Enzalutamide (Xtandi®) as monotherapy or in combination with androgen deprivation therapy (ADT) for the treatment of high risk biochemical recurrent (BCR) non-metastatic hormone sensitive prostate cancer (nmHSPC)

General information

Drug description [1]

Enzalutamide (Xtandi®) is a potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. Enzalutamide competitively inhibits androgen binding to androgen receptors and consequently inhibits nuclear translocation of activated receptors and inhibits the association of the activated androgen receptor with DNA, even in the setting of androgen receptor overexpression and in prostate cancer cells resistant to anti-androgens. Enzalutamide treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression.

Indication [2]

Enzalutamide (Xtandi®) is indicated as monotherapy or in combination with ADT for the treatment of adult men with high-risk BCR nmHSPC who are unsuitable for salvage radiotherapy.

Incidence [3]

In Austria, in 2022, 7,000 men were newly diagnosed with prostate cancer. The age-standardised[1] incidence rate was 165.3/per 100,000 men.

Current treatment [4, 5]

The ESMO treatment recommendation for the treatment of high-risk localised and locally advanced prostate cancer is displayed in Figure 1 of the Appendix.

Regulatory status

EMA [2]	FDA [6, 7]
Approval status for this indication: On 21 March 2024, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Xtandi®. The CHMP adopted a new indication as follows: ❖ Xtandi® is indicated as monotherapy or in combination with ADT for the treatment of adult men with high-risk BCR nmHSPC who are unsuitable for salvage radiotherapy. **Other indications**: Xtandi® is indicated: ❖ In combination with ADT for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC). ❖ For the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC). ❖ For the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated. ❖ For the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.	**Approval status for this indication**: On 16 November 2023, the FDA approved enzalutamide (Xtandi®) for non-metastatic castration-sensitive prostate cancer (nmCSPC) with high-risk BCR. **Other indications**: Xtandi® is indicated for the treatment of patients with: ❖ CRPC. ❖ Metastatic castration-sensitive prostate cancer.

Manufacturer

Xtandi® is manufactured by Astellas Pharma.

Costs [8]

4x28 Xtandi® film tablets 40 mg = **€ 2,501.06** (ex-factory price)

Posology [1]

❖ The recommended dose is 160 mg enzalutamide (four 40 mg film-coated tablets or two 80 mg film-coated tablets) as a single oral daily dose.
❖ Medical castration with a luteinising hormone-releasing hormone analogue should be continued during the treatment of patients not surgically castrated.

[1] European Standard Population 2013.

Warnings and precautions [1]

