AKEEGA® (niraparib and abiraterone acetate)
Comparison of AKEEGA with ZYTIGA

SUMMARY

- AKEEGA is a combination of niraparib, a poly adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitor, and abiraterone acetate, an inhibitor of the enzyme 17-α-hydroxylase/C17,20-lyase (CYP17).[1]
  - Niraparib is an orally available, highly selective PARP inhibitor with potent activity against the PARP-1 and PARP-2 (deoxyribonucleic acid) DNA repair polymerases.
  - Abiraterone acetate, the active ingredient of ZYTIGA, is a prodrug that is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor, tt selectively inhibits CYP17. CYP17 is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis.[2]
- **MAGNITUDE** (NCT03748641) is a phase 3, randomized, double-blind, placebo-controlled, global study, evaluating the efficacy and safety of AKEEGA with prednisone compared to placebo/abiraterone acetate with prednisone (AAP) as first-line (L1) therapy in metastatic castration-resistant prostate cancer (mCRPC) for patients with certain homologous recombination repair (HRR) mutations, including *BRCA1/2*. The primary endpoint is radiographic progression-free survival (rPFS). Key secondary endpoints include time to cytotoxic chemotherapy (TCC), time to symptomatic progression (TSP), and overall survival (OS).[1,3-7]
  - Patients were prospectively allocated to cohort 1 or 2 based on prescreening for HRR+ or HRR- status and subsequently randomized to receive niraparib or matching placebo in combination with AAP.
- Prespecified primary and key secondary endpoint results are described in Table: Prespecified Primary and Key Secondary Endpoints.
  - At the first interim analysis[4]:
    - In patients with *BRCA1/2* mutations with a median follow-up of 16.7 months, a statistically significant improvement in median rPFS (as assessed by blinded independent central review [BICR]) was observed in the niraparib/AAP group compared to the placebo/AAP group: 16.6 months vs 10.9 months (HR, 0.53; 95% CI, 0.36-0.79; *P*=0.001).
  - At the second interim analysis[6]:
    - In all *BRCA1/2* patients, at a median follow-up of 24.8 months, a total of 43 death events occurred in the niraparib/AAP group compared to 49 events in the placebo/AAP group (HR, 0.88; 95% CI, 0.58-1.34; nominal *P*=0.5505). These endpoints were not adjusted for multiple comparisons. Therefore, the *P*-values displayed are nominal, and statistical significance has not been established.
  - At the final analysis[7]:
    - Across all *BRCA1/2* patients, after a median follow-up of 35.9 months, median OS favored the niraparib/AAP group compared to the placebo/AAP group: 30.4 months vs 28.6 months (HR 0.788; 95% CI, 0.554-1.120; nominal *P*=0.1828). These endpoints were not adjusted for multiple comparisons. Therefore, the *P*-values displayed are nominal, and statistical significance has not been established.
    - OS benefit in the niraparib/AAP group was also demonstrated in a preplanned multivariate analysis using prespecified prognostic factors (HR 0.663; 95% CI, 0.464-0.947; nominal *P*=0.0237). These endpoints were not adjusted for multiple comparisons. Therefore, the *P*-values displayed are nominal, and statistical significance has not been established.
  - A summary of treatment-emergent adverse events (TEAEs) is described in Table: Summary of Most Common (≥10% in Either Group) TEAEs. Grade ≥3 adverse events (AEs) were reported in 153 (72.2%) and 104 (49.3%) patients in the niraparib/AAP

and in the placebo/AAP group, respectively. Discontinuation of niraparib or placebo due to a TEAE occurred in 15.1% of patients in the niraparib/AAP group and 5.7% of patients in the placebo/AAP group.[6] Safety profiles at the final analysis[7] and second interim analysis[5] were consistent with that of the first interim analysis, with no new safety signals observed.

