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Clinical Trial Results

Radium-223 plus Enzalutamide Versus Enzalutamide in Metastatic Castration-Refractory Prostate Cancer: Final Safety and Efficacy Results

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Key Words. Radium-223 • Enzalutamide • Metastatic castration-refractory prostate cancer

Trial Information

- **ClinicalTrials.gov Identifier:** NCT02199197
- **Sponsor**: University of Utah
- **Principal Investigator**: Neeraj Agarwal
- **IRB Approved**: Yes

Lessons Learned

- Long-term safety of radium-223 with enzalutamide was confirmed in this clinical trial.
- PSA-PFS2 was prolonged with the combination compared with enzalutamide alone.

Abstract

Background. Previously, we showed the combination of radium-223 and enzalutamide to be safe and associated with improved efficacy based on a concomitant decline in serum bone metabolism markers compared with enzalutamide alone in a phase II trial of men with metastatic castration-resistant prostate cancer (mCRPC) [1].

Methods. Secondary endpoints were not included in our initial report, and we include them herein, after a median follow-up of 22 months. These objectives included long-term safety, prostate-specific antigen (PSA)–progression-free survival (PFS), and radiographic progression-free survival; PSA-PFS2 (time from start of protocol therapy to PSA progression on subsequent therapy); time to next therapy (TTNT); and overall survival (OS). Survival analysis and log-rank tests were performed using the R statistical package v.4.0.2 (https://www.r-project.org). Statistical significance was defined as $p < .05$.

Results. Of 47 patients (median age, 68 years), 35 received the combination and 12 enzalutamide alone. After a median follow-up of 22 months, final safety results did not show any increase in fractures or other adverse events in the combination arm. PSA-PFS2 was significantly improved, and other efficacy parameters were numerically improved in the combination over the enzalutamide arm.

Conclusion. The combination of enzalutamide and radium-223 was found to be safe and associated with promising efficacy in men with mCRPC. These hypothesis-generating results portend well for the ongoing phase III PEACE III trial in this setting. ***The Oncologist*** 2021;26:1006–e2129

Discussion

After an initial safety lead-in cohort of 8 patients treated with the combination, 39 patients were randomized (2:1) to the combination of radium-223 plus enzalutamide versus enzalutamide monotherapy [1] at approved doses (Fig. 1). Receipt of prior abiraterone and docetaxel was allowed and was balanced between the two groups [1]. Primary endpoints of safety and decline in bone metabolism markers were reported earlier and only included the randomized patients [1]. Herein, we report on

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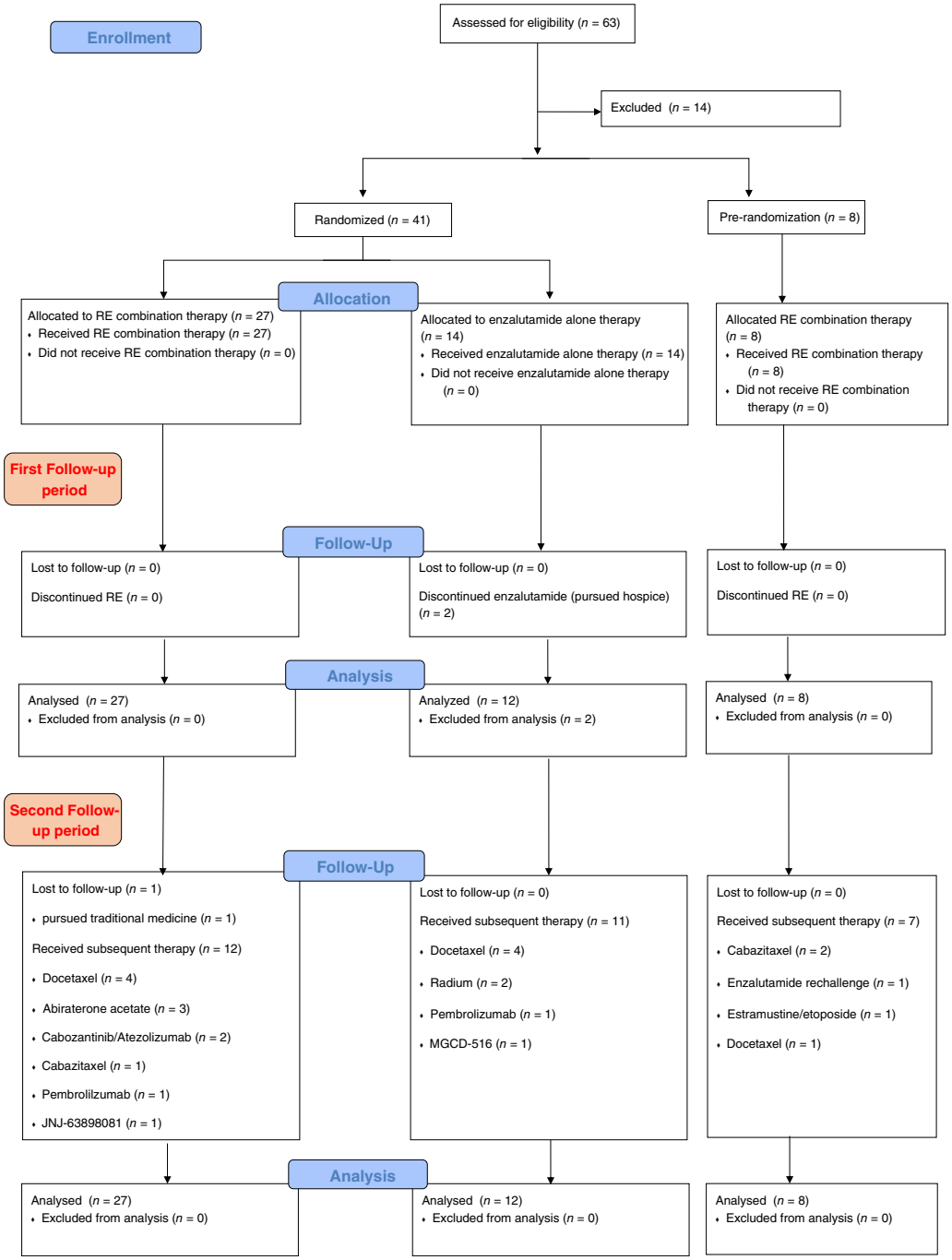