- **Risk of seizure**
  - The use of enzalutamide has been associated with seizures. The decision to continue treatment in patients who develop seizures should be taken case by case.
- **Posterior reversible encephalopathy syndrome**
  - There have been rare reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving Xtandi. PRES is a rare, reversible neurological disorder which can present with rapidly evolving symptoms, including seizure, headache, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinuation of Xtandi in patients who develop PRES is recommended.
- **Second primary malignancies**
  - In clinical studies, cases of second primary malignancies have been reported in patients treated with enzalutamide. In phase 3 clinical studies, the most frequently reported events in enzalutamide-treated patients, and greater than placebo, were bladder cancer (0.3%), adenocarcinoma of the colon (0.2%), transitional cell carcinoma (0.2%) and bladder transitional cell carcinoma (0.1%).
  - Patients should be advised to promptly seek the attention of their physician if they notice signs of gastrointestinal bleeding, macroscopic haematuria, or other symptoms such as dysuria or urinary urgency develop during treatment with enzalutamide.
- **Concomitant use with other medicinal products**
  - Enzalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products. A review of concomitant medicinal products should, therefore, be conducted when initiating enzalutamide treatment. Concomitant use of enzalutamide with medicinal products that are sensitive substrates of many metabolising enzymes or transporters should generally be avoided if their therapeutic effect is of large importance to the patient and if dose adjustments cannot easily be performed based on monitoring of efficacy or plasma concentrations.
  - Co-administration with warfarin and coumarin-like anticoagulants should be avoided. If Xtandi® is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin or acenocoumarol), additional INR monitoring should be conducted.
- **Renal impairment**
  - Caution is required in patients with severe renal impairment, as enzalutamide has not been studied in this patient population.
- **Severe hepatic impairment**
  - An increased half-life of enzalutamide has been observed in patients with severe hepatic impairment, possibly related to increased tissue distribution. The clinical relevance of this observation remains unknown. A prolonged time to reach steady state concentrations is, however, anticipated, and the time to maximum pharmacological effect, as well as time for onset and decline of enzyme induction, may be increased.
- **Recent cardiovascular disease**
  - The phase 3 studies excluded patients with recent myocardial infarction (in the past six months) or, unstable angina (in the past three months), NYHA III or IV heart failure except if LVEF ≥ 45%, bradycardia or uncontrolled hypertension. This should be taken into account if Xtandi® is prescribed to these patients.
- **ADT may prolong the QT interval**
  - In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval, physicians should assess the benefit-risk ratio, including the potential for Torsade de pointes prior to initiating Xtandi®.
- **Use with chemotherapy**
  - The safety and efficacy of concomitant use of Xtandi® with cytotoxic chemotherapy has not been established. Co-administration of enzalutamide has no clinically relevant effect on the pharmacokinetics of intravenous docetaxel; however, an increase in the occurrence of docetaxel-induced neutropenia cannot be excluded.
- **Hypersensitivity reactions**
  - Hypersensitivity reactions manifested by symptoms including, but not limited to, rash or face, tongue, lip, or pharyngeal oedema have been observed with enzalutamide. Severe cutaneous adverse reactions have been reported with enzalutamide. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions.
- **Excipients**
  - This medicine contains less than 1 mmol sodium (less than 23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

Study characteristics (REF)

Trial name	*n*	Intervention (I)	Intervention2 (I2)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)

EMBARK NCT02319837	1,068 1:1:1	**enzalutamide + leuprolide** (combination group, double-blind)	**placebo + leuprolide** (leuprolide-alone group, double-blind)	**enzalutamide monotherapy** (monotherapy group, open-label)	metastasis-free survival by BICR in the combination group as compared with the leuprolide-alone group.	60.7 months	**ongoing**[2], international, randomised, phase 3 trial	PSA	Pfizer and Astellas Pharma	EMBARK [9]

