of data  
 ↑↑: statistically significant and relevant positive effect with high reliability of data  
 ↓↓: statistically significant and relevant negative effect with high reliability of data  
 ↔: no statistically significant or relevant difference  
 ∅: There are no usable data for the benefit assessment.  
 n.a.: not assessable

## 2. Number of patients or demarcation of patient groups eligible for treatment

approx. 1090–3800 patients

## 3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Xtandi (active ingredient: enzalutamide) at the following publicly accessible link (last access: 23 September 2020):

[https://www.ema.europa.eu/documents/product-information/xtandi-epar-product-information\\_en.pdf](https://www.ema.europa.eu/documents/product-information/xtandi-epar-product-information_en.pdf)

Treatment with enzalutamide should be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in urology, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with prostate cancer.

Patients who have not undergone surgical castration should continue receiving chemical castration with GnRH agonists or antagonists during treatment.

## 4. Treatment costs

### Annual treatment costs:

Adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC)

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Enzalutamide	€ 43,464.98
GnRH agonist/GnRH antagonist	€ 1,246.78 – 2,096.72
Total:	€ 44,711.76 – 45,561.70
Appropriate comparator therapy:	
GnRH agonist/GnRH antagonist	€ 1,246.78 – 2,096.72

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 October 2020

Costs for additionally required SHI services: not applicable