Figure 1. CONSORT flow diagram.
Abbreviation: RE, radium-223 plus enzalutamide.

the prespecified secondary endpoints of PSA-PFS, radiographic PFS, and OS, which included all 47 eligible patients (35 received the combination and 12 received enzalutamide alone). In addition, we report a post hoc analysis on PSA-PFS2 and TTNT, as well as long-term safety of the combination (Fig. 2).

Regarding safety, no patients on the enzalutamide arm and 2 of 35 patients on the combination arm developed fractures, both incidentally detected on imaging: one had rib fractures after a fall; the second had a vertebral fracture at the site of bone metastasis. There was no difference in any adverse events or any incidence of bone marrow disorders. These results are consistent with those seen with radium-223 monotherapy [2–5].

Secondary efficacy endpoints were numerically but not statistically improved in the combination arm: median OS (30.8 vs. 20.6 months; $p = .73$), PSA-PFS (8.9 vs. 3.38 months; $p = .97$), and radiographic PFS (11.5 vs. 7.35 months; $p = .96$). The significant improvement in PSA-PFS2 (18.7 vs. 8.41 months; $p = .033$) and near-significant improvement in TTNT (15.9 vs. 3.47 months; $p = .067$) suggest delayed effect of radium-223 on the disease trajectory, which was also evident in the pivotal ALSYMPCA trial, in which OS was significantly improved with radium-223 without improvement in PFS [4]. The small sample size and the post hoc nature of some of the endpoints reported here are the limitations of this report.

Trial Information	
Disease	Advanced cancer, prostate cancer
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	No designated number of regimens
Type of Study	Phase II, randomized
Primary Endpoint	Safety, bone metabolism markers
Secondary Endpoint	Overall survival, PSA–progression-free survival, radiographic progression-free survival
Additional Details of Endpoints or Study Design	Post hoc analysis values of PSA-PFS2 (time from start of protocol therapy to PSA progression on subsequent therapy) and TTNT
Investigator's Analysis	Active and should be pursued further

Drug Information: Combination	
Generic Name	Radium-223
Drug Type	Bone targeting radiotherapeutic
Dose	55 kBq per kg
Route	Intravenous (IV)
Schedule of Administration	55 kBq/kg IV every 4 weeks for six doses
Generic Name	Enzalutamide
Drug Type	Nonsteroidal antiandrogen
Drug Class	Androgen receptor
Dose	160 mg per flat dose
Route	p.o.
Schedule of Administration	160 mg p.o. daily