Inclusion criteria[3]	Exclusion criteria	Patient characteristics at baseline (I vs. I2 vs. C, n=355 vs. n=358 vs. n=355)
❖ ≥18 years or older with histologically or cytologically confirmed adenocarcinoma of the prostate at initial biopsy, without neuroendocrine differentiation, signet cell, or small cell features. ❖ Prostate cancer is initially treated by radical prostatectomy or radiotherapy (including brachytherapy) or both, with curative intent. ❖ PSA doubling time ≤ 9 months as calculated by the sponsor. ❖ Screening PSA by the central laboratory ≥ 1 ng/mL for patients who had radical prostatectomy (with or without radiotherapy) as primary treatment for prostate cancer and at least two ng/mL above the nadir for patients who had radiotherapy only as primary treatment for prostate cancer. ❖ Serum testosterone ≥ 150 ng/dL (5.2 nmol/L) at screening. ❖ ECOG PS of 0 or 1 at screening. ❖ Estimated life expectancy of ≥ 12 months. ❖ Throughout the study, the patient and his female partner, who is of childbearing potential, must use two acceptable methods of birth control from screening through 3 months after the last dose of the study drug or per local guidelines where these require additional description of contraceptive methods. Two acceptable methods of birth control thus include the ❖ Throughout the study, the patient must use a condom if having sex with a pregnant woman. ❖ Must agree not to donate sperm from the first dose of study drug through 3 months after the last dose of study drug.	❖ Prior or present evidence of distant metastatic disease as assessed by CT or, MRI or chest x-ray for soft tissue disease and whole-body radionuclide bone scan for bone disease. ❖ Prior hormonal therapy. Neoadjuvant/adjuvant therapy to treat prostate cancer ≤ 36 months in duration and ≥ 9 months before randomisation, or a single dose or a short course (≤ 6 months) of hormonal therapy given for rising PSA ≥ 9 months before randomisation is allowed. ❖ Prior cytotoxic chemotherapy, aminoglutethimide, ketoconazole, abiraterone acetate, or enzalutamide for prostate cancer. ❖ Prior systemic biologic therapy, including immunotherapy, for prostate cancer. ❖ Major surgery within four weeks before the randomisation date. ❖ Treatment with 5-α reductase inhibitors within four weeks of randomisation. ❖ For patients who had a prior prostatectomy, a suitable candidate for salvage radiotherapy is determined by the investigator in consideration of appropriate guidelines. ❖ Participation in a clinical study of an investigational agent that inhibits the androgen receptor or androgen synthesis; patients who received a placebo are allowed. ❖ Use of any other investigational agent within four weeks before the randomisation date. ❖ Known or suspected brain metastasis or active leptomeningeal disease. ❖ History of another invasive cancer within three years before screening, with the exception of fully treated cancers with a remote probability of recurrence. ❖ Absolute neutrophil count < 1500/µL, platelet count < 100,000/µL, or haemoglobin < 10 g/dL (6.2 mmol/L) at screening. ❖ Total bilirubin ≥ 1.5 times the ULN (except patients with documented Gilbert's disease), or alanine aminotransferase or aspartate aminotransferase ≥ 2.5 times the ULN at screening. ❖ Creatinine > 2 mg/dL (177 µmol/L) at screening. ❖ Albumin < 3.0 g/dL (30 g/L) at screening. ❖ History of seizure or any condition that may predispose to seizure. History of loss of consciousness or transient ischemic attack within 12 months before randomisation. ❖ Clinically significant cardiovascular disease including the following: • Myocardial infarction within six months before screening • Unstable angina within three months before screening	❖ Median age (range): 69 (51–87) vs. 70 (50–92) vs. 69 (49–93) ❖ Age group: • <65 years: 22.8% vs. 25.4% vs. 25.6% • 65 to <75 years: 56.6% vs. 50.3% vs. 49.0% • ≥75 years: 20.6% vs. 24.3% vs. 25.4% ❖ Race or ethnic group: • White: 82.5% vs. 84.1% vs. 83.1% • Asian: 7.3% vs. 7.3% vs. 7.3% • Black: 4.5% vs. 4.5% vs. 4.2% • American Indian or Alaska Native: 1.1% vs. 0.3% vs. 0 • Native Hawaiian or other Pacific Islander: 0.3% vs. 0 vs. 0 • Other: 1.4% vs. 2.5% vs.1.4% • Not reported: 2.8% vs. 1.4% vs. 3.9% ❖ Geographic region: • North America: 40.6% vs. 38.3% vs. 37.5% • Europe: 36.6% vs. 35.8% vs. 41.1% • Rest of the world: 22.8% vs. 26.0% vs. 21.4% ❖ ECOG PS score: • 0: 92.4% vs. 93.9% vs. 90.4% • 1: 7.3% vs. 5.9% vs. 9.6% • >1: 0.3% vs. 0 vs. 0 • Missing data: 0 vs. 0.3 vs. 0 ❖ PSA doubling time: • ≤3 months: 19.4% vs. 22.3% vs. 21.4%

[2] The EMBARK trial is currently ongoing; the estimated study completion date is 09/2026.
[3] For detailed in- and exclusion criteria, please see trial protocol.