- ProBio (Prostate-Biomarker, NCT03903835) is an ongoing, phase 3, outcome-adaptive, multiarm, multiple-assignment, randomized, open-label, international biomarker-driven platform study in patients with de novo metastatic hormone-sensitive prostate cancer (mHSPC) or L1 mCRPC. Patients will be randomized to receive either standard of care (SOC) or an experimental treatment including abiraterone acetate or AKEEGA, based on predefined biomarker signatures. The study has a planned enrollment of 750 patients. The efficacy and safety results have not been published.[8,9]

CLINICAL DATA

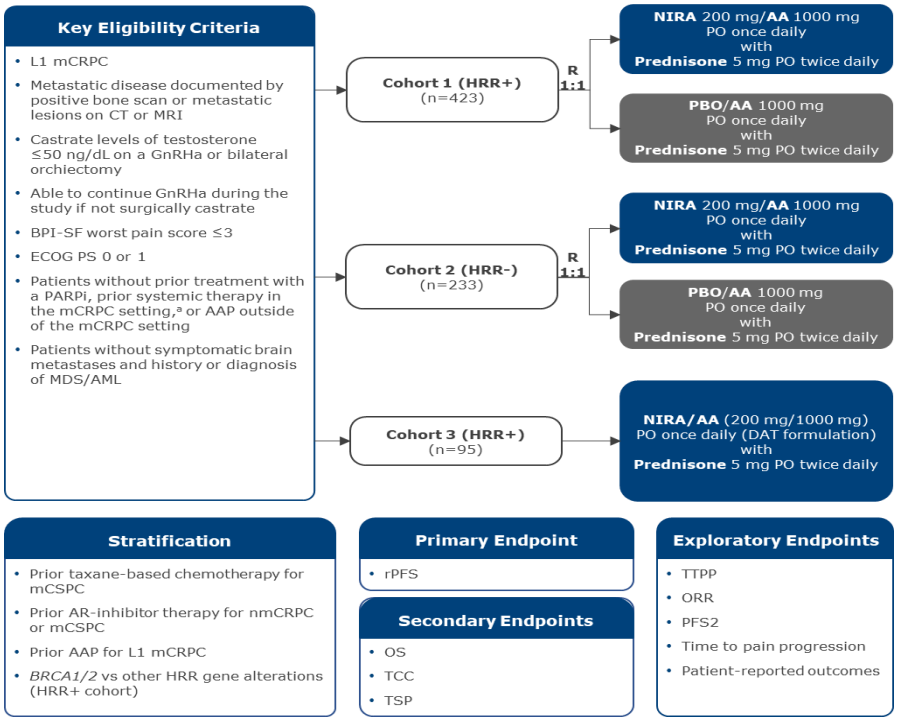
MAGNITUDE Study

Chi et al (2023)[4,6,7] and **Efstathiou et al (2023)**[5] reported the efficacy and safety of AKEEGA with prednisone compared to placebo/AAP in mCRPC for patients with (n=423) and without (n=233) certain HRR gene mutations, including *BRCA1/2* (n=225).

Study Design/Methods

- Ongoing, phase 3, randomized, double-blind, placebo-controlled, global study.
- Patients were prospectively allocated to cohort 1 or 2 based on prescreening for HRR+ or HRR- status.[4,10]
- A third, open-label cohort (cohort 3) was added to evaluate niraparib 200 mg and abiraterone acetate 1000 mg orally once daily with prednisone 5 mg twice daily.
- The study design is presented in Figure: MAGNITUDE Study Design.

MAGNITUDE Study Design[1]



Abbreviations: AA, abiraterone acetate; AAP, abiraterone acetate with prednisone; AML, acute myeloid leukemia; AR, androgen receptor; BPI-SF, Brief Pain Inventory-Short Form; CT, computed tomography; DAT, dual action tablet; ECOG PS, Eastern Cooperative Oncology Group

performance status; GnRHa, gonadotropin-releasing hormone analog; HRR, homologous recombination repair; L1, first-line therapy; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; MDS, myelodysplastic syndrome; MRI, magnetic resonance imaging; NIRA, niraparib; nmCRPC, non-metastatic castration-resistant prostate cancer; ORR, objective response rate; OS, overall survival; PARPi, poly ADP-ribose polymerase inhibitor; PBO, placebo; PFS2, progression-free survival on first subsequent therapy; PO, orally; PSA, prostate-specific antigen; R, randomization; rPFS, radiographic progression-free survival; TCC, time to cytotoxic chemotherapy; TSP, time to symptomatic progression; TTPP, time to PSA progression.
[a]Novel second-generation AR-targeted therapy such as enzalutamide, apalutamide, or darolutamide; taxane-based chemotherapy; or >4 months of AAP before randomization.