Drug Information: Control	
Generic Name	Enzalutamide
Drug Type	Nonsteroidal antiandrogen
Drug Class	Androgen receptor
Dose	160 mg per flat dose
Route	p.o.
Schedule of Administration	160 mg p.o. daily

Patient Characteristics: Combination	
Number of Patients, Male	35
Number of Patients, Female	0
Age	Median: 71 years
Number of Prior Systemic Therapies	None
Performance Status: ECOG	0 — 17 1 — 18 2 — 0 3 — 0 Unknown — 0
Other	Prior therapies: nine of the patients in the enzalutamide-only arm had prior progression on abiraterone; three of the patients in the enzalutamide-only arm had prior progression on docetaxel.

Patient Characteristics: Control	
Number of Patients, Male	14
Number of Patients, Female	0
Age	Median: 71 years
Number of Prior Systemic Therapies	None
Performance Status: ECOG	0 — 7 1 — 7 2 — 0 3 — 0 Unknown — 0
Other	Prior therapies: nine of the patients in the enzalutamide-only arm had prior progression on abiraterone; three of the patients in the enzalutamide-only arm had prior progression on docetaxel.

Secondary Assessment Method: Combination	
Title	Overall survival
Number of Patients Screened	35
Number of Patients Enrolled	35
Number of Patients Evaluable for Toxicity	35
Number of Patients Evaluated for Efficacy	35
(Median) Duration Assessments OS	30.8 months, CI: 17.9–not evaluable
Title	PSA-PFS
Number of Patients Screened	35
Number of Patients Enrolled	35
Number of Patients Evaluable for Toxicity	35
Number of Patients Evaluated for Efficacy	35
Evaluation Method	Prostate Cancer Working Group 2 (PCWG2)
(Median) Duration Assessments PFS	8.9 months, CI: 4.73–21.4
Title	Radiographic PFS
Number of Patients Screened	35
Number of Patients Enrolled	35
Number of Patients Evaluable for Toxicity	35
Number of Patients Evaluated for Efficacy	35
Evaluation Method	Progressive disease on imaging
(Median) Duration Assessments PFS	11.5 months, CI: 9.2–29
Title	Radiographic objective response rate
Number of Patients Screened	35
Number of Patients Enrolled	35
Number of Patients Evaluable for Toxicity	35
Number of Patients Evaluated for Efficacy	35
Evaluation Method	Radiographic Response
Response Assessment CR	$n = 0$ (0%)
Response Assessment PR	$n = 3$ (9%)
Response Assessment SD	$n = 28$ (80%)
Response Assessment PD	$n = 4$ (11%)
Title	Post hoc: PSA-PFS2
Number of Patients Screened	35
Number of Patients Enrolled	35
Number of Patients Evaluable for Toxicity	35

Number of Patients Evaluated for Efficacy	35
Evaluation Method	PCWG2—time from start of protocol therapy to PSA progression on subsequent therapy
(Median) Duration Assessments PFS	18.7 months, CI: 12.2–42.8
Title	Post hoc: TTNT
Number of Patients Screened	35
Number of Patients Enrolled	35
Number of Patients Evaluable for Toxicity	35
Number of Patients Evaluated for Efficacy	35
Evaluation Method	time to subsequent therapy
(Median) Duration Assessments PFS	15.9 months, CI: 9.7–35.5

Primary Assessment Method: Combination	
Title	Safety
Number of Patients Screened	35
Number of Patients Enrolled	35
Number of Patients Evaluable for Toxicity	35
Number of Patients Evaluated for Efficacy	35
Evaluation Method	Occurrences of adverse events
Outcome Notes	Fracture rate: 2 out of 35 participants (5.7%) in the combination and 0% for enzalutamide alone.

Secondary Assessment Method: Control	
Title	Overall survival
Number of Patients Screened	14
Number of Patients Enrolled	14
Number of Patients Evaluable for Toxicity	12
Number of Patients Evaluated for Efficacy	12
Evaluation Method	Overall survival of patient
(Median) Duration Assessments OS	20.6 months, CI: 16.8–NA
Title	PSA-PFS
Number of Patients Screened	14
Number of Patients Enrolled	14
Number of Patients Evaluable for Toxicity	12
Number of Patients Evaluated for Efficacy	12
Evaluation Method	PCWG2
(Median) Duration Assessments PFS	3.38 months, CI: 2.7–NA
Title	Radiographic PFS
Number of Patients Screened	14
Number of Patients Enrolled	14
Number of Patients Evaluable for Toxicity	12
Number of Patients Evaluated for Efficacy	12
Evaluation Method	Progression on imaging
(Median) Duration Assessments PFS	7.35 months, CI: 2.8–NA
Title	Radiographic objective response rate
Number of Patients Screened	14
Number of Patients Enrolled	14
Number of Patients Evaluable for Toxicity	12
Number of Patients Evaluated for Efficacy	12

