ZYTIGA® (abiraterone acetate)
Combination of ZYTIGA with Radium Ra 223 Dichloride in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

SUMMARY

- The use of ZYTIGA plus prednisone in combination with radium Ra 223 dichloride (Ra223) is not recommended.[1] Please refer to product labeling for related safety information.
- ERA-223: A phase 3, randomized, double-blind, placebo-controlled, multinational study evaluated the combination of Ra223 and ZYTIGA plus prednisone/prednisolone in men with asymptomatic or mildly symptomatic chemotherapy-naïve castration-resistant prostate cancer (CRPC) with bone metastases (N=806). The study was unblinded early based on an Independent Data Monitoring Committee (IDMC) recommendation after more fractures and deaths were observed in patients who received Ra223 in combination with ZYTIGA plus prednisone/prednisolone.[1] At primary analysis:
  - The median symptomatic skeletal event-free survival (SSE-FS), the primary study endpoint, was 22.3 months (95% confidence interval [CI], 20.4-24.8 months) in the Ra223 with ZYTIGA plus prednisone/prednisolone group and 26 months (95% CI, 21.8-28.3 months) in the placebo with ZYTIGA plus prednisone/prednisolone group (hazard ratio [HR], 1.122; 95% CI, 0.917-1.374; *P*=0.2636). Median overall survival (OS) was 30.7 months (95% CI, 25.8-not estimable [NE] months) in the Ra223 with ZYTIGA plus prednisone/prednisolone group and 33.3 months (95% CI, 30.2-41.1 months) in the placebo with ZYTIGA plus prednisone/prednisolone group (HR, 1.195; 95% CI, 0.950-1.505; *P*=0.1280).
  - An increased incidence of fractures (29% vs 11%) was observed in the Ra223 with ZYTIGA plus prednisone/prednisolone group compared to the placebo with ZYTIGA plus prednisone/prednisolone group, respectively. In patients taking bone health agents (BHAs), 15% experienced a fracture in the Ra223 with ZYTIGA plus prednisone/prednisolone group and 7% in the placebo with ZYTIGA plus prednisone/prednisolone group. Without BHAs, 37% vs 15% experienced a fracture in the Ra223 with ZYTIGA plus prednisone/prednisolone group and placebo with ZYTIGA plus prednisone/prednisolone group, respectively.
- A phase 2a, randomized, open-label, multicenter study evaluated the use of Ra223 alone or in combination with ZYTIGA plus prednisone or enzalutamide in patients with CRPC and bone metastases (N=68). The bone scan lesion area response rate (BSLA RR) at week 24 was 22%, 58%, and 50% for the Ra223 alone, Ra223 in combination with ZYTIGA plus prednisone, and Ra223 plus enzalutamide groups, respectively. Any grade treatment-emergent adverse events (TEAEs) were reported for 18, 22, and 22 patients receiving Ra223 alone, Ra223 in combination with ZYTIGA plus prednisone, and Ra223 plus enzalutamide, respectively. Fracture rates were generally lower in patients taking baseline BHAs (3/23) vs without BHAs (10/40).[2]
- ERADICATE: In a phase 2, open-label study evaluating concomitant administration of ZYTIGA and Ra223 on quality of life (QOL) and bone pain in patients with metastatic castration-resistant prostate cancer (mCRPC) with symptomatic bone metastases (N=36), 65% of patients experienced positive clinically meaningful improvement on the Functional Assessment of Cancer Therapy-Prostate (FACT-P), and 81% on the Prostate Cancer Subscale in 31 evaluable patients. Overall, 58% of patients demonstrated reduced pain intensity, and 39% demonstrated reduction of pain interference in their lives. The most common adverse events (AEs) were diarrhea, nausea, and fatigue. Of 6 serious AEs reported, 1 was attributed to study medication.[3]
- Two publications report outcomes data from expanded access and early access studies of combination therapy with Ra223 and ZYTIGA plus prednisone/prednisolone.[4, 5]

CLINICAL DATA

Phase 3 Study

Smith et al (2019)[1] reported analyses from a study evaluating Ra223 or placebo use in combination with ZYTIGA plus prednisone/prednisolone in men with asymptomatic or mildly symptomatic chemotherapy-naïve mCRPC with bone metastases (N=806).

