Darolutamide (Nubeqa®) in combination with docetaxel and androgen deprivation therapy (ADT) for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC)

General information

Drug description [1]	Indication [2]
Darolutamide (Nubeqa®, ODM-201) is a potent androgen-receptor inhibitor.	Darolutamide (Nubeqa®) is indicated for the treatment of adult men with mHSPC in combination with docetaxel and ADT.

Current treatment [3]

- For people with metastatic prostate cancer NICE recommendation the following:
  - Offer docetaxel chemotherapy for newly diagnosed metastatic prostate cancer, if patient does not have significant comorbidities. Starting within 12-weeks of commencing ADT and use six 3-weekly cycles at a dose of 75 mg/m² (with or without daily prednisolone).
  - Offer bilateral orchidectomy to all people with metastatic prostate cancer as an alternative to continuous LHRH agonist therapy.
  - Do not offer combined androgen blockade as a first-line treatment for people with metastatic prostate cancer. For people who are willing to accept the adverse impact on OS and gynaecomastia with the aim of retaining sexual function, offer anti-androgen monotherapy with bicalutamide (150 mg). Begin ADT and stop bicalutamide treatment in people with metastatic prostate cancer who are taking bicalutamide monotherapy and who do not maintain satisfactory sexual function.
  - Degarelix as an option for treating advanced hormone-dependent prostate cancer in people with spinal metastases, only if the commissioner can achieve at least the same discounted drug cost as that available to the NHS in June 2016.
- For people with hormone-relapsed metastatic prostate cancer NICE recommendations advise the following options of treatment if bone metastasis is present:
  - Spinal MRI if patient has extensive metastases to the spine.
  - Zoledronic acid to prevent or reduce skeletal-related events.
  - Bisphophonates (oral or IV) for pain relief, when other treatments (incl. analgesics and palliative radiotherapy) have not given satisfactory pain relief.
  - Radium-223 dichloride if they have already had docetaxel or docetaxel is contraindicated/not suitable for them. Only recommended if the company provides it with the discount agreed in the patient access scheme.
- For people with hormone-relapsed metastatic prostate cancer NICE recommendations advise the following options of treatment before chemotherapy is indicated:
  - Corticosteroids, such as dexamethasone (0.5 mg daily), as a third-line hormonal therapy after ADT and anti-ADT are recommended.
  - Abiraterone in combination with prednisone or prednisolone is recommended, in people who have no or mild symptoms after ADT has failed, and before chemotherapy. Only when the company provides abiraterone in accordance with the commercial access arrangement as agreed with NHS England.
  - Enzalutamide is recommended in people who have no or mild symptoms after ADT has failed and before chemotherapy is indicated. Only when the company provides it with the discount agreed in the patient access scheme.
- Docetaxel is recommended for the treatment of hormone-refractory metastatic prostate cancer, only if their Karnofsky performance status score is 60% or more.

Regulatory status

EMA [2]	FDA [4, 5]
Approval status for this indication: On 26 January 2023, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for darolutamide (Nubeqa®). <u>The CHMP adopted a new indication:</u> ❖ Nubeqa® is indicated for the treatment of adult men with mHSPC in combination with docetaxel and ADT. **Other indications**: ❖ Nubeqa® is indicated for the treatment of adult men with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease.	**Approval status for this indication**: On 5 August 2022, the FDA approved darolutamide (Nubeqa®) tablets in combination with docetaxel for adult patients with mHSPC. ✓ **Priority review** **Other indications**: ❖ Nubeqa® is indicated for the treatment of adult patients with nmCRPC.

✓ **Medicine under additional monitoring**	

Costs

112 Nubeqa® tablets 300 mg = € 2,817.36 (ex-factory price) [6].

Posology [7]

- Treatment should be initiated and supervised by a specialist physician experienced in treatment of prostate cancer.
- The recommended dose is 600 mg darolutamide (two tablets of 300 mg) taken twice daily, equivalent to a total daily dose of 1200 mg.
- Darolutamide should be continued until disease progression or unacceptable toxicity.
- Medical castration with a luteinising hormone-releasing hormone analogue should be continued during treatment of patients not surgically castrated.
- mHSPC patients should start darolutamide in combination with docetaxel. The first of 6 cycles of docetaxel should be administered within 6 weeks after the start of darolutamide treatment. The recommendation in the product information of docetaxel should be followed. Treatment with darolutamide should be continued until disease progression or unacceptable toxicity even if a cycle of docetaxel is delayed, interrupted, or discontinued.