Evaluation Method	Radiographic progression
Response Assessment CR	$n = 0$ (0%)
Response Assessment PR	$n = 0$ (0%)
Response Assessment SD	$n = 8$ (67%)
Response Assessment PD	$n = 4$ (33%)
Title	Post hoc: PSA-PFS2
Number of Patients Screened	14
Number of Patients Enrolled	14
Number of Patients Evaluable for Toxicity	12
Number of Patients Evaluated for Efficacy	12
Evaluation Method	PCWG2—time from start of protocol therapy to PSA progression on subsequent therapy
(Median) Duration Assessments PFS	8.41 months, CI: 5.52–NA
Title	Post hoc: TTNT
Number of Patients Screened	14
Number of Patients Enrolled	14
Number of Patients Evaluable for Toxicity	12
Number of Patients Evaluated for Efficacy	12
Evaluation Method	Time to next subsequent therapy
(Median) Duration Assessments PFS	3.47 months, CI: 3.3–NA

Primary Assessment Method: Control

Title	Safety
Number of Patients Screened	14
Number of Patients Enrolled	14
Number of Patients Evaluable for Toxicity	12
Number of Patients Evaluated for Efficacy	12
Evaluation Method	Occurrences of adverse events
Outcome Notes	Fractures rates were 0 out of 12 participants

Adverse Events: Combination, All Cycles (percentages)

Name	NC/NA	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades
Fracture	94	6	0	0	0	0	6
Bone marrow hypocellular	100	0	0	0	0	0	0
Abdominal pain	91	9	0	0	0	0	9
Alkaline phosphatase increased	97	0	3	0	0	0	3
Allergic reaction	97	3	0	0	0	0	3
Anaphylaxis	97	0	0	3	0	0	3
Anemia	74	17	9	0	0	0	26
Anorexia	66	17	17	0	0	0	34
Anxiety	97	0	3	0	0	0	3
Arthralgia	80	17	3	0	0	0	20
Arthritis	97	3	0	0	0	0	3
Atrial fibrillation	97	3	0	0	0	0	3
Back pain	80	3	14	3	0	0	20
Bloating	97	3	0	0	0	0	3
Bone pain	89	3	9	0	0	0	11
Bronchial infection	97	0	3	0	0	0	3

Bruising	97	3	0	0	0	0	3
Chest wall pain	97	0	3	0	0	0	3
Chills	94	6	0	0	0	0	6
Constipation	71	23	6	0	0	0	29
Cough	83	14	3	0	0	0	17
Creatinine increased	97	0	3	0	0	0	3
Depression	97	0	3	0	0	0	3
Diarrhea	46	40	11	3	0	0	54
Dizziness	89	11	0	0	0	0	11
Dysesthesia	97	3	0	0	0	0	3
Dysgeusia	86	3	11	0	0	0	14
Dysphagia	97	0	3	0	0	0	3
Dyspnea	89	11	0	0	0	0	11
Ear and labyrinth disorders	94	6	0	0	0	0	6
Edema limbs	83	11	6	0	0	0	17
Epistaxis	97	3	0	0	0	0	3
Fall	97	0	3	0	0	0	3
Fatigue	54	6	37	3	0	0	46
Flatulence	97	0	3	0	0	0	3
Flu like symptoms	83	9	9	0	0	0	17
Gastroesophageal reflux disease	97	3	0	0	0	0	3
Gastrointestinal disorders	97	0	0	3	0	0	3
Generalized muscle weakness	91	3	6	0	0	0	9
Gum infection	94	0	3	3	0	0	6
Headache	86	11	3	0	0	0	14
Hemorrhoidal hemorrhage	97	3	0	0	0	0	3
Hoarseness	97	3	0	0	0	0	3
Hot flashes	89	9	3	0	0	0	11
Hyperglycemia	94	0	0	3	3	0	6
Hypertension	91	3	6	0	0	0	9
Hypoalbuminemia	94	3	3	0	0	0	6
Hypocalcemia	91	9	0	0	0	0	9
Hypokalemia	94	6	0	0	0	0	6
Hyponatremia	89	11	0	0	0	0	11
Hypotension	97	0	0	3	0	0	3
Insomnia	94	6	0	0	0	0	6
Laryngeal inflammation	97	3	0	0	0	0	3
Lip infection	97	3	0	0	0	0	3
Localized edema	97	3	0	0	0	0	3
Lung infection	97	0	0	3	0	0	3
Lymphocyte count decreased	49	11	20	20	0	0	51
Memory impairment	97	3	0	0	0	0	3
Musculoskeletal and connective tissue disorder	97	0	3	0	0	0	3
Myalgia	77	17	6	0	0	0	23
Nail discoloration	97	3	0	0	0	0	3
Nasal congestion	91	3	6	0	0	0	9
Nausea	54	26	20	0	0	0	46
Neck pain	94	3	3	0	0	0	6
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	97	0	3	0	0	0	3

