Effects of concomitant use of abiraterone and/or enzalutamide with radium-223 on safety and overall survival in metastatic castration-resistant prostate cancer (mCRPC) patients treated in an international early access program (iEAP)

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Abstract 2561

BACKGROUND

Radium-223 dichloride (Ra-223)

- In the pivotal ALSYMPCA study,[1] in mCRPC patients with bone metastases, Ra-223 in combination with best standard of care (BSoC) vs placebo and BSoC:
  - Improved overall survival (OS; median 14.9 vs 11.3 months, HR=0.70; p<0.001)[1]
  - Delayed time to first symptomatic skeletal event[2]
  - Was generally well tolerated with minimal hematological toxicity reported.
- The ALSYMPCA study was conducted when few treatment alternatives with OS benefit were available.

Ra-223 in an iEAP

- Ra-223 appeared to be as effective as in the ALSYMPCA study with no new safety concerns reported for patients treated in everyday practice.[3]
- At the time of this iEAP novel endocrine agents with approval in this setting (abiraterone and enzalutamide) were also available.

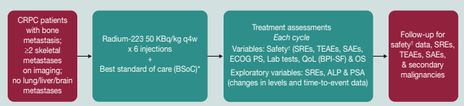
OBJECTIVE

- To investigate safety and OS in patients receiving Ra-223 with concomitant abiraterone and/or enzalutamide in a post hoc analysis of iEAP data.

PATIENTS AND METHODS

- The iEAP was a phase 3b single-arm, international, prospective, interventional, open-label multicenter EAP (Figure 1).[3]

Figure 1. iEAP study design



*BSoC according to local clinical practice. If chemotherapy/radiotherapy was considered BSoC, Ra-223 had to be discontinued. †Adverse events were coded according to MedDRA version 17.1 and graded by NCI-CTCAE version 4.03. ALP=alkaline phosphatase; CRPC=castration-resistant prostate cancer; ECOG PS=Eastern Cooperative Oncology Group performance status; MedDRA=Medical Dictionary for Regulatory Activities; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; OS=overall survival; PSA=prostate specific antigen; q4w=every 4 weeks; QoL (BPI-SF)=quality of life (by brief pain inventory-short form); SREs=skeletal related events; SAEs=serious adverse events; TEAEs=treatment emergent adverse events.

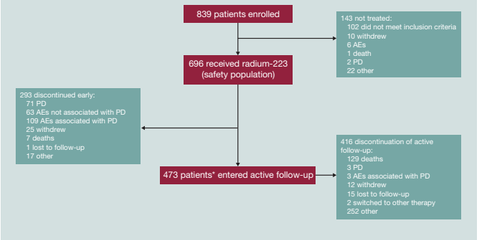
- Eligibility criteria were similar to ALSYMPCA except that asymptomatic patients were allowed in the iEAP.
- In this study concomitant use was defined as any agent started after the first injection of Ra-223 (concurrent) or started prior to the first injection of Ra-223 and continued during Ra-223 treatment (continuous).

RESULTS

Patients

- 839 patients were enrolled from 113 sites in 14 countries (Europe, Canada and Israel) and 696 were treated with ≥1 dose of Ra-223 (safety population, Figure 2).[3]

Figure 2. Patient disposition



*70 patients who discontinued treatment early were allowed to enter active follow-up.
AE=adverse event; PD=progressive disease.

- Use of new endocrine agents in the iEAP is shown in Table 1:
  - In total 189 Ra-223 treated patients received concomitant abiraterone and/or enzalutamide
  - 15 patients were treated concomitantly with both abiraterone and enzalutamide.

Table 1. Use of abiraterone and enzalutamide

Agent use	Safety population (N=696)
Abiraterone	
Prior-only	277 (40)
Concomitant*	154 (22)
Continuous	82 (12)
Concurrent	72 (10)
Enzalutamide	
Prior-only	56 (8)
Concomitant*	50 (7)
Continuous	18 (3)
Concurrent	32 (5)

Data are n (%). *Defined in the methods.15 patients were treated concomitantly with both abiraterone and enzalutamide.

- Baseline characteristics were generally comparable between treatment groups (Table 2):
  - Prostate specific antigen (PSA) and alkaline phosphatase (ALP) levels were lower in patients receiving concomitant endocrine agents than in those not receiving such agents
  - Most patients treated with endocrine agents had received prior docetaxel.
- Median duration of Ra-223 treatment was 20.1 weeks:
  - Patients received a median of 6 (range 1–6) Ra-223 injections.
- Median time on concomitant abiraterone or enzalutamide from first Ra-223 injection was 24.9 and 15.5 weeks, respectively.

Table 2. Baseline demographics

Characteristic	Abi N=154	Enza N=50	Abi/Enza N=189	None N=507
Median age, years (range)	71 (49–88)	70 (52–85)	70 (49–88)	73 (45–94)
Race				
White	151 (98)	49 (98)	185 (98)	494 (97)
Weight				
N	154	50	189	506
Median, kg (range)	82 (58–155)	85 (58–120)	83 (58–155)	80 (49–151)
ECOG PS				
0	69 (45)	18 (36)	82 (43)	179 (35)
1	73 (47)	26 (52)	91 (48)	257 (51)
≥2	12 (8)	6 (12)	16 (8)	71 (14)
Pain*				
No	40 (27)	11 (22)	46 (25)	93 (18)
Mild	78 (53)	32 (64)	101 (55)	269 (53)
Moderate	24 (16)	7 (14)	30 (16)	93 (18)
Severe	6 (4)	0	6 (3)	29 (6)
Missing	0	0	0	23 (5)
PSA				
N	152	49	187	506
Median µg/L (range)	94 (0–9697)	140 (0–2556)	99 (0–9697)	164 (0–12150)
ALP				
N	154	50	189	505
Median U/L (range)	139 (22–1554)	142 (38–1071)	142 (22–1554)	161 (19–4236)
Hemoglobin				
Median, g/L (range)	13 (8–16)	12 (9–16)	13 (8–16)	12 (9–18)
Prior docetaxel	111 (72)	42 (84)	142 (75)	276 (54)

Data are n (%) unless otherwise stated. Abi=abiraterone; ALP=total alkaline phosphatase; ECOG PS=Eastern Cooperate Oncology Group performance status; Enza=enzalutamide.

