Niraparib / abiraterone acetate (Akeega®) for the treatment of metastatic castration-resistant prostate cancer (mCRPC)

General information [1]

Drug description	Indication
Niraparib inhibits the poly (ADP-ribose) polymerase (PARP) enzymes PARP-1 and PARP-2, which play a role in DNA repair. The inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes result in DNA damage and tumour cell death. **Abiraterone acetate** is converted to abiraterone, which inhibits 17α-hydroxylase/C17,20-lyase (CYP17), an enzyme required for androgen synthesis. By inhibiting CYP17, abiraterone acetate inhibits the production of androgens in the testes, adrenal glands and prostate.	Niraparib/ abiraterone acetate (Akeega®) is indicated with prednisone or prednisolone for the treatment of adult patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated.

Incidence

- In Austria in 2020, 6,126 men were newly diagnosed with prostate cancer. The age-standardised incidence rate[1] in 2020 was 149.9/100,000 men [2].
- In Europe, in 2020, the crude rate[2] of prostate cancer was 130.9/100,000 men [3].
- Around 55-65% of people with prostate cancer develop metastatic disease. Over 90% of people with metastatic prostate cancer initially respond to hormonal therapy but eventually become resistant [4].

Current treatment[3]

- For the treatment of mCRPC, the ESMO recommends the following [5]:
  - Abiraterone or enzalutamide (ESMO-MCBS v1.1 scores: 4) is recommended for asymptomatic/mildly symptomatic men with chemotherapy-naive mCRPC (I, A).
  - Docetaxel (ESMO-MCBS v1.1 score: 4) is recommended for men with mCRPC (I, A).
  - In patients with mCRPC in the post-docetaxel setting, abiraterone (ESMO-MCBS v1.1 score: 4), enzalutamide (ESMO-MCBS v1.1 score: 4) and cabazitaxel (ESMO-MCBS v1.1 score: 3) are recommended options (I, A).
  - In patients with bone metastases from CRPC at risk for clinically significant skeletal-related events, a bisphosphonate or denosumab is recommended (I, B).
  - 223Ra (ESMO-MCBS v1.1 score: 5) is recommended for men with bone-predominant, symptomatic mCRPC without visceral metastases (I, B).
  - 223Ra is not recommended in combination with abiraterone and prednisolone (I, E).
  - The use of a second AR inhibitor (abiraterone after enzalutamide or vice versa) is not recommended (II, D).

Regulatory status

EMA [1]	FDA [6, 7]
Approval status for this indication: On 23 February 2023, the CHMP adopted a positive opinion, recommending granting marketing authorisation for Akeega®. <u>The full indication is:</u>	**Approval status for this indication**: not approved On 1 March 2023, the Janssen Pharmaceutical Companies of Johnson & Johnson announced the submission of a New Drug Application to the FDA seeking approval of niraparib in combination with abiraterone acetate, in the form of a dual-action tablet, plus prednisone, for the treatment of patients with BRCA-positive mCRPC. If approved, this will be the first dual-

[1] European Standard Population 2013
[2] For a specific tumour in a given population, crude rates are calculated simply by dividing the number of new cancers or cancer deaths observed during a given time period by the corresponding number of individuals in the population at risk. For cancer, the result is commonly expressed as an annual rate per 100,000 individuals at risk.
[3] Due to an ongoing update, there is currently no Onkopedia-guideline available.

❖ Akeega® is indicated with prednisone or prednisolone for the treatment of adult patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated. Akeega® will be available as film-coated tablets containing **fixed-dose combinations** of 50 mg niraparib / 500 mg abiraterone acetate or 100 mg niraparib / 500 mg abiraterone acetate. **Other indications**: none ✓ Medicine is under additional monitoring	action tablet formulation available in the U.S. to patients with mCRPC with BRCA mutations, which are a type of homologous recombination repair (HRR)[4] gene alteration. **Other indications**: none

Manufacturer

Akeega® is manufactured by Janssen-Cilag International N.V.