Study Design/Methods

- Phase 3, randomized, double-blind, placebo-controlled, multinational study (ERA-223 study; NCT02043678)
- Participants were randomized 1:1 to receive Ra223 or placebo in combination with ZYTIGA plus prednisone/prednisolone. Those who had not undergone orchiectomy had to have received luteinizing-hormone releasing hormone agonists or antagonists for at least 4 weeks before randomization and had to continue this therapy throughout the study.
- BHAs (bisphosphonates or denosumab) were permitted if the patient was receiving them at baseline only.
- Patients with visceral metastases were excluded.
- **Primary endpoint:** SSE-FS
- **Secondary endpoints:** radiographic progression-free survival (rPFS; by central review), time to toxic chemotherapy, and time to opiate use for cancer pain
- **Exploratory endpoints:** prostate-specific antigen (PSA) response, time to PSA progression (TTPP), alkaline phosphatase (ALP) response, time to ALP progression, and time to deterioration in health-related QOL

Patient Characteristics

- At baseline, 39% and 42% of patients were receiving bisphosphonates or denosumab in the Ra223 with ZYTIGA plus prednisone/prednisolone and placebo with ZYTIGA plus prednisone/prednisolone groups, respectively.
- Minor imbalances in baseline factors were noted between treatment groups; fewer patients in the Ra223 with ZYTIGA plus prednisone/prednisolone group had spinal cord compression than in the placebo with ZYTIGA plus prednisone/prednisolone group.

Efficacy

- The trial was unblinded early after more fractures and deaths were observed in the Ra223 with ZYTIGA plus prednisone/prednisolone group. All patients had completed study-specified Ra223 or placebo treatment prior to unblinding.
- At primary analysis, median SSE-FS was 22.3 months (95% CI, 20.4-24.8 months) in patients in the Ra223 with ZYTIGA plus prednisone/prednisolone group and 26.0 months (95% CI, 21.8-28.3 months) in patients in the placebo with ZYTIGA plus prednisone/prednisolone group (HR, 1.122; 95% CI, 0.917-1.374; *P*=0.2636).
- Median OS was 30.7 months (95% CI, 25.8-NE months) in the Ra223 with ZYTIGA plus prednisone/prednisolone group and 33.3 months (95% CI, 30.2-41.1 months) in the placebo with ZYTIGA plus prednisone/prednisolone group (HR, 1.195; 95% CI, 0.950-1.505; *P*=0.1280).
- Results for secondary and exploratory endpoints are summarized in the Table: Secondary and Exploratory Endpoints.

Secondary and Exploratory Endpoints[1]

	Ra223 + ZYTIGA + prednisone/ prednisolone Group (n=401)	Placebo + ZYTIGA + prednisone/ prednisolone Group (n=405)	HR (95% CI)
Secondary endpoints			
rPFS (central review), median (95% CI), months	11.2 (9.1-11.8)	12.4 (10.8-14.5)	1.152 (0.960-1.383)
Time to cytotoxic chemotherapy, median (95% CI), months	29.5 (26.5-35.7)	28.5 (23.7-NE)	1.033 (0.816-1.308)
Time to opiate use for cancer pain, median (95% CI), months	19.0 (14.4-23.2)	22.6 (18.0-25.7)	1.126 (0.921-1.378)
Exploratory endpoints			
Overall confirmed PSA response, n/N (%)	287/396 (72)	267/401 (67)	-
Time to PSA progression, median (95% CI), months	9.6 (8.2-10.8)	9.0 (7.9-10.1)	0.937 (0.792-1.108)
Overall confirmed ALP response, n/N (%)	218/398 (55)	104/402 (26)	-
Time to ALP progression, median (95% CI), months	7.4 (7.1-7.9)	6.8 (5.3-8.4)	1.083 (0.918-1.276)
Time to deterioration in health-related QOL[a], median (95% CI), months	9.5 (6.9-12.0)	10.5 (8.3-13.0)	1.079 (0.865-1.345)

Abbreviations: ALP, alkaline phosphatase; CI, confidence interval; HR, hazard ratio; NCCN-FACT FPSI, National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy Prostate Symptom Index; NE, not estimable; PSA, prostate-specific antigen; QOL, quality of life; rPFS, radiographic progression-free survival.

[a]As reported in the safety population (Ra223 + ZYTIGA + prednisone/prednisolone), N=392; placebo + ZYTIGA + prednisone/prednisolone, N=394) using the NCCN-FACT FPSI-17 physical disease-related symptoms subscale score measured during the treatment period.