	• NYHA class III or IV congestive heart failure or a history of NYHA class III or IV congestive heart failure unless a screening echocardiogram or multigated acquisition scan performed within 3 months before the randomisation date demonstrates a LVEF ≥ 45% • History of clinically significant ventricular arrhythmias • History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place • Hypotension as indicated by systolic blood pressure < 86 mm Hg at screening • Bradycardia as indicated by a heart rate of ≤ 45 beats per minute on the screening ECG. • Uncontrolled hypertension as indicated by a minimum of 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mm Hg or diastolic blood pressure > 105 mm Hg at screening ❖ Gastrointestinal disorder affecting absorption. ❖ Hypersensitivity reaction to enzalutamide or any of the capsule components. ❖ Contraindication to the use of leuprolide, such as a previous hypersensitivity reaction to an LHRH analogue or any of the excipients in the leuprolide injection. ❖ Ongoing drug or alcohol abuse as per investigator judgment. ❖ Any concurrent disease, infection, or comorbid condition that interferes with the ability of the patient to participate in the study, which places the patient at undue risk, or complicates the interpretation of data, in the opinion of the investigator or medical monitor.	• >3 to 6 months: 52.7% vs. 39.7% vs. 46.2% • >6 to 9 months: 27.6% vs. 37.7% vs. 32.1% ❖ Missing data: 0.3 vs. 0.3 vs. 0.3 ❖ Median PSA doubling time (months): 4.6 vs. 5.0 vs. 5.0 ❖ Median serum PSA level (ng/ml): 5.0 vs. 5.5 vs. 5.3 ❖ Previous hormonal therapy: • Yes: 30.1% vs. 31.6% vs 31.5% • No: 69.9% vs. 68.4% vs. 68.5% ❖ Primary definitive therapy: • Prostatectomy alone: 25.4% vs. 20.9 vs. 27.9% ❖ Radiation therapy alone: 24.2% vs. 29.1% vs. 25.4 ❖ Prostatectomy and radiation therapy: 50.4% vs. 50.0% vs. 46.8%

Efficacy (I vs. I2 vs. C); interim analysis data	**Safety** (I vs. I2 vs. C); interim analysis data
Data-cutoff date 31 January 2023; median follow-up 60.7 months **5-year metastasis-free survival**: 87.3% (95% CI, 83.0-90.6) in I vs. 71.4% (95% CI, 65.7-76.3); HR 0.42 (95% CI, 0.30-0.61); p<0.001 **5-year metastasis-free survival in C**: 80.0% (95% CI, 75.0-84.1); HR for metastasis or death (I2 vs. C) 0.63 (95% CI, 0.46-0.87); p=0.005 **Estimated percentage of patients who were free from PSA progression at 5 years**: 97.4% (95% CI, 94.7-98.8) vs. 70.0% (95% CI, 64.1-75.1) vs. 88.9% (95% CI, 84.6-92.1) **Estimated percentage of patients who were free from antineoplastic therapy at 5 years**: 83.0% (95% CI, 78.3-86.8) vs. 61.7% (95% CI, 56.1-66.8) vs. 75.7% (95% CI, 70.6-80.0) **Risk of PSA progression**: HR (I) 0.07 (95% CI, 0.03-0.14); p<0.001; HR (I2) 0.33 (95% CI, 0.23-0.49; p<0.001 **Time to first use of new antineoplastic therapy**: HR (I) 0.36 (95% CI, 0.26-0.49; p<0.001); HR (I2) 0.54 (95% CI, 0.41-0.71); p<0.001 **5-year OS**: 92.2% (95% CI, 88.7-94.7) vs. 87.2% (83.0-90.4) vs. 89.5% (85.6-92.4); HR (I vs. I2) 0.59 (95% CI, 0.38-0.91); p= 0.02 (interim efficacy boundary, p≤0.0001); HR (I2 vs. C) 0.78 (95% CI, 0.52-1.17); p=0.23	**Any AE of any grade**: 97.2% vs. 97.5% 98.0% **Any AE of grade ≥3**: 46.5% vs. 42.7% vs. 50.0% **Treatment-related AE of any grade**: 86.4% vs. 79.9% vs. 88.1% **Treatment-related AE of grade ≥3**: 17.6% vs. 8.8% vs. 16.1% **SAE of any grade**: 34.8% vs. 31.6% vs. 37.0% **SAE of grade ≥3:** 31.2% vs. 28.2% vs. 32.8% **Treatment-related SAE of any grade**: 7.4% vs. 2.3% vs. 2.3% **Treatment-related SAE of grade ≥3**: 6.2% vs. 2.0% vs. 4.8% **AE of any grade leading to permanent discontinuation of treatment:** 20.7% vs. 10.2% vs. 17.8% **AE of grade ≥3 leading to permanent discontinuation of treatment:** 8.8% vs. 5.4% vs. 9.6% **AEs leading to death[4]:** 1.7% vs. 0.8% vs. 2.3% **Fractures:** 18.4%vs. 13.6% vs. 11.0% **Cognitive and memory impairment**: 15.0% vs. 6.5% vs. 14.1% **Seizures**: 1.1% vs. 0 vs. 0.8%
Patient-reported outcomes [10, 11]	

[4] AEs leading to death were not considered by the site investigators to be related to treatment.

