Darolutamide (Nubeqa®) in nonmetastatic, castration-resistant prostate cancer (nmCRPC)

General information [1]

Drug description	Indication
an androgen-receptor antagonist	patients with with nmCRPC and a PSA doubling time of 10 months or less

Current treatment [2]

- There are several treatment options available to patients with nmCRPC. Many men with localised prostate cancer will not benefit from definitive treatment, and 45% of men with PSA-detected prostate cancer are candidates for deferred management (watchful waiting). In men with comorbidity and limited life expectancy, treatment of localised prostate cancer may be deferred to avoid loss of QoL.
- Guidelines recommend the use of:
  - Watchful waiting or observation
  - Radical prostatectomy
  - External beam radiotherapy
  - Brachytherapy
  - Cryotherapy
  - Hormone therapy (androgen deprivation or anti-androgens)
  - Treatment recommendations are dependent on the disease and patient characteristics; currently there is no standard treatment for castrated patients with rising PSA and no evidence of metastases.

Regulatory status

EMA [3]	FDA [4]
Approval status for this indication: positive CHMP-opinion UPDATE: **authorised** for use in the European Union (27/03/2020) **Other indications**: - ✓ **Medicine under additional monitoring**	**Approval status for this indication**: approved (2019-07-30) **Other indications**: -

Posology [5]

Medical castration with a LHRH analogue should be continued during treatment of patients not surgically castrated.

Costs

112 Nubeqa® tablets 300 mg = € 2,997.70 (ex-facory price) [6]

ARAMIS trial patients received darolutamide at a dose of 600 mg daily. Costs for 28 days of darolutamide treatment → €1,498.85

Study characteristics [1, 5]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
ARAMIS NCT02200614	1,509	Darolutamide + ADT	Placebo + ADT	MFS	multinational, randomized, double-blind, placebo-controlled, phase 3	-	Bayer HealthCare and Orion Pharma	Link [1]

Efficacy (I vs. C)

MFS, median[1]: 40.4 vs. 18.4 months with placebo (HR for metastasis or death 0.41; 95% CI 0.34-0.50; p<0.001)
OS[2]: median OS not reached, HR for death 0.71; 95% CI 0.50-0.99; p=0.045)
Time to pain progression, median: 40.3 vs. 25.4 months (HR 0.65, 95% CI 0.53-0.78, p= 0.000008)

Safety (I vs. C)

Grade ≥3 AEs: n=236/954 (24.7%) vs. n=108/554 (19.5%)
SAEs grade ≥3: n=151/954 (15.8%) vs. n=70/554 (12.6%)
Death[3]: n=37/954 (3.9%) vs. 18/554 (3.2%)
Discontinuation due to AE of any grade: n=85/954 (8.9%) vs. 48/554 (8.7%)

[1] primary analysis results, trial is ongoing until 12/2020
[2] interim analysis results
[3] death due to AE(s)

Time to initiation of first cytotoxic chemotherapy, median: NR vs. 38.2 months (HR 0.43, 95% CI 0.31-0.59, p= 0.000001) **Time to first symptomatic skeletal event, median**: NR vs. NR (HR 0.43, 95%CI 0.22-0.84, p= 0.011262) **PFS, median:** 36.8 vs. 14.8 months (HR=0.380, nominal p<0.000001) **Time to PSA progression, median**: 33.2 vs 7.3 months (HR=0.130, nominal p<0.000001) **QoL**: Patient-reported QoL was similar in either group. Differences in least-squares mean time-adjusted AUC scores consistently favored darolutamide and were significant for BPI-SF (pain severity and pain interference scores), FACT-P (Physical Well-Being, Emotional Well-Being, PCS, General, FACT-P total, and TOI), and the EORTC-QLQPR25 urinary symptoms subscale, although the clinically meaningful thresholds were not reached.	**Discontinuation due to AE of grade ≥3:** n= n=32/954 (3.4%) vs. 24/554 (4.3%)

ESMO-MCBS version 1.1

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2b	>6 m	PFS: +22 m	PFS: 0.38 (0.32–0.45)	HR ≤0.65 AND Gain >3 months	3	x	ND	x	3
Adapted	NC	2b	>6 m	PFS: +22 m	PFS: 0.38 (0.32–0.45)	HR ≤0.65 AND Gain >3 months	3	+5.2 grade 3-4 AEs, +0.2 DR	ND	x	3

Risk of bias (study level)

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	yes	yes[4]	low

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Abbreviations: ADT=androgen deprivation therapy, AE=adverse event, AJ=adjustments, AUC=area under the curve, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, DR=discontinuation rate, EMA=European Medicines Agency, ESMO-MCBS=European Society of Medical Oncology–Magnitude of Clinical Benefit Scale, EORTC-QLQ=European Organisation for Research and Treatment of Cancer quality of life questionnaire, FACT-P=Functional Assessment of Cancer Therapy–Prostate, FACT-P PCS=the prostate cancer-specific subscale of the FACT-P, FDA=Food and Drug Administration, FM=final grade, HR=hazard ratio, Int.=treatment intention, LHRH=luteinising hormone-releasing hormone, m=months, MFS=metastasis-free survival, MG=median gain, n=number, NC=non-curative, nmCRP=nonmetastatic castration-resistant prostate cancer, ND=no difference, NR=not reached, PM=preliminary grade, SAE=serious adverse event, TOI=Trial Outcome Index, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PSA=prostate-specific antigen, ST=standard treatment, QoL=quality of life.

References:

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[4] The data were collected by the investigators, analyzed by statisticians who were employed by the sponsors, and interpreted by the authors, including employees of the sponsors. Bayer HealthCare provided funding for medical writing and editing assistance.