Costs

56 Akeega® tablets 100 mg/ 500 mg = € 4,600.00 (ex-factory price) [8]

Study characteristics [9-13]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
MAGNITUDE NCT03748641	423 (1;1), 3 cohorts[5]	niraparib 200 mg once daily + abiraterone acetate and prednisone (AAP)	placebo + AAP	investigator-evaluated radiographic PFS (rPFS) in all HRR-positive patients, as well as patients with BRCA mutations	26.8 months	**ongoing**[6], randomised, multi-centre, global, double-blind, phase 3 study	BRCA1/2	Janssen Research & Development, LLC	MAGNITUDE trial [10] Abstract [9]

Inclusion criteria	Exclusion criteria	Patient characteristics at baseline
❖ HRR gene alteration (as identified by the sponsor's required assays) as follows: • Cohort 1: positive for HRR gene alteration • Cohort 2: not positive for DRD (that is, HRR gene alteration) • Cohort 3: eligible by HRR status ❖ Metastatic disease documented by positive bone scan or metastatic lesions on CT or MRI ❖ Metastatic prostate cancer in the setting of castrate levels of testosterone ≤ 50 ng/dL on a GnRHa or bilateral orchiectomy	❖ Prior treatment with a PARP inhibitor ❖ Systemic therapy (that is, novel second-generation AR-targeted therapy such as enzalutamide, apalutamide, or darolutamide; taxane-based chemotherapy, or more than 4 months of abiraterone acetate plus prednisone prior to randomization) in the mCRPC setting; or AAP outside of the mCRPC setting ❖ Symptomatic brain metastases ❖ History or current diagnosis of myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML)	❖ Median age: 69 years ❖ 23% had prior abiraterone acetate and prednisone ❖ 21% had visceral metastases ❖ 53% had BRCA1/2 mutations

[4] Genes that are directly or indirectly implicated in HRR include BRCA1, BRCA2, CHEK2, ATM, PALB2, FANCA, and RAD51D, among others.
[5] One cohort of patients with predefined HRR gene alterations (including ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2 alterations) and one cohort of patients without HRR gene alterations. In a third, open-label cohort, all patients received a combination tablet of niraparib and abiraterone and a separate tablet of prednisone.
[6] Estimated study completion date is 02/2027.

❖ Able to continue GnRHa during the study if not surgically castrate ❖ Score of ≤3 on the brief pain inventory-short form (BPI-SF) question number 3 (worst pain in last 24 hours)	❖ Other prior malignancy (exceptions: adequately treated basal cell or squamous cell skin cancer, superficial bladder cancer, or any other cancer in situ currently in complete remission) ≤2 years prior to randomisation or malignancy that currently requires active systemic therapy	

Efficacy (I vs. C)

Primary interim analysis (median follow-up 18.6 months) [9]:

- Niraparib + AAP significantly improved rPFS by BICR in the BRCA1/2 subgroup and all HRR-positive patients, reducing the risk of progression or death by 47% (16.6 vs. 10.9 months, HR 0.53; 95% CI, 0.36-0.79; p= 0.0014) and 27% (16.5 vs. 13.7 months, HR 0.73; 95% CI, 0.56-0.96; p= 0.0217) respectively, vs. placebo + AAP
- Investigator assessed rPFS was consistent with BICR:
- Niraparib + AAP delayed TTCC (HR 0.59; 95% CI 0.39-0.89; p= 0.0108), TTSP (HR 0.69; 95% CI 0.47-0.99; p= 0.0444) and TTPP (HR 0.57, 95% CI, 0.43-0.76; p= 0.0001) and improved ORR (relative risk 2.13; 95%CI 1.45-3.13; p< 0.001) in HRR-positive patients
- First interim analysis of OS is immature. The pre-planned futility analysis in 233 HRR BM-negative patients showed no benefit of adding niraparib to AAP in the prespecified composite endpoint (first of PSA progression or rPFS; HR 1.09; 95% CI, 0.75-1.57)
- Niraparib + AAP prolonged time to PSA progression and led to higher ORR in the HRR+ and BRCA1/2 groups
- Time to PSA progression and rPFS were strongly correlated, with an overall r=0.6 (95% CI, 0.56-0.75)

Second interim analysis data (cutoff: 17 June 2022, median follow-up 26.8 months) [11]:

- Updated descriptive rPFS results were consistent with the primary analysis in the HRR+ cohort
- In the BRCA subgroup, niraparib with abiraterone acetate and prednisone extended median rPFS to 19.5 months vs. 10.9 months with placebo + abiraterone acetate and prednisone
- Niraparib with abiraterone acetate and prednisone led to statistically significant benefit in time to symptomatic progression in the HRR+ cohort with consistent benefit in the BRCA subgroup
- Continued consistent improvement of time to cytotoxic chemotherapy was seen with niraparib with abiraterone acetate and prednisone in the HRR+ cohort and the BRCA subgroup
- There was a trend towards improved OS with niraparib with abiraterone acetate and prednisone in the BRCA subgroup in the primary stratified analysis and the multivariate analysis accounting for imbalances in key baseline characteristics