Safety

- Treatment-emergent fractures occurred in 103 (26%) of 392 patients in the Ra223 with ZYTIGA plus prednisone/prednisolone group and 38 (10%) of 394 patients in the placebo with ZYTIGA plus prednisone/prednisolone group. Grade 1 fractures (asymptomatic) occurred in 23 (6%) patients in the Ra223 with ZYTIGA plus prednisone/prednisolone group vs 12 (3%) patients in the placebo with ZYTIGA plus prednisone/prednisolone group, and grade 2 fractures (symptomatic but non-displaced) occurred in 44 (11%) vs 13 (3%), respectively. When events reported during the post-treatment follow-up period were included, fractures occurred in 29% of patients in the Ra223 with ZYTIGA plus prednisone/prednisolone group vs 11% patients in the placebo with ZYTIGA plus prednisone/prednisolone group.
- Median time to fracture was 31.7 months (95% CI, 27.6–NE) in the Ra223 with ZYTIGA plus prednisone/prednisolone group but could not be estimated (HR, 3.135; 95% CI, 2.206–4.455) in the placebo with ZYTIGA plus prednisone/prednisolone group.
- In patients taking BHAs, 15% experienced a fracture in the Ra223 with ZYTIGA plus prednisone/prednisolone group and 7% in the placebo with ZYTIGA plus prednisone/prednisolone group. Without BHAs, 37% vs 15% experienced a fracture in the Ra223 with ZYTIGA plus prednisone/prednisolone group and placebo with ZYTIGA plus prednisone/prednisolone group, respectively.

- A post-hoc analysis showed that 35 (9%) of 392 patients in the Ra223 with ZYTIGA plus prednisone/prednisolone group and 41 (10%) of 394 in the placebo with ZYTIGA plus prednisone/prednisolone group had ALP flares. In the Ra223 group, 6 (17%) of 35 patients with flares in ALP concentrations had fractures, compared with 102 (30%) of 343 patients without flares. In the placebo group, 3 (7%) of 41 patients with flares in ALP had fractures, compared with 41 (12%) of 329 patients without flares (two-sided $P_{interaction}$=0.7917).
- The most common grade 3–4 TEAEs were hypertension (43 [11%] patients in the Ra223 with ZYTIGA plus prednisone/prednisolone group vs 52 [13%] patients in the placebo with ZYTIGA plus prednisone/prednisolone group), fractures (36 [9%] vs 12 [3%]), and increased alanine aminotransferase (ALT) levels (34 [9%] vs 28 [7%]), respectively. Serious TEAEs occurred in 160 (41%) patients in the Ra223 with ZYTIGA plus prednisone/prednisolone group and 155 (39%) in the placebo with ZYTIGA plus prednisone/prednisolone group. Treatment-related deaths occurred in 2 patients in the Ra223 with ZYTIGA plus prednisone/prednisolone group (acute myocardial infarction and interstitial lung disease) and 1 in the placebo with ZYTIGA plus prednisone/prednisolone group (arrhythmia).
- The cause of the higher number of deaths in the Ra223 group is unknown. The final analysis of OS will be conducted after 500 events have been recorded. At the current interim analysis, 211 (73%) of the 291 deaths in the safety population were due to progressive disease.

Phase 2 Studies

Petrylak et al (2021)[2] evaluated BSLA RR, safety, and additional outcomes of Ra223 alone or in combination with either ZYTIGA plus prednisone or enzalutamide in patients with CRPC and bone metastases (N=68).

Study Design/Methods

- Phase 2a, randomized, open-label, multicenter study (NCT02034552)
- Patients were randomized 1:1:1 to receive Ra223 55 kBq/kg intravenously every 4 weeks for a total of 6 doses alone or in combination with ZYTIGA 1,000 mg orally (PO) once daily plus prednisone 5 mg PO twice daily or enzalutamide 160 mg PO daily.
- Patients with visceral metastases, treatment with >1 chemotherapy agent for prostate cancer, or prior ZYTIGA plus prednisone, Ra223, enzalutamide, or systemic radiotherapy were excluded.
- Patients were assessed at screening and at weeks 8, 16, and 24 using a whole-body technetium-99m bone scan and MRI/CT imaging of the chest, abdomen, and pelvis. Assessment continued every 12 weeks or until confirmed radiologic progression (bone and/or soft tissue).
- **Primary endpoint:** BSLA RR (defined as ≥30% decrease from baseline) at week 24 based on central evaluation of quantified technetium-99m bone scans
- **Secondary endpoints:** rPFS (non-bone or bone progression, whichever occurred first), time to radiologic non-bone (soft-tissue) progression (modified Response Evaluation Criteria In Solid Tumors [RECIST] 1.1), time to radiologic bone progression (adapted Prostate Cancer Working Group 2 [PCWG2] guidelines), SSE-FS, time to first SSE, OS, and safety

Results

Patient Characteristics

- 68 patients were randomized and 63 received treatment.

- 37% of patients were using BHAs at baseline.
- Baseline patient characteristics are provided in Table: Baseline Patient Characteristics (ITT Population).