Results

Patient Characteristics

- Baseline characteristics were broadly comparable between treatment arms; however, rates of visceral metastases, bone metastases, and Eastern Cooperative Oncology Group performance status (ECOG PS) of 1 were imbalanced to the disadvantage of the niraparib/AAP group.[4]

HRR+ Cohort

Efficacy

- A summary of results for the patients in the HRR+ cohort is provided in Table: Prespecified Primary and Key Secondary Endpoints.

Prespecified Primary and Key Secondary Endpoints[4,6,7]

***BRCA1/2* Mutations**				
	NIRA/AAP (n=113)	**PBO/AAP (n=112)**	**Hazard Ratio (95% CI)**	***P*-Value**
Primary Endpoint at IA1				
Median rPFS (BICR-assessed), months	16.6	10.9	0.53 (0.36-0.79)	0.001
Primary Endpoint at IA2[a]				
Median rPFS (BICR-assessed), months	19.5	10.9	0.55 (0.39-0.78)	Nominal *P*=0.0007[b]
Key Secondary Endpoints at IA2				
Median TCC, months	NR	27.3	0.56 (0.35-0.90)	Nominal *P*=0.0152[b]
Median TSP, months	NR	23.6	0.54 (0.35-0.85)	Nominal *P*=0.0071[b]
Median OS, months	29.3	28.6	0.88 (0.58-1.34)	Nominal *P*=0.5505[b]
Key Secondary Endpoints at FA				
Median OS, months	30.4	28.6	0.788 (0.554-1.120)	Nominal *P*=0.1828[b]
OS with MVA	-	-	0.663 (0.464-0.947)	Nominal *P*=0.0237[b]
Median TCC, months	-	-	0.598 (0.387-0.924)	Nominal *P*=0.0192[b]
Median TSP, months	-	-	0.562 (0.371-0.849)	Nominal *P*=0.0056[b]
All HRR+ Mutations				
	NIRA/AAP (n=212)	**PBO/AAP (n=211)**	**Hazard Ratio (95% CI)**	***P*-Value**
Primary Endpoint at IA1				
Median rPFS (BICR-assessed), months	16.5	13.7	0.73 (0.56-0.96)	0.022

Primary Endpoint at IA2[a]				
Median rPFS (BICR-assessed), months	16.7	13.7	0.76 (0.60-0.97)	Nominal *P*=0.0280[b]
Key Secondary Endpoints at IA2				
Median TCC, months	NR	NR	0.67 (0.47-0.94)	0.0206
Median TSP, months	NR	30.6	0.60 (0.42-0.84)	0.0029
Median OS, months	29.3	32.2	1.01 (0.75-1.36)	0.9480

Abbreviations: AAP, abiraterone acetate with prednisone; BICR, blinded independent central review; CI, confidence interval; HRR, homologous recombination repair; IA1, first interim analysis; IA2, second interim analysis; NIRA, niraparib; NR, not reached; OS, overall survival; PBO, placebo; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival; TCC, time to cytotoxic chemotherapy; TSP, time to symptomatic progression.
[a]As rPFS was found to be statistically significant at IA1, no formal statistical testing was performed for IA2.
[b]These endpoints were not adjusted for multiple comparisons. Therefore, the *P*-values displayed are nominal, and statistical significance has not been established.

Safety

- At the second interim analysis, a total of 211 patients in the niraparib/AAP group and 203 patients in the placebo/AAP group reported AEs, described in Table: Summary of Most Common (≥10% in Either Group) TEAEs.[6]
- Safety profiles across the first interim analysis, second interim analysis[6], and the final analysis[7] were consistent, with no new safety signals.

Summary of Most Common (≥10% in Either Group) TEAEs[6]

