The PREVAIL Study: Primary Outcomes by Site and Extent of Baseline Disease for Enzalutamide-Treated Men with Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer

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ABSTRACT

Background: Enzalutamide, an oral androgen receptor inhibitor, significantly improved overall survival (OS) and radiographic progression-free survival (rPFS) versus placebo in the PREVAIL trial of men with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC).

Objective: Assess effect of enzalutamide versus placebo in patients from PREVAIL based on site and extent of baseline disease.

Design, Setting, and Participants: 1717 asymptomatic or minimally symptomatic patients were randomized to enzalutamide (n = 872) or placebo (n = 845). Subgroup analyses included: nonvisceral (only bone and/or nodal; n = 1513), visceral (lung and/or liver; n = 204), low-volume bone disease (<4 bone metastases; n = 867), high-volume bone disease (≥4 bone metastases; n = 850), lymph node only disease (n = 195).

Intervention: Oral enzalutamide (160 mg) or placebo once daily while continuing androgen deprivation therapy.

Outcome Measurements and Statistical Analysis: Coprimary endpoints (rPFS, OS) were prospectively evaluated in nonvisceral and visceral subgroups. All other efficacy analyses were post hoc.

Results and Limitations: Enzalutamide improved rPFS versus placebo in patients with nonvisceral disease (hazard ratio [HR], 0.175; 95% confidence interval [CI], 0.14–0.22), visceral disease (HR, 0.283; 95% CI, 0.16–0.49), low- or high-volume bone disease (HR, 0.155; 95% CI, 0.11–0.22; HR, 0.215; 95% CI, 0.16–0.29, respectively), and lymph node only disease (HR, 0.092; 95% CI, 0.04–0.19). For OS, HRs favored enzalutamide (<1) across all disease subgroups, although 95% CI was

>1 in patients with visceral disease (HR, 0.822; 95% CI, 0.55–1.23). Enzalutamide was well tolerated in patients with or without visceral disease.

Conclusions: Enzalutamide provided clinically significant benefit in men with chemotherapy-naïve mCRPC, with or without visceral disease, low- or high-volume bone disease, or lymph node only disease.

Patient summary: Patients with mCRPC—including those with or without visceral disease, or widespread bone disease—benefitted from enzalutamide, an active well-tolerated therapy.

Introduction

Prostate cancer is the second most common cancer in men, trailing only lung cancer in global incidence [1]. In 2012, approximately 1.1 million men worldwide were diagnosed with prostate cancer. In the United States, it is estimated that in 2015 there will be 220,080 new cases of prostate cancer and 27,540 deaths due to this disease, accounting for 5% of all US cancer deaths [2]. The majority of deaths occur due to metastatic castration-resistant prostate cancer (mCRPC), when disease progression occurs despite maintaining castrate levels of testosterone with medical or surgical castration. Bone and/or lymph node metastases are common in patients with mCRPC, with bone metastases contributing to skeletal-related complications that can reduce quality of life and increase the risk of death [3,4]. Visceral disease in the lung and/or liver occurs in about 20–30% of mCRPC patients and is associated with a particularly poor prognosis [5–10].

Until recently, standard first-line therapy for patients progressing on androgen deprivation therapy (ADT) was docetaxel plus prednisone [5]. Over the last few years, several agents with distinct mechanisms of action have demonstrated benefit in phase 3 trials in men with asymptomatic or minimally symptomatic mCRPC who had not received previous chemotherapy. Sipuleucel-T, an autologous immunotherapy, prolonged survival but did not delay disease progression in this setting [11]. Abiraterone acetate, an androgen biosynthesis inhibitor, significantly improved radiographic progression-free survival (rPFS) and overall survival (OS) [12]. Most recently, the oral androgen receptor inhibitor enzalutamide significantly prolonged OS and rPFS in the PREVAIL trial of men with chemotherapy-naïve

mCRPC progressing despite ADT [13]. The benefit of enzalutamide was demonstrated for all prespecified secondary endpoints.

The primary findings of PREVAIL were reported previously [13]. The current analyses focus on the effect of enzalutamide versus placebo on clinical outcomes in PREVAIL patients based on the extent of bone and lymph node disease at baseline (including those with or without visceral disease), low- or high-volume bone disease, or lymph node only disease. Our analyses include secondary outcomes in patients with only bone and or nodal soft-tissue disease, a patient population commonly treated by urologists and medical oncologists.