Baseline Patient Characteristics (ITT Population)[2]

	Ra223 alone Group (n=22)	Ra223 + ZYTIGA + prednisone Group (n=24)	Ra223 + enzalutamide Group (n=22)
Median age, years	72	68	73
ECOG PS, n (%) 0 1	 10 (45) 9 (41)	 13 (54) 9 (38)	 11 (50) 11 (50)
Median total ALP, U/l	96	101	98
Median PSA, µg/l	31	17	19
Median time since PC diagnosis, months	25	52	48
Median time since first cancer progression, months	15	32	20
Median time since bone metastasis initial diagnosis, months	10	15	22
Extent of disease, n (%) <6 metastases 6-20 metastases >20 lesions Superscan	 9 (41) 7 (32) 3 (14) 1 (5)	 6 (25) 11 (46) 5 (21) 0	 6 (27) 12 (55) 4 (18) 0
Median baseline BSLA, mm²	4315	7479	7516
Prior systemic anticancer therapies, n (%)[a] Sipuleucel-T Docetaxel	 5 (23) 4 (18)	 6 (25) 3 (13)	 3 (14) 5 (23)
Prior BHA use, n (%) Denosumab Zoledronic acid	8 (42)[b] 7 (37)[b] 1 (5)[b]	7 (32)[c] 6 (27)[c] 1 (5)[c]	8 (36) 7 (32) 1 (5)

Abbreviations: ALP, alkaline phosphatase; BHA, bone health agent; BSLA, bone scan lesion area; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; PC, prostate cancer; PSA, prostate-specific antigen.
[a]>15% of patients overall. [b]n=19. [c]n=22.

Efficacy

- Results for the primary and secondary endpoints are summarized in Table: Primary and Secondary Efficacy Endpoints (mITT Population).

Primary and Secondary Efficacy Endpoints (mITT Population)[2]

	Ra223 alone Group (n=19)	Ra223 + ZYTIGA + prednisone Group (n=22)	Ra223 + enzalutamide Group (n=22)
BSLA RR at week 24,[a] % (80% CI), *P* value	22 (10-40); *P*=0.0109[b]	58 (41-74); *P*<0.0001[b]	50 (32-68); *P*<0.0001[b]
Median rPFS, months (80% CI)[c]	4 (4-12)	NE (19-NE)	NE (10-NE)

Median time to radiologic disease (non-bone) progression, months (80% CI)[c]	5 (4-NE)	NE (NE-NE)	NE (NE-NE)
Median time to radiologic bone progression, months (80% CI)[c]	12 (4-12)	NE (NE-NE)	NE (NE-NE)
Patients with an SSE, n (%)	6 (32)	7 (32)	7 (32)
Median SSE-FS, months (80% CI)	12 (10-25)	NE (17-NE)	20 (12-28)
Median time to first SSE, months (80% CI)	NE (13-NE)	NE (17-NE)	NE (20-NE)
Median OS, months (80% CI)	36 (21-41)	38 (36-NE)	30 (27-NE)

Abbreviations: BSLA, bone scan lesion area; CI, confidence interval; mITT, modified intention-to-treat; NE, not estimable; OS, overall survival; rPFS, radiologic progression-free survival; RR, response rate; SSE, symptomatic skeletal event; SSE-FS, SSE-free survival.
[a]Imaging population: Ra223 + ZYTIGA/prednisone, n=19; Ra223 + enzalutamide, n=16; Ra223 monotherapy, n=18.
[b]Test of the null hypothesis of BSLA RR ≤5% at week 24 using an exact single-arm binomial test in each treatment group with one-sided alpha=0.10.
[c]Central review.

Safety

- Safety results are summarized in Table: TEAEs (Any Grade) Occurring in ≥20% of Patients in Any Treatment Arm (Safety Population).
- Treatment-related TEAEs were reported in 8 (42%), 17 (77%), and 18 (82%) in the Ra223 monotherapy, Ra223 plus ZYTIGA/prednisone, and Ra223 plus enzalutamide groups, respectively.
- One treatment-related serious TEAE of nausea was reported in 1 patient in the Ra223 plus ZYTIGA/prednisone group.
- Fracture rates were generally lower in patients taking baseline BHAs (3/23) vs without BHAs (10/40).