n (%)	NIRA/AAP (n=212)			PBO/AAP (n=211)		
	All Grades	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Patients with ≥1 SAE	93 (43.9)	-	-	61 (28.9)	-	-
Any TEAEs	211 (99.5)	121 (57.1)	32 (15.1)	203 (96.2)	91 (43.1)	13 (6.2)
Hematologic						
Anemia	106 (50.0)	61 (28.8)	3 (1.4)	48 (22.7)	18 (8.5)	0 (0.0)
Thrombocytopenia	49 (23.1)	8 (3.8)	8 (3.8)	20 (9.5)	5 (2.4)	0 (0.0)
Neutropenia	32 (15.1)	11 (5.2)	3 (1.4)	15 (7.1)	4 (1.9)	1 (0.5)
Leukopenia	23 (10.8)	4 (1.9)	0 (0.0)	5 (2.4)	1 (0.5)	0 (0.0)
Lymphopenia	22 (10.4)	8 (3.8)	1 (0.5)	4 (1.9)	1 (0.5)	1 (0.5)
Cardiovascular						
Hypertension	70 (33.0)	33 (15.6)	0 (0.0)	47 (22.3)	26 (12.3)	0 (0.0)
Hypokalemia	29 (13.7)	7 (3.3)	1 (0.5)	21 (10.0)	7 (3.3)	0 (0.0)
Hyperglycemia	25 (11.8)	6 (2.8)	1 (0.5)	18 (8.5)	2 (0.9)	0 (0.0)
ALP increased	23 (10.8)	10 (4.7)	2 (0.9)	16 (7.6)	5 (2.4)	0 (0.0)
ALT increased	11 (5.2)	0 (0.0)	0 (0.0)	22 (10.4)	10 (4.7)	0 (0.0)
General disorders						
Fatigue	63 (29.7)	8 (3.8)	0 (0.0)	40 (19.0)	11 (5.2)	0 (0.0)
Dyspnea	38 (17.9)	5 (2.4)	0 (0.0)	14 (6.6)	4 (1.9)	0 (0.0)
Back pain	36 (17.0)	6 (2.8)	0 (0.0)	47 (22.3)	2 (0.9)	0 (0.0)
Asthenia	35 (16.5)	2 (0.9)	1 (0.5)	21 (10.0)	1 (0.5)	0 (0.0)

n (%)	NIRA/AAP (n=212)			PBO/AAP (n=211)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Arthralgia	32 (15.1)	1 (0.5)	0 (0.0)	23 (10.9)	2 (0.9)	0 (0.0)
Dizziness	27 (12.7)	1 (0.5)	0 (0.0)	13 (6.2)	0 (0.0)	0 (0.0)
Insomnia	24 (11.3)	0 (0.0)	0 (0.0)	8 (3.8)	0 (0.0)	0 (0.0)
Bone pain	23 (10.8)	4 (1.9)	0 (0.0)	24 (11.4)	1 (0.5)	0 (0.0)
Urinary tract infection	22 (10.4)	7 (3.3)	0 (0.0)	18 (8.5)	4 (1.9)	0 (0.0)
Weight decreased	22 (10.4)	3 (1.4)	0 (0.0)	7 (3.3)	1 (0.5)	0 (0.0)
Fall	16 (7.5)	2 (0.9)	0 (0.0)	29 (13.7)	6 (2.8)	0 (0.0)
Gastrointestinal						
Constipation	70 (33.0)	1 (0.5)	0 (0.0)	33 (15.6)	0 (0.0)	0 (0.0)
Nausea	52 (24.5)	1 (0.5)	0 (0.0)	31 (14.7)	1 (0.5)	0 (0.0)
Decreased appetite	33 (15.6)	2 (0.9)	0 (0.0)	15 (7.1)	1 (0.5)	0 (0.0)
Vomiting	31 (14.6)	2 (0.9)	0 (0.0)	16 (7.6)	2 (0.9)	0 (0.0)

Abbreviations: AAP, abiraterone acetate with prednisone; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; PBO, placebo; SAE, severe adverse event; TEAE, treatment-emergent adverse event.

HRR- Cohort

Efficacy and Safety

- A prespecified futility analysis was conducted in the HRR- population after enrolling 233 of the planned 600 patients and approximately 125 composite progression events (first of rPFS, PSA progression, or death) occurred.[10]
  - The composite progression endpoint (n=233) met futility criteria (HR, 1.09; 95% CI, 0.75-1.59), where futility was defined as ≥1.
  - A total of 83 PSA events (HR, 1.03; 95% CI, 0.67-1.59) and 65 rPFS events (HR, 1.03; 95% CI, 0.63-1.67) occurred.
- Additional grade 3/4 toxicity was observed in the niraparib/AAP group compared to the placebo/AAP group.[10]
- Based on the efficacy and safety results in patients with HRR- mCRPC, the independent data monitoring committee (IDMC) recommended stopping enrollment in this cohort to support patient safety and prevent overtreatment.[10]

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) was conducted on 24 June 2024. Summarized in this response are relevant data pertaining to this topic in patients with prostate cancer.

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