Safety (I vs. C)

Primary interim analysis [9]:

- No new safety signals were seen
- Grade 3/4 AEs in HRR-positive patients: 67.0% vs. 46.4%
- ≥1 serious TEAE in HRR+ patients: 38.8 vs. 24.6%
- Grade 3 TEAEs in HRR+ patients: 56.1% vs. 42.7%
- Grade 4 TEAEs in HRR+ patients: 10.8 vs. 3.8%
- Treatment discontinuation: 9% vs. 3.8%
- The most common grade AEs were anaemia (28.3% vs. 7.6%) and hypertension (14.6% vs. 12.3%) with niraparib + AAP versus placebo + AAP, respectively
- Other grade 3/4 AEs of note include thrombocytopenia (6.6% vs. 2.4%) and neutropenia (6.6% vs. 1.4%) with niraparib + AAP vs. placebo + AAP. Patients who died on study treatment[7] (HRR+ cohort): 9.0% vs. 9.0%
  - AE: 5.2% vs. 3.3%
  - Progressive disease: 3.8% vs. 5.7%
- Patients who died in follow-up[8]: 17.0% vs. 19.0%
  - AE: 0.5% vs. 0
  - Progressive disease: 13.7% vs. 14.7%
  - Other: 2.8% vs. 4.3
- Patients with ≥1 AE leading to death (HRR+ cohort): 5.7% vs. 3.3%
- Grade 3 AEs in the HRR- cohort: 60.2% vs. 39.8%
- Grade 4 AEs in the HRR- cohort: 13.0% vs. 4.1%

Second interim analysis [11]:

- The safety profile was consistent with the primary analysis's, with no new safety signals observed.

Patient-reported outcomes

Primary interim analysis [9]:

- There were no clinically significant differences in overall quality of life (FACT-P).

Second interim analysis [11]:

[7] On-study treatment death is defined as death that occurs within 30 days of the last dose of study drug.

[8] Follow-up death is defined as the death that occurs >30 days after the last dose of study drug.

- ❖ BRCA patients treated with niraparib and abiraterone acetate + prednisone experienced delayed time to worst pain intensity (HR 0.70; 95% CI, 0.44-1.12; nominal p=0.1338) and pain interference (HR 0.67; 95% CI, 0.40-1.12; nominal p=0.1275) compared to placebo and abiraterone + prednisone.

ESMO-MCBS version 1.1 [14]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2B	>6 months	rPFS: + 5.7 months	0.53 (0.36-0.79)	HR ≤0.65 AND gain ≥3 months	3	-	Delayed time to worst pain intensity and pain interference	+1[9]	4
Adapted	NC	2B	>6 months	rPFS: + 6 months	0.53 (0.36-0.79)	HR≤0.65 AND gain ≥3 months	3	-	-	-	3

Risk of bias (RCT) [15]

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[10]	yes[11]	**unclear**

Ongoing trials [16]

NCT number/trial name	Description	Estimated study completion date
NCT03748641/ MAGNITUDE	Please see above.	02/2027
NCT03903835/ProBio	An outcome-adaptive and randomised multi-arm biomarker-driven study in patients with metastatic prostate cancer.	12/2026
NCT04812366/GUNS	Genomic biomarker-selected umbrella neoadjuvant study for high-risk localised prostate cancer.	04/2026
NCT04947254	Phase II trial of primary radiotherapy with androgen ablation with or without adjuvant niraparib for selected high-risk locoregional prostate cancer.	06/2026
NCT03431350	Phase 1b-2 study of niraparib combination therapies for the treatment of metastatic castration-resistant prostate cancer.	07/2023
NCT05689021	Phase 2 study of CJNJ-67652000 (niraparib/abiraterone acetate fixed-dose combination) and prednisone in patients with mCRPC associated with SPOP mutation with or without homologous recombination deficiency.	09/2025
NCT04194554/ASCLEPIuS	Multi-centre trial of androgen suppression with abiraterone acetate, leuprolide, PARP inhibition and stereotactic body radiotherapy: A phase I/2 trial in high risk and node-positive prostate cancer.	05/2027
NCT04497844/AMPLITUDE	Phase 3 randomised, placebo-controlled, double-blind study of niraparib in combination with abiraterone acetate and prednisone vs. abiraterone acetate and prednisone for the treatment of participants with deleterious germline or somatic homologous recombination repair gene-mutated metastatic castration-sensitive prostate cancer.	05/2027
NCT04577833	Open-label, randomised study to assess the relative bioavailability and bioequivalence of comparative formulations of niraparib and abiraterone acetate in men with prostate cancer.	12/2023

[9] Upgrade due to improvement in QoL.
[10] MAGNITUDE trial is ongoing; currently, only interim analysis data is available.
[11] Industry-funded.