Nervous system disorders	97	3	0	0	0	0	3
Neutrophil count decreased	60	20	11	3	6	0	40
Non-cardiac chest pain	94	3	0	3	0	0	6
Oral pain	97	3	0	0	0	0	3
Osteonecrosis of jaw	97	3	0	0	0	0	3
Pain	97	0	3	0	0	0	3
Pain in extremity	89	6	6	0	0	0	11
Paresthesia	89	11	0	0	0	0	11
Peripheral motor neuropathy	97	0	3	0	0	0	3
Peripheral sensory neuropathy	97	0	3	0	0	0	3
Platelet count decreased	80	17	0	0	3	0	20
Pleural effusion	94	3	3	0	0	0	6
Productive cough	97	3	0	0	0	0	3
Pruritus	86	14	0	0	0	0	14
Rash acneiform	97	3	0	0	0	0	3
Rash maculo-papular	94	6	0	0	0	0	6
Renal calculi	97	3	0	0	0	0	3
Rhinitis infective	97	3	0	0	0	0	3
Skin and subcutaneous tissue disorders	94	3	3	0	0	0	6
Sneezing	97	3	0	0	0	0	3
Stomach pain	97	3	0	0	0	0	3
Syncope	94	0	0	6	0	0	6
Testicular pain	94	3	3	0	0	0	6
Thromboembolic event	97	0	3	0	0	0	3
Toothache	97	0	3	0	0	0	3
Transient ischemic attacks	97	3	0	0	0	0	3
Tremor	97	3	0	0	0	0	3
Urinary frequency	94	3	3	0	0	0	6
Urinary tract infection	97	0	0	3	0	0	3
Urinary tract obstruction	97	0	0	3	0	0	3
Urinary tract pain	97	3	0	0	0	0	3
Urinary urgency	94	3	3	0	0	0	6
Vertigo	97	0	3	0	0	0	3
Vomiting	89	11	0	0	0	0	11
Weight loss	89	9	3	0	0	0	11
White blood cell decreased	43	26	23	6	3	0	57
Wound complication	97	0	3	0	0	0	3
Wound infection	97	0	3	0	0	0	3

Abbreviation: NC/NA, no change from baseline/no adverse event.

Serious Adverse Events

Name	Grade	Attribution
Anaphylaxis	3	Unrelated
Back pain	3	Unrelated
Gastrointestinal disorders - Other, specify	3	Unrelated
Lung Infection	3	Unrelated
Neutrophil count decreased	2	Possible
Syncope	3	Unlikely
Urinary tract infection	3	Unrelated

After a median follow-up of 22 months, adverse events for radium-223 plus enzalutamide versus enzalutamide alone are reported.

Adverse Events: Control, All Cycles (percentages)