Safety

- Adverse events were comparable across the treatment groups (Table 3).
- Grade 5 adverse events were reported in 7 (4%) and 50 (10%) patients treated with or without concomitant endocrine agents, respectively; these were most commonly due to general health deterioration (3 vs 21 patients)

Efficacy

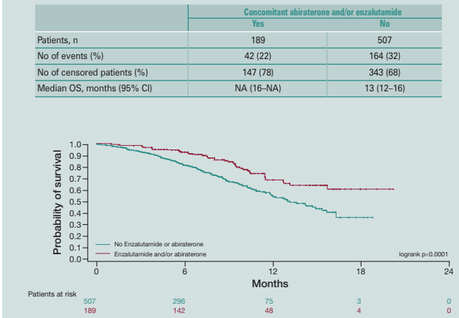
- In the safety population, median follow up was 7.5 months; 210 deaths were reported and 70% of patients were censored
  - Median OS was 16 months (95% CI 13–not available).[3]
- OS was longer in patients treated with Ra-223 in combination with endocrine agents than those treated without concomitant endocrine agents (Figures 3–5).

Table 3. Summary of adverse events by preferred term and severity*

	Abi/Enza (N=189)		None (N=507)	
Preferred term	Any	Grade 3/4	Any	Grade 3/4
Any	152 (80)	75 (40)	394 (78)	195 (38)
Anemia	37 (20)	23 (12)	111 (22)	60 (12)
Thrombocytopenia	7 (4)	2 (1)	25 (5)	17 (3)
Leukopenia	6 (3)	2 (1)	10 (2)	4 (<1)
Neutropenia	4 (2)	2 (1)	9 (2)	7 (1)
Nausea	27 (14)	1 (<1)	66 (13)	1 (<1)
Constipation	6 (3)	0	27 (5)	7 (1)
Diarrhea	26 (14)	1 (<1)	55 (11)	5 (<1)
Vomiting	16 (8)	1 (<1)	27 (5)	7 (1)
Fatigue	16 (8)	2 (1)	59 (12)	14 (3)
GPHD	10 (5)	5 (3)	31 (6)	5 (<1)
Weight decreased	13 (7)	1 (<1)	43 (8)	4 (<1)
PC decreased	6 (3)	2 (1)	19 (4)	10 (2)
Decreased appetite	10 (5)	2 (1)	45 (9)	2 (<1)
Bone pain	40 (21)	8 (4)	89 (18)	24 (5)
Back pain	25 (13)	11 (6)	32 (6)	11 (2)
Arthralgia	14 (7)	2 (1)	11 (2)	1 (<1)
SCC	7 (4)	6 (3)	17 (3)	16 (3)
Hypertension	2 (1)	1 (<1)	7 (1)	5 (1)
Hypokalemia	1 (<1)	1 (<1)	3 (<1)	1 (<1)

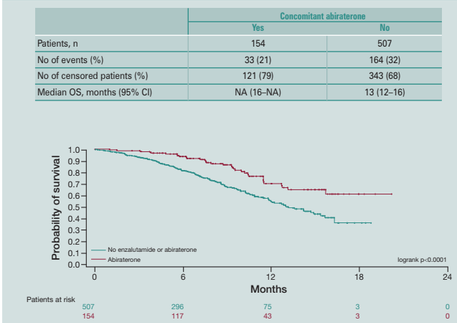
Data are n (%). *Adverse events were coded according to MedDRA version 17.1 and graded by NCI-CTCAE version 4.03, shown are those occurring in >5% of either subgroup or those of special interest. Note that hematological events were considered by assessing preferred terms coded under the System Organ Class of 'Blood and lymphatic disorders' and 'Investigations.'
GPHD=general physical health deterioration; Abi=abiraterone; enza=enzalutamide; PC=platelet count; SCC=spinal cord compression.

Figure 3. OS by concomitant use of abiraterone and/or enzalutamide



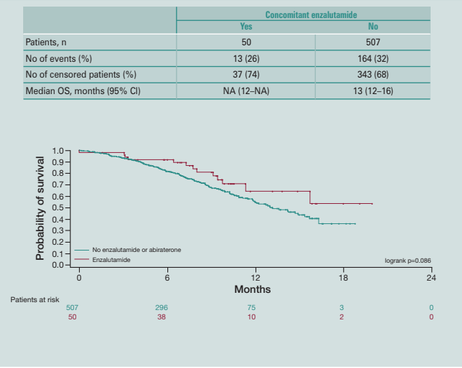
OS=overall survival; NA=not available.

Figure 4. OS by concomitant use of abiraterone



OS=overall survival; NA=not available.

Figure 5. OS by concomitant use of enzalutamide



OS=overall survival; NA=not available.

CONCLUSIONS

- **Ra-223 administered with either abiraterone and/or enzalutamide was generally well tolerated in mCRPC patients with bone metastases, with no new safety signals reported.**
- **OS appeared to be longer in patients receiving Ra-223 with concomitant novel endocrine agents than in those treated with Ra-223 without these agents.**
- **Studies are ongoing to prospectively assess the safety and efficacy of these treatment combinations.**

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