- At baseline, all groups had high HRQoL.
- For worst pain, the median TTFD was 19.35 months with leuprolide alone, 13.93 months with the combination (HR 1.08; 95% CI, 0.89 -1.30) and 16.59 months with monotherapy (HR 1.09; 95% CI, 0.90-1.31).
- The median TTCD was 66.27 months with leuprolide alone, 80.00 months with the combination (HR 0.82; 95% CI, 0.65-1.04), and 60.91 months with monotherapy (HR 1.02; 95% CI, 0.82-1.28).
- For Functional Assessment of Cancer Therapy–Prostate total score, the median TTFD was 11.10 months with leuprolide alone, 8.31 months with the combination (HR 1.14; 95% CI, 0.95-1.36), and 8.38 months with monotherapy (HR 1.17; 95% CI, 0.98-1.39).
- The median TTCD was 36.53 months with leuprolide alone, 38.77 months with the combination (HR 1.04; 95% CI, 0.85-1.28), and 30.55 months with monotherapy (HR 1.16; 95% CI, 0.95-1.41).
- Prespecified PRO analysis of sexual activity (SA)
  - measured as a composite score using the European Organization for Research and Treatment of Cancer QoL Questionnaire-Prostate 25.
  - SA was better preserved with enzalutamide monotherapy vs. placebo+leuprolide in terms of interest, activity, satisfaction, and maintaining an erection.
  - no significant difference between enzalutamide+leuprolide vs. placebo+leuprolide.
  - A post hoc analysis at the HRQoL item level was conducted to understand the effect on SA in each comparison and enable shared decision-making between physicians and patients.

ESMO-MCBS version 1.1 [12]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2B	Median >60 months; 5 years 71.4%	5-year metastasis-free survival: +15.9%	0.42 (0.30 - 0.61)	HR≤0.65 AND gain ≥ 3 months	3	-	Not statistically significant	-	3
Adapted	NC	2B	Median >60 months; 5 years 71.4%	5-year metastasis-free survival: +15.9%	0.42 (0.30 - 0.61)	HR≤0.65 AND gain ≥ 3 months	3	-	Not statistically significant	-	3

Risk of bias (RCT) [13]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	unclear[5] unclear risk	unclear[6] unclear risk	unclear[7] unclear risk	yes[8] high risk	unclear

Ongoing trials

NCT number/trial name	Description	Estimated study completion date
NCT02319837/EMBARK	Please see above.	09/2026

Available assessments

- In July 2022, NIHR published a Health Technology Briefing, "Enzalutamide for treating non-metastatic prostate cancer after radical prostatectomy and/or radiotherapy" [14].
- Two assessments evaluating enzalutamide + ADT in patients with high-risk nmHSPC were published by
  - IQWIG (2019): Enzalutamid (Prostatakarzinom) – Nutzenbewertung [15] and
  - ICER (2019): pCODR pERC Final Recommendation [16].
- No further assessment was identified via ICER.