Name	NC/NA	1	2	3	4	5	All grades
Fracture	100	0	0	0	0	0	0
Bone marrow hypocellular	100	0	0	0	0	0	0
Abdominal pain	86	7	0	7	0	0	14
Alkaline phosphatase increased	79	0	21	0	0	0	21
Alopecia	93	7	0	0	0	0	7
Anemia	93	0	7	0	0	0	7
Anxiety	93	0	7	0	0	0	7
Arthralgia	71	0	21	7	0	0	29
Back pain	93	0	7	0	0	0	7
Bloating	93	7	0	0	0	0	7
Blood bilirubin increased	93	7	0	0	0	0	7
Bone pain	86	14	0	0	0	0	14
Chills	93	7	0	0	0	0	7
Cough	93	7	0	0	0	0	7
Creatinine increased	93	7	0	0	0	0	7
Depression	93	7	0	0	0	0	7
Diarrhea	93	7	0	0	0	0	7
Dysgeusia	93	7	0	0	0	0	7
Dyspnea	93	7	0	0	0	0	7
Facial pain	93	7	0	0	0	0	7
Fatigue	79	7	7	7	0	0	21
Flatulence	93	7	0	0	0	0	7
Gastroesophageal reflux disease	93	7	0	0	0	0	7
Gastrointestinal disorders	93	0	0	7	0	0	7
Generalized muscle weakness	93	7	0	0	0	0	7
Gynecomastia	93	7	0	0	0	0	7
Hypoalbuminemia	93	7	0	0	0	0	7
Lymphocyte count decreased	71	14	14	0	0	0	29
Muscle weakness lower limb	86	14	0	0	0	0	14
Muscle weakness upper limb	93	7	0	0	0	0	7
Musculoskeletal and connective tissue disorder	93	7	0	0	0	0	7
Myalgia	79	7	14	0	0	0	21
Nasal congestion	86	14	0	0	0	0	14
Nausea	93	7	0	0	0	0	7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	86	7	0	0	0	7	14
Non-cardiac chest pain	93	7	0	0	0	0	7
Pain	93	0	0	7	0	0	7
Pain in extremity	93	7	0	0	0	0	7
Palpitations	93	7	0	0	0	0	7
Peripheral sensory neuropathy	93	0	7	0	0	0	7
Productive cough	86	7	7	0	0	0	14
Psychiatric disorders	93	7	0	0	0	0	7
Skin ulceration	93	7	0	0	0	0	7
Sore throat	93	7	0	0	0	0	7
Urinary frequency	93	7	0	0	0	0	7
Vertigo	93	7	0	0	0	0	7

After a median follow-up of 22 months, adverse events for radium-223 plus enzalutamide versus enzalutamide alone are reported.
Abbreviation: NC/NA, no change from baseline/no adverse event.

Serious Adverse Events		
Name	**Grade**	**Attribution**
Neoplasms benign, malignant, and unspecified (incl cysts and polyps) - Other, specify	5	Unrelated
Pain	3	Unrelated

Assessment, Analysis, and Discussion	
Completion	Study completed
Investigator's Assessment	Active and should be pursued further

We previously reported that in men with progressive metastatic castration-resistant prostate cancer (mCRPC), treatment with the combination of radium-223 plus enzalutamide is safe and associated with a significant decrease in bone metabolism markers, such as N-terminal propeptide of type 1 collagen, compared with enzalutamide [1]. The relative change in serum bone metabolism marker N-telopeptide levels from baseline to 6 months between the two arms and the safety and feasibility of the combination were coprimary endpoints for the study. Decline in bone markers directly correlated with prostate-specific antigen (PSA) response, objective response rate, and radiographic progression-free survival (PFS). These results were supported by a previously published trial—Morris et al. [7] conducted a randomized phase II clinical trial of radium-223 (55 kBq/kg every 6 weeks $\times$ five doses) plus docetaxel (60 mg/m^2 every 3 weeks) versus docetaxel (75 mg/m^2) and reported improved bone metabolism markers with the combination compared with docetaxel alone in the setting of a more robust PSA response and longer median radiographic PFS.

In the current report, we present updated results on safety and efficacy with a median follow-up of 22 months and provide the findings on the secondary endpoints not previously reported. The fracture rates observed in our trial of 5.7% (2 out of 35 patients) for the combination and 0% for enzalutamide are comparable with rates previously reported with radium-223. It should be noted that only 2 of 47 patients in our study did not receive bone strengthening agents per their wishes. This further emphasizes the value of concurrent bisphosphonate or denosumab use in preventing bone fractures. The fracture rate reported in the PEACE III clinical trial [8], which did not initially mandate bone protective therapy, was 13% for enzalutamide and 33% for the radium-223 plus enzalutamide arm. Following an amendment mandating use of a bone protective agent in response to published ERA 223 data, the fracture risk was almost abolished with bone protective therapy, 0% and 3%, respectively [6]. The fracture rate in the ALSYMPCA trial, 5% (32/614 patients) for the patients treated with radium-223 [9], is also similar to our study.