Materials and Methods

Study population

Eligibility criteria for PREVAIL were described in detail previously [13]. Briefly, eligible patients had asymptomatic or minimally symptomatic mCRPC, an Eastern Cooperative Oncology Group Performance Status grade of 0 to 1, and had not previously received chemotherapy. PREVAIL allowed patients with visceral disease (metastases to the lung and/or liver).

Study design and treatment

PREVAIL was a phase 3, multinational, double-blind, randomized, placebo-controlled study (NCT01212991) comparing the efficacy of enzalutamide versus placebo in men with minimally symptomatic or asymptomatic metastatic prostate cancer who had not received chemotherapy. Patients were enrolled at 207 sites in 22 countries between September 2010 and September 2012. Patients were randomized 1:1 to receive either oral enzalutamide (160 mg) or placebo once daily,

which they continued until confirmed radiographic disease progression and initiation of cytotoxic chemotherapy or an investigational agent for prostate cancer. Randomization was central and stratified by study site. Patients were required to continue ADT during the study. Patients were allowed to continue or initiate corticosteroids. Radiation therapy and initiation of bisphosphonates or other approved bone-targeting agents were permitted.

Study endpoints have been defined previously [13]. The coprimary endpoints were rPFS and OS. Secondary endpoints included time to first skeletal-related event, time to initiation of cytotoxic chemotherapy, best overall soft-tissue response, time to PSA progression, and PSA response ≥50% from baseline. Prespecified exploratory endpoints included quality-of-life assessments using the Functional Assessment of Cancer Therapy–Prostate (FACT-P) and PSA response ≥90% from baseline.

Our analyses were conducted in the following subgroups: the nonvisceral subgroup (patients with only bone or nodal disease at screening); the visceral subgroup (patients with lung and/or liver metastases); the low- and high-volume bone disease subgroups (patients with <4 vs ≥4 bone metastases, respectively); and the subgroup of patients with lymph node only disease. Patients in the visceral subgroup may have also had bone or nodal disease. The coprimary endpoints of rPFS and OS were prospectively evaluated in the nonvisceral and visceral subgroups. All other efficacy analyses were post hoc. These included evaluation of secondary endpoints and an exploratory analysis of rPFS and OS in patients with three or fewer bone metastases at baseline and those with four or more bone metastases at baseline, for all patients and separately for the nonvisceral and visceral subgroups. For this analysis, the cutoff (<4 vs ≥4 bone metastases) was

selected based on the definition for high-volume disease used in the CHAARTED trial [14].

Statistical analysis

A two-sided, unstratified log-rank test was used to compare rPFS and OS between the enzalutamide and placebo groups. Estimates of medians and 95% confidence intervals (CIs) were determined using the Kaplan-Meier method. Hazard ratios (HRs) were determined using an unstratified Cox regression model (with treatment as the only covariate) and were relative to placebo, with <1 favoring enzalutamide. Similarly, time to cytotoxic chemotherapy, FACT-P total score decline, and PSA progression were analyzed using the Kaplan-Meier method, log-rank test Cox regression model. For PSA response, only patients who had both baseline and postbaseline PSA assessments were included in the analysis; 95% CIs were reported using the Clopper-Pearson method. P values are not provided for the subgroup analyses as testing for statistical significance was not prespecified.

The data cutoff date for all analyses (overall study population and subgroup analyses) was September 16, 2013, except for rPFS, which had a cutoff date of May 6, 2012. Results from the overall study population have been previously reported.

Results

Patients and treatments

Of 1717 patients randomized to treatment in PREVAIL, 1513 (88.1%) presented at screening with only nonvisceral disease to the bone and/or nodal disease, and 204 (11.9%) presented with visceral disease to the lung and/or liver. In both the nonvisceral and visceral subgroups, patient demographics and disease

characteristics were generally similar between treatment groups (Table 1). Patients without visceral disease had lower baseline median PSA, better performance status, and less lymph node disease than patients with visceral disease, but similar rates of bone disease (Table 1).

Median treatment duration with enzalutamide was 16.8 mo and 13.9 mo in the nonvisceral and visceral subgroups, respectively, and 4.7 mo and 3.7 mo, respectively with placebo. In the nonvisceral subgroup, 69.1% of patients receiving enzalutamide versus 19.6% receiving placebo had at least 12 mo of treatment. In the visceral subgroup, these percentages were 58.1% and 6.6%, respectively. Median follow-up for survival in the nonvisceral subgroup was 22.1 mo in the enzalutamide group and 22.2 mo in the placebo group, and was 22.8 mo and 24.4 mo, respectively, in the visceral subgroup.