Warnings and precautions [4, 7]

- **Ischemic heart disease**
  - Optimise management of cardiovascular risk factors. Monitor for signs and symptoms of coronary artery disease. Discontinue Nubeqa® for Grade 3-4 events.
- **Recent cardiovascular disease**
  - Patients with clinically significant cardiovascular disease in the past 6 months including stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, and symptomatic congestive heart failure were excluded from the clinical studies. Therefore, the safety of darolutamide in these patients has not been established. If Nubeqa® is prescribed, patients with clinically significant cardiovascular disease should be treated for these conditions according to established guidelines.
- **Seizure**
  - Consider discontinuation of Nubeqa® in patients who develop a seizure during treatment.
- **Embryo-foetal toxicity**
  - Nubeqa® can cause foetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception.
- **Renal impairment**
  - The available data in patients with severe renal impairment are limited. As exposure might be increased those patients should be closely monitored for adverse reactions.
- **Hepatic impairment**
  - The available data in patients with moderate hepatic impairment are limited, and darolutamide has not been studied in patients with severe hepatic impairment. As exposure might be increased those patients should be closely monitored for adverse reactions.
- **Hepatic transaminase elevations**
  - In case of hepatic transaminase elevations suggestive of idiosyncratic drug-induced liver injury related to darolutamide, permanently discontinue treatment with darolutamide.
- **Concomitant use with other medicinal products**
  - Use of strong CYP3A4 and P-gp inducers during treatment with darolutamide may decrease the plasma concentration of darolutamide and is not recommended, unless there is no therapeutic alternative. Selection of an alternate concomitant medicinal product with less potential to induce CYP3A4 or P-gp should be considered.
  - Patients should be monitored for adverse reactions of BCRP, OATP1B1 and OATP1B3 substrates as co-administration with darolutamide may increase the plasma concentrations of these substrates.
  - Co-administration with rosuvastatin should be avoided unless there is no therapeutic alternative.
- **Androgen deprivation therapy may prolong the QT interval**
  - In patients with a history of 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 Nubeqa®.
- **Information about excipients**
  - Nubeqa® contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Study characteristics [1, 8-10]

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

					up for PE				
ARASENS NCT02799602	1,306 (1:1)	darolutamide at a dose of 600 mg (two 300-mg tablets) twice daily with food[1] + docetaxel + ADT	placebo + docetaxel + ADT	OS	43.7 months vs. 42.2 months	**ongoing[2]**, international, randomised, double-blind, placebo-controlled, phase 3 trial	-	Bayer and Orion Pharma	[1]

Inclusion criteria	Exclusion criteria	Patient characteristics (I vs. C)
❖ ≥18 years ❖ ECOG PS score of 0 or 1 ❖ Histologically or cytologically confirmed prostate cancer, and metastases detected on bone scanning, contrast-enhanced CT, or MRI ❖ Eligible patients had to be candidates for ADT and docetaxel, in the investigator's judgment	❖ Regional lymph-node involvement only (N1, below the aortic bifurcation) ❖ ADT more than 12 weeks before randomisation ❖ Second-generation androgen-receptor pathway inhibitors, chemotherapy, or immunotherapy for prostate cancer before randomisation ❖ Radiotherapy within 2 weeks before randomisation	❖ Median age: 67 vs. 67 years ❖ ECOG PS score 0: 71.6% vs. 70.6% ❖ ECOG PS score 1: 28.4% vs. 29.1% ❖ Gleason score[3] ≤8 at initial diagnosis: 18.7 vs. 18.0 ❖ Gleason score ≥8 at initial diagnosis: 77.6 vs. 78.9; data missing: 3.7 vs. 3.1 ❖ Metastasis stage at initial diagnosis: • M1, distant metastasis: 85.7% vs. 86.5% • M0, no distant metastasis: 13.2% vs. 12.5% • MX, distant metastasis not assessed: 1.1% vs. 0.9% ❖ Metastasis stage at screening: • M1a, nonregional lymph node metastases only: 3.5% vs. 2.4% • M1b, bone metastases with or without lymph node metastases: 79.4% vs. 79.5% • M1c, visceral metastases with or without lymph nodes or bone metastases: 17.1% vs. 18.0% ❖ Median serum PSA level: 30.3 ng/ml vs. 24.2 ng/ml

Efficacy (I vs. C)	Safety (I vs. C)
Data cut-off date for the primary analysis: 25 October 2021[4] (median treatment duration 41.0 months vs. 16.7 months) **Median follow-up for OS**: 43.7 months vs. 42.4 months **Risk of death**: 32.5% lower in I than C; HR 0.68; 95% CI, 0.57-0.80; p<0.001 **OS at 4 years**: 62.7% (95% CI, 58.7-66.7) vs. 50.4% (95% CI, 46.3-54.6) **Median OS**: NE vs. 48.9 months **Median time to castration-resistant disease**: NE vs. 19.1 months; HR for disease progression 0.36; 95% CI, 0.30-0.42; p<0.001 **Median time to pain progressio**n: NE vs. 27.5 months; HR for pain progression 0.79; 95% CI, 0.66-0.95; p=0.01	**AEs grade 3 or 4:** n=431/652 (66.1%) vs. n=413/650 (63.5%) **Serious AEs**: n=292/652 (44.8%) vs. n=275/650 (42.3%) **AE grade 5**: n=27/652 (4.1%) vs. n=26/650 (4.0%) **AE leading to permanent discontinuation of darolutamide or placebo**: n=88/652 (13.5%) vs. n=69/650 (10.6%) **AE leading to permanent discontinuation of docetaxel**: n=52/652 (8.0%) vs. n=67/650 (10.3%)