TEAEs (Any Grade) Occurring in ≥20% of Patients in Any Treatment Arm (Safety Population)[2]

AE (MedDRA preferred term)[a], n (%)	Ra223 alone Group (n=19)	Ra223 + ZYTIGA + prednisone Group (n=22)	Ra223 + enzalutamide Group (n=22)
Any TEAE	18 (95)	22 (100)	22 (100)
Fatigue	6 (32)	8 (36)	9 (41)
Back pain	5 (26)	8 (36)	9 (41)
Diarrhea	4 (21)	8 (36)	9 (41)
Nausea	2 (11)	9 (41)	6 (27)
Arthralgia	3 (16)	5 (23)	6 (27)
Decreased appetite	3 (16)	3 (14)	5 (23)
Hypertension	3 (16)	2 (9)	6 (27)
Constipation	1 (5)	6 (27)	3 (14)
Dizziness	1 (5)	3 (14)	6 (27)
Hot flush	1 (5)	3 (14)	5 (23)
Vomiting	2 (11)	6 (27)	1 (5)
Headache	1 (5)	5 (23)	1 (5)
Upper respiratory tract infection	0	5 (23)	2 (9)

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.
[a]All AEs were coded according to the MedDRA v.21.0, graded according to the CTCAE v.4.0, and assessed by the investigator for their relationship to treatment.

Shore et al (2018)[3] conducted a prospective study evaluating concurrent use of ZYTIGA and Ra223 on QOL and bone pain in patients with CRPC and symptomatic bone metastases (N=36).

Study Design/Methods

- Phase 2, open-label study (ERADICATE study; NCT02097303)
- Patients received Ra223 50 kBq/kg body weight every 4 weeks for a total of 6 doses and ZYTIGA 1,000 mg once daily plus prednisone 5 mg twice daily <90 days prior to or <30 days after the first Ra223 dose.
- QOL and bone scan assessments were performed at baseline, on day 1 of each of the 6 cycles, and at 30 days following the final Ra223 treatment.[6]
- **Primary endpoints:** QOL and bone pain, as measured by FACT questionnaires and Bone Pain Index Short Form (BPI-SF), respectively
- **Secondary endpoints:** safety, disease progression, Eastern Cooperative Oncology Group (ECOG) performance status changes, ALP response, PSA response, skeletal-related events, and progression to further antineoplastic therapy

Results

Patient Characteristics

- Median age was 75 years (range, 51-90 years), and 6/36 (17%) had received prior chemotherapy.
- The majority of patients (92%) had ECOG performance <2, and 44% were receiving opioid pain medications at baseline.
- Baseline laboratory values and disease characteristics are included in the efficacy summary.

Efficacy

- Efficacy data were evaluated for the 31 patients who completed baseline testing as well as all 6 Ra223 cycles and final treatment visit.
- Significant increases in QOL measurements and a stability of ECOG scores were noted.
    - Twenty patients (65%) experienced positive clinically meaningful improvement changes on the FACT-P, and 25 (81%) on the Prostate Cancer Subscale.
    - Almost one-half of patients (47%) reported stable ECOG scores, 9 (25%) patients had a sustained or intermittent improvement of 1 point, and 8 (22%) of 36 patients worsened.
    - 18 patients (58%) demonstrated reduced pain intensity, and 12 (39%) demonstrated reduction of pain interference in their lives.
- Bone imaging response was assessed at baseline and at end of treatment (EOT). The mean number of bone scan lesions decreased at EOT to 5.6±2.4 (P=0.0002) from baseline (11.6±2.8 lesions). Twenty-nine (94%) of 31 patients had stable disease by EOT and 2 (6%) of 31 had progressed, defined as 2 or more additional lesions.
    - Sixteen (44.4%) of 36 patients reduced their use of pain medication during the study. Most patients (19 [52.3%]) were stable in their medication use and only 1 patient increased his use during the study.
- ALP at baseline was 261±284 ng/dL and at EOT 111±187 ng/dL (P<0.00001). PSA at baseline was 87±223 ng/dL and at EOT was 137±441 ng/dL (P=0.4870).

Safety

- All 36 patients were evaluated for safety. Overall, 30 patients (83%) reported 186 AEs; 179 (96%) were grade 1 or 2, of which 70 (39%) were treatment related, including clinically significant laboratory abnormalities.
- No SREs or progression to antineoplastic therapy occurred during the study.
- The most frequent treatment-related events were diarrhea (17%), nausea (17%), and fatigue (14%).
- Six serious AEs were reported with only 1 attributed to study medication. One patient died of cardiopulmonary arrest unrelated to study medication.

Expanded and Early Access Studies

Evaluation of Ra223 efficacy and safety from 2 expanded/early access programs in patients with mCRPC receiving concomitant ZYTIGA plus prednisone/prednisolone have been identified in the literature.[4, 5]

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 14 July 2023. Summarized in this response are relevant data limited to prospective clinical trials.

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