Other aspects and conclusions

- In March 2024, the **CHMP adopted a new indication** for Xtandi®, indicated as monotherapy or in combination with ADT for the treatment of adult men with high-risk BCR nmHSPC who are unsuitable for salvage radiotherapy. In November 2023, the **FDA approved** enzalutamide (Xtandi®) for nmCSPC with high-risk BCR.
- **EMBARK (**NCT02319837) is an **ongoing,** randomised phase 3 trial assessing the efficacy and safety of enzalutamide plus ADT and enzalutamide monotherapy, as compared with ADT alone. Adult patients with prostate cancer who had had biochemical recurrence after local therapy were eligible if, at the time of the initial biopsy before primary definitive therapy, they had histologically or cytologically

[5] No information was found regarding the allocation procedure.
[6] Enzalutamide-monotherapy group was open-label.
[7] The EMBARK trial is currently ongoing; currently, only interim analysis data is available.
[8] Data were collected by the investigators, analyzed by statisticians who were employed by the sponsors, and interpreted by the authors, some of whom are employees of the sponsors. The sponsors provided and funded editorial and medical writing support for the preparation of the manuscript.

confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet-cell features, or small-cell features and an ECOG of 0 or 1. Patients were excluded if they had undergone previous cytotoxic chemotherapy, had a history of seizure or a condition that may confer a predisposition to seizure, showed evidence of distant metastatic disease, or if, after radical prostatectomy, they were considered by the investigator to be a candidate for salvage radiation therapy.

- The **primary endpoint was metastasis-free survival**, as assessed by BICR, in the combination group as compared with the leuprolide-alone group. At five years, metastasis-free survival was 87.3% in the combination group, 71.4% in the leuprolide-alone group, and 80.0% in the monotherapy group. With respect to metastasis-free survival, enzalutamide plus leuprolide was superior to leuprolide alone (HR for metastasis or death 0.42; 95% CI, 0.30-0.61; p<0.001); enzalutamide monotherapy was also superior to leuprolide alone (HR for metastasis or death, 0.63; 95% CI, 0.46-0.87; p=0.005).
- According to **the PROs analysis, no substantial difference was noted in the time to first deterioration of FACT-P total scores in the combination group or the monotherapy group** compared with the leuprolide-alone group.
- The **original and adapted ESMO-MCBS** was applied, resulting in a final adjusted magnitude of clinical benefit of **3** each.
- The **risk of bias** was considered **unclear** due to the ongoing status of the trial. However, this is increased partly by the open-label design and the industry-funded background.
- Besides EMBARK, no further phase 3 trial assessing enzalutamide monotherapy in patients with high-risk nmHSPC was identified.
- Final analysis data and further phase 3 data are required to sufficiently assess the efficacy and safety of enzalutamide monotherapy or enzalutamide+ADT combination therapy in patients with high-risk BCR nmHSPC.

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Abbreviations: ADT=androgen deprivation therapy, AE=adverse event, AJ=adjustment, BCR= biochemical recurrent BICR=blinded independent central review, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CRPC=castration-resistant prostate cancer, CT=computed tomography, DNA=deoxyribonucleic acid, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group performance status, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HR=hazard ratio, HRQoL=health-related quality of life, I=intervention, ICER=Institute for Clinical and Economic Review, INR=International Normalised Ratio, Int.=intention, LVEF=Left Ventricular Ejection Fraction, MG=median gain, MRI=magnetic resonance imaging, n=number of patients, NICE=National Institute for Health Care Excellence, nmHSPC=non-metastatic hormone sensitive prostate cancer, NYHA=New York Heart Association Class, OS=overall survival, pCODR=pan-Canadian Oncology Drug Review, PE=primary endpoint, pERC=pan-Canadian Oncology Drug Review Expert Review Committee, PFS=progression-free survival, PM=preliminary grade, PRES=posterior reversible encephalopathy syndrome, PRO=patient-reported outcomes, PSA=prostate specific antigen, QoL=quality of life, ER=radiotherapy, SA=sexual activity, SAE=serious adverse event, ST=standard treatment, TTCD=time to clinically meaningful deterioration, TTFD=time to first deterioration, ULN=upper limit of normal