NCT05401214	Pre-approval access single patient request for niraparib / abiraterone acetate combination.	Expanded access status: available[12]

Available assessments

- A Health Technology Briefing, "Niraparib with abiraterone acetate and prednisone for metastatic castration-resistant prostate cancer," was published by NIHR in July 2022 [4].
- No assessments are available from NICE, CADTH, G-BA or ICER.

Other aspects and conclusions

- In February 2023, the **CHMP** adopted a **positive opinion**, recommending the granting of a marketing authorisation for Akeega® with prednisone or prednisolone for the treatment of adult patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated; this indication is currently **not approved by the FDA.**
- NCT03748641, the **MAGNITUDE trial**, evaluates the efficacy and safety of niraparib with abiraterone acetate and prednisone in patients with mCRPC. Patients with HRR gene alteration, metastatic disease documented by positive bone scan or metastatic lesions on CT or MRI, castrate levels of testosterone ≤50 ng/dL on a GnRHa or bilateral orchiectomy and a score of ≤3 on the BPI-SF question number 3 were **included**. Patients prior treated with a PARP inhibitor, a systemic therapy in the mCRPC setting (or AAP outside of the mCRPC setting), patients with symptomatic brain metastases, a history or current diagnosis of MDS/AML or another prior malignancy ≤2 years prior to randomisation, or malignancy that currently requires active systemic therapy were **excluded**.
- Niraparib + AAP significantly improved rPFS by BICR in the BRCA1/2 subgroup and all HRR+ patients, reducing the risk of progression or death by 47% (16.6 vs. 10.9 months, HR 0.53; 95% CI, 0.36-0.79; p= 0.0014) and 27% (16.5 vs. 13.7 months, HR 0.73; 95% CI, 0.56-0.96; p= 0.0217) respectively, vs. placebo + AAP.
- According to second interim analysis of QoL, BRCA patients treated with niraparib and abiraterone acetate + prednisone experienced delayed time to worst pain intensity (not statistically significant) as compared to placebo and abiraterone + prednisone.
- The original and adapted ESMO-MBCS was applied, resulting in a final magnitude of clinical benefit grade of 4 and 3, respectively.
- Since the MAGNITUDE trial is ongoing until 2027 and currently only interim analysis data is available, the risk of bias was considered unclear.
- **Ten ongoing trials** were identified, evaluating niraparib and abiraterone acetate in different settings. More data, including final analysis data of the MAGNITUDE trial is required.

First published: 04/2023
Last updated: 07/2023

Abbreviations: 223Ra=Radium-223, AAP=abiraterone acetate and prednisone, ADT=androgen deprivation therapy, AE=adverse event, AJ=adjustment, AML=acute myeloid leukemia, AR=androgen-receptor, BICR=blinded independent central review, BPI-SF=Brief Pain Inventory-Short Form, BRCA=breast cancer gene, C=comparator, CADTH=Canada's Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CT=computed tomography, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FACT-P=Functional Analysis of Cancer Therapy, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GNRHa=gonadotropin releasing hormone analog, HR=hazard ratio, HRR=homologous recombination repair, I=intervention, ICER=Institute for Clinical and Economic Review, IDMC=Independent Data Monitoring Committee, Int.=intention, mCRPC=metastatic castration-resistant prostate cancer, MDS= myelodysplastic syndrome, MG=median gain, MRI=magnetic resonance imaging, n=number of patients, NICE=National Institute for Health Care Excellence, ORR=overall response rate, OS=overall survival, PARP=poly adenosine diphosphate-ribose polymerase, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, rPFS=radiographic progression-free survival, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse event, TTCC=time to initiation of cytotoxic chemotherapy, TTPP=time to PSA progression, TTSP=time to symptomatic progression

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[12] Expanded access is currently available for this investigational treatment, and patients who are not participants in the clinical study may be able to gain access to the drug, biologic, or medical device being studied.

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