There are previous reports of increased rates of bone marrow failure after radium-223 treatment. Huynh-Le et al. [2] reported an overall incidence of pancytopenia or bone marrow failure of 7.1% (154/2,182 patients) of patients undergoing radium-223 therapy. Etchebehere et al. [3] reported even higher rates of bone marrow failure of 35% (32/92 patients) of patients treated with radium-223. The ALSYMPCA trial [4] did not report any events of bone marrow failure. We did not observe any bone marrow failure events. It is possible that our sample size was insufficient to detect this uncommon side effect. Of particular importance is the early access study [5] of radium-223 ($n = 696$), in which 27% of patients received concurrent treatment with abiraterone or enzalutamide or both, and only one patient developed bone marrow failure (1/696, <1%). The larger PEACE III clinical trial may further clarify the magnitude of this risk, specifically in combination with enzalutamide.

In this clinical trial, despite numerical improvement, no significant difference was observed between treatment arms regarding median overall survival (OS), PSA-PFS, and radiographic PFS even with longer follow-up. The statistically significant improvement in time from start of protocol therapy to PSA progression on subsequent therapy (PSA-PFS2) and strong numerical trend for delay of subsequent therapy with radium-223 are suggestive of a favorable effect of radium-223 on the disease trajectory, especially in combination with enzalutamide. The lack of significant OS benefit possibly is explained by the small sample size of this trial, which was not designed to have sufficient power to detect a true difference in any of the secondary endpoints. In the ERA 223 clinical trial [6], no improvement in OS was demonstrated with radium-223 plus abiraterone compared with abiraterone alone with a median OS of 30.7 months (95% confidence interval [CI], 25.8 months–NE) and 33.3 months (95% CI, 30.2–41.1 months), respectively (hazard ratio, 1.20; 95% CI, 0.95–1.51; $p = .13$). Similarly, there was no difference in the primary endpoint of symptomatic skeletal event–free survival, reported as 22.3 months (95% CI, 20.4–24.8) for radium-223 plus abiraterone and 26.0 months (21.8–28.3) for abiraterone alone (hazard ratio, 1.122; 95% CI, 0.92–1.37; $p = .26$). However, the efficacy results are currently awaited from the ongoing phase III trial of combination of radium-223 plus enzalutamide (PEACE III trial) in mCRPC.

Although there was a statistically significant improvement in PSA-PFS2 in our clinical trial, it is important to emphasize that this is a post hoc analysis and may be the result of α error.

The results of our trial are hypothesis generating, and routine use of radium-223 concurrently with enzalutamide may not be recommended based on these results. The ongoing phase III clinical trial (PEACE III trial) randomizing patients to radium-223 plus enzalutamide versus enzalutamide alone in men with mCRPC will conclusively determine the therapeutic role of this combination for our patients in the clinic.

In summary, treatment with radium-223 plus enzalutamide combination appears to be safe and has promising efficacy. As seen with the ERA 223 and PEACE III clinical trials, we observed few bone fractures in

patients concurrently receiving bone modifying therapy. These data portend well for the ongoing phase III trial (PEACE III trial) investigating the role of this combination in men with mCRPC.

Disclosures

Benjamin L Maughan: Roche/Genentech, Pfizer, AVEO Oncology, Janssen Oncology, Astellas, Bristol-Myers Squibb, Clovis, Tempu, Merck, Exelixis, Bayer Oncology, Peloton Therapeutics (C/A), Exelixis, Bavarian-Nordic, Clovis,Genentech, Bristol-Myers Squibb (FR–institutional); **John M. Hoffman:** NexEos Dx (OI); Umang Swami: Seattle Genetics (C/A), Janssen (RF); Neeraj Agarwal: Astellas, Argos Therapeutics, AstraZeneca, Aveo, Bayer, Bristol Myers Squibb, Calithera, Clovis, Eisai, Eli Lilly, EMDSerono, Exelixis, Foundation Medicine, Genentech, Gilead, Janssen, Merck, MEIPharma, Nektar, Novartis, Pfizer, Pharmacyclics, Seattle Genetics (C/A), AstraZeneca, Bavarian Nordic, Bayer, Bristol-Myers Squibb, Calithera, Celldex, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Genentech, Glaxo Smith Kline, Immunomedics, Janssen, Medivation, Merck, Nektar, New Link Genetics, Novartis, Pfizer, Prometheus, Rexahn, Roche, Sanofi, Seattle Genetics, Takeda, Tracon (RF). The other authors indicated no financial relationships.