[1] **All patients** received **ADT** (a LHRH agonist or an LHRH antagonist) or underwent orchiectomy within 12 weeks before randomisation and received 6 cycles of **docetaxel** (75 mg/m² of BSA on day 1 and every 21 days), with prednisone or prednisolone administered at the investigator's discretion, initiated within 6 weeks after randomisation. The recommended premedication to prevent docetaxel-related hypersensitivity reactions and fluid retention was oral dexamethasone, administered at a dose of 8 mg at 12 hours, 3 hours, and 1 hour before infusion. For patients receiving LHRH agonists, the use of these agonists in combination with a first-generation antiandrogen for at least 4 weeks before randomisation was recommended. First-generation antiandrogen therapy was discontinued before randomisation.

[2] The ARASENS trial is currently ongoing; the estimated study completion date is June 2023.

[3] Gleason scores for the histologic pattern of carcinoma range from 6 to 10, with higher scores indicating a more aggressive form of prostate cancer.

[4] 1,305 patients (651 vs. 654) were included in the full analysis set, and 1,302 patients (652 vs. 650) were included in the safety analysis set.

HR for symptomatic skeletal event (SSE[5])–free survival[6]: 0.61; 95% CI, 0.52-0.72; p<0.001 **HR for time to a first symptomatic skeletal event:** 0.71; 95% CI, 0.54-0.94; p=0.02 **HR for time to the initiation of subsequent systemic antineoplastic therapy**: 0.39; 95% CI, 0.33-0.46; p<0.001	

Patient-reported outcomes

- Time to worsening of physical symptoms of disease based on functional assessment of cancer therapy / National Comprehensive Cancer Network prostate cancer symptom index 17 item questionnaire (NCCN–FACT FPSI–17) is a secondary objective of the ARASENS trial but results are not reported yet.
- The exploratory objectives of this study include analysis of QoL, but data is not available yet.

UPDATE (only abstract data available) [11]:

- Most patients had high baseline QoL scores that were maintained over time, with comparable time to worsening in both arms.
- QoL was maintained over time, and darolutamide had no adverse impact on QoL, including in patients with poor prognosis.

ESMO-MCBS version 1.1 [12]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Due to immature OS data, the ESMO-MCBS is currently not applicable.											

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	yes	yes	unclear[7]	yes[8]	unclear

Other aspects and conclusions

- In NCT02799602, the ARASENS trial, patients aged ≥18 years with histologically or cytologically confirmed, metastatic prostate cancer and an ECOG PS score of 0 or 1 were included. Patients with regional lymph node involvement only, ADT more than 12 weeks before randomisation, second-generation androgen-receptor pathway inhibitors, chemotherapy, or immunotherapy for prostate cancer before randomisation and radiotherapy within 2 weeks before randomisation were excluded.
- The herein assessed indication is approved by the FDA since 07/2022; the EMA adopted a positive opinion recommending a change to the terms of the marketing authorisation for Nubeqa® in 01/2023.
- Since the ARASENS trial is currently ongoing; there is no final analysis data for efficacy, safety and QoL/PROs available.
- The ongoing status (selective outcome reporting unclear) of the trial as well as the extensive involvement of the sponsor reinforce the risk of bias.
- Since ARASENS trial included only patients with an ECOG PS of 0 or 1, the safety and efficacy of the assessed therapeutic regimen are unknown in patients with a poor performance status.

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Abbreviations: ADT=androgen deprivation therapy, AE=adverse event, AJ=adjustment, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CT=computed tomography, EGOC 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, HR=hazard ratio, I=intervention, Int.=intention, IV=intravenous, MG=median gain, mHSPC=metastatic hormone-sensitive prostate cancer, MRI=magnetic resonance imaging, n=number of patients, NCCN–FACT FPSI–17=National Comprehensive Cancer Network prostate cancer symptom index 17 item questionnaire, NHS=National Health Service, NICE=National Institute for Health and Care Excellence, nmCRPC=non-metastatic castration resistant prostate

[5] An SSE is defined as external-beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic bone fracture, or occurrence of spinal cord compression or tumour-related orthopaedic surgical intervention, whichever occurred first.
[6] SSE-free survival is the time from randomisation to the first occurrence of an SSE or death from any cause, whichever occurred first.
[7] The ARASENS trial is ongoing; currently, primary analysis data is available.
[8] The trial was designed by the sponsor and the first and last authors, with support from the protocol steering committee. An independent data and safety monitoring board reviewed unblinded safety and efficacy data throughout the trial. The data were collected by the investigators, analysed by statisticians who were employed by the sponsor, and interpreted by the authors, including employees of the sponsors. The sponsor provided funding for medical writing assistance.

cancer, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PROs=patient-reported outcomes, QoL=quality of life, SAE=serious adverse event, SSE=symptomatic skeletal event, ST=standard treatment

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