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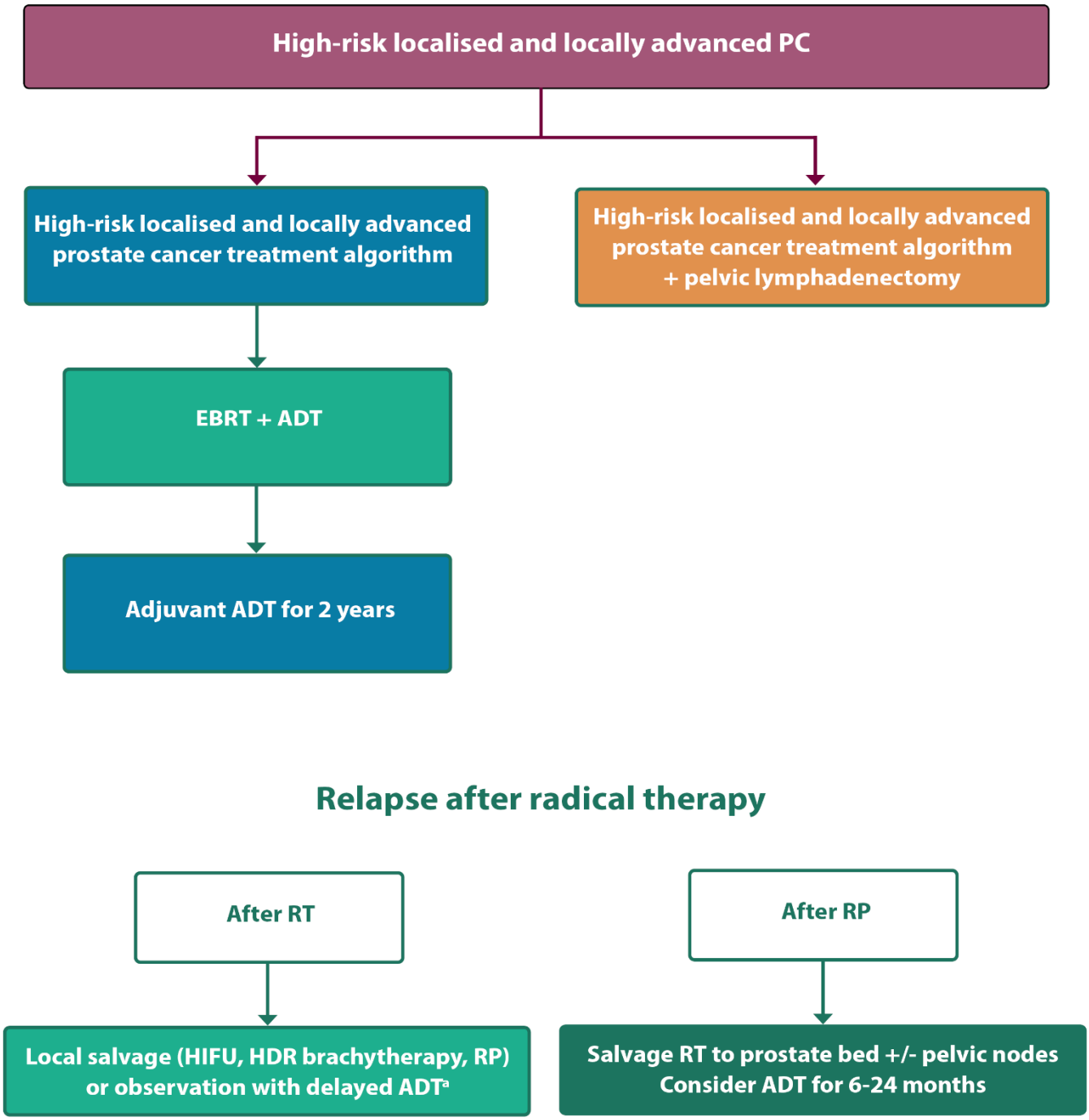
Appendix – Figure 1[9]: Therapy algorithm for the treatment of localised prostate cancer



Abbreviations: ADT, androgen deprivation therapy; EBRT, electron beam radiotherapy; HDR, high-dose rate; HIFU, high-intensity focused ultrasound; PC, prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiotherapy. a For men with biochemical relapse and symptomatic local disease, proven metastases or a PSA doubling time of <3 months.

[9] According to the updated treatment recommendations from the ESMO, abiraterone acetate with prednisone improved MFS and OS for very-high-risk localised prostate cancer undergoing RT and ADT.