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Figure

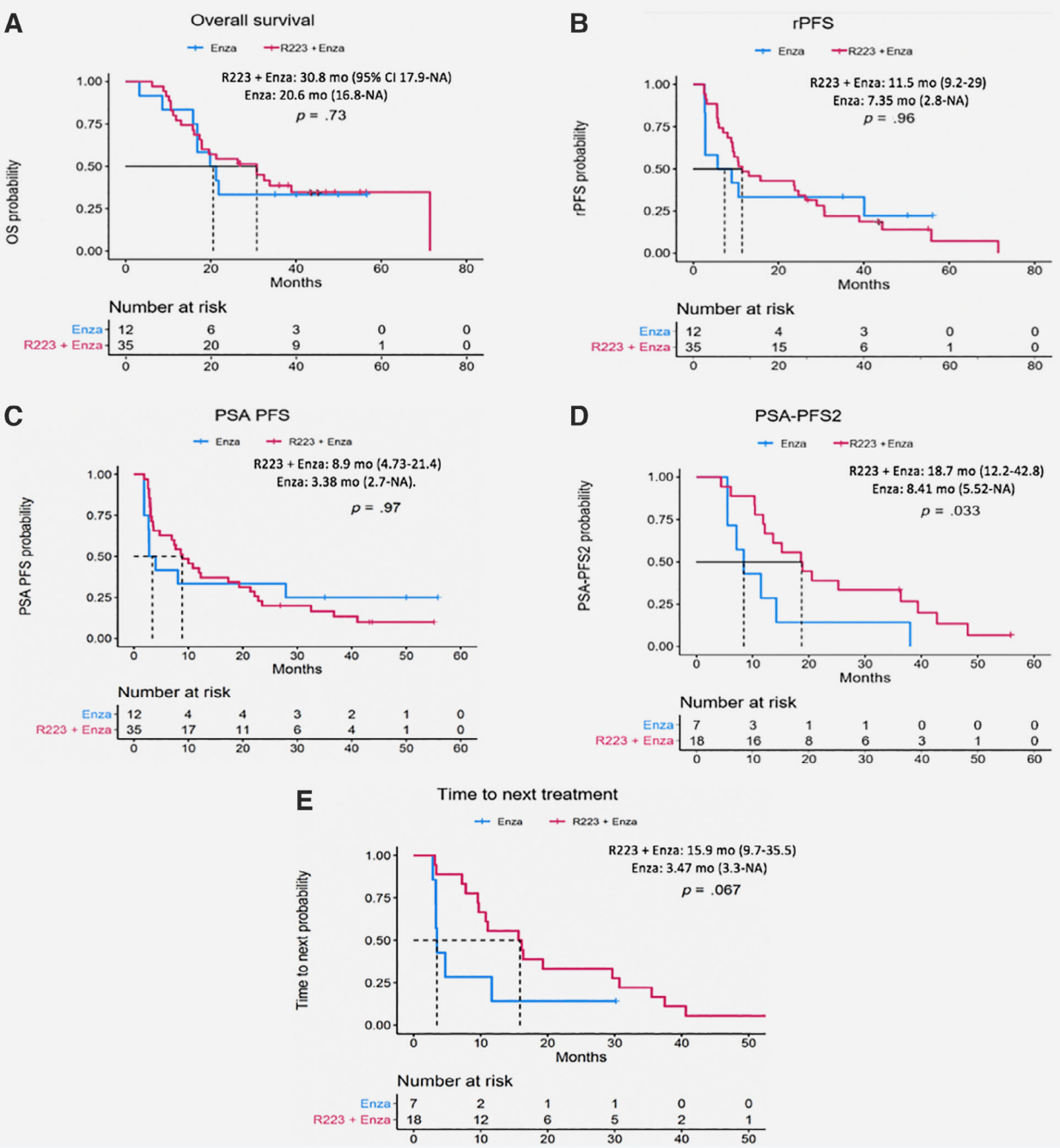

Figure 2. Kaplan-Meier plots for trial secondary endpoints and post hoc clinical endpoints. Secondary endpoints: overall survival **(A)**, radiographic progression-free survival **(B)**, PSA progression-free survival **(C)**. Post hoc clinical endpoints: time to PSA progression on subsequent therapy **(D)**, time to next treatment **(E)**.

Abbreviations: CI, confidence interval; Enza, enzalutamide; PFS, progression-free survival; PSA, prostate-specific antigen; PSA-PFS2, time from start of protocol therapy to PSA progression on subsequent therapy; NE, not evaluable; R223, radium-223; rPFS, radiographic PFS.