Efficacy

Primary endpoints

Prespecified analyses in patients with or without visceral disease. Consistent with results in the overall population, treatment with enzalutamide reduced the risk of radiographic progression or death in both the nonvisceral (82% risk reduction; HR, 0.175; 95% CI, 0.14–0.22) and visceral subgroups (72% risk reduction; HR, 0.283; 95% CI, 0.16–0.49) (Fig. 1A). In the nonvisceral subgroup, median rPFS was 14.1 mo with enzalutamide and 4.0 mo with placebo. In the visceral subgroup, median rPFS was not yet reached with enzalutamide and 3.6 mo with placebo.

Enzalutamide treatment also reduced the risk of death in both the nonvisceral (31% risk reduction; HR, 0.692; 95% CI, 0.57–0.83) and visceral subgroups (18% risk reduction; HR, 0.822; 95% CI, 0.55–1.23) (Fig. 1B). In the nonvisceral subgroup,

median OS was not yet reached in the enzalutamide group compared with 30.2 mo in the placebo group. In the visceral subgroup, median OS was 27.8 mo in the enzalutamide group and 22.8 mo in the placebo group.

Post-hoc analyses by extent of baseline disease. The beneficial treatment effect of enzalutamide on rPFS was observed in patients with low-volume (<4 metastases) or high-volume (≥4 metastases) bone disease (Fig. 2A), with HRs (HR, 0.155; 95% CI, 0.11–0.22 and HR, 0.215; 95% CI, 0.16–0.29, respectively) similar to those observed in the overall population. In both bone disease subsets, an rPFS benefit was observed in those with and those without visceral disease (Table 2; Supplemental Fig. 1). For OS, HRs favored enzalutamide in patients with low- or high-volume bone disease (HR, 0.623; 95% CI, 0.47–0.84 and HR, 0.745; 95% CI, 0.61–0.92, respectively) (Fig. 2B). Of note, among patients with high-volume bone disease, those with nonvisceral only disease achieved a similar OS benefit with enzalutamide as those with less extensive bone disease (Table 2; Supplemental Fig. 2A), whereas those with visceral disease showed no OS benefit (HR, 1.134; 95% CI, 0.69–1.86) (Table 2; Supplemental Fig. 2).

Among patients with lymph node only disease at baseline, enzalutamide reduced the risk of radiographic progression or death by 91% versus placebo (HR, 0.092; 95% CI, 0.04–0.19) (Table 2; Fig. 3A). Median OS in patients with lymph node only disease was not reached with either treatment (HR, 0.681; 95% CI, 0.35–1.32) (Fig. 3B).

Additional analyses for the nonvisceral subgroup

Subsequent antineoplastic therapy. In the nonvisceral subgroup, fewer patients in the enzalutamide group than in the placebo group (39.7% vs 69.8%) received

subsequent treatment with antineoplastic agents that have previously demonstrated a survival benefit in metastatic prostate cancer. The two most common therapies used by patients after discontinuing study drug were docetaxel (received by 32.9% and 55.8% of patients in the enzalutamide and placebo groups, respectively) and abiraterone (20.3% and 46.0%, respectively).

Secondary and exploratory endpoints. Post hoc analyses included evaluation of secondary and exploratory endpoints in the nonvisceral subgroup (Table 3). Enzalutamide was associated with clinically significant delays for all progression endpoints, including a 16.8-mo delay (28.4 vs 11.6 mo) in median time to initiation of cytotoxic chemotherapy (HR, 0.356; 95% CI, 0.31–0.42) (Table 3). Median time to PSA progression was 11.3 mo with enzalutamide versus 2.8 mo with placebo, a median difference of 8.5 mo (HR, 0.169; 95% CI, 0.15–0.20). Median time to deterioration in quality of life, as measured by a decline in FACT-P total score, was 11.2 mo with enzalutamide versus 5.6 mo with placebo (HR, 0.626; 95% CI, 0.54–0.73).

Confirmed PSA responses (≥50% PSA decline relative to baseline) were achieved by 78% of patients receiving enzalutamide versus 3.7% of patients receiving placebo. Confirmed PSA responses ≥90% were achieved by 47.3% of patients receiving enzalutamide versus 1.2% of patients receiving placebo.

Safety

Nearly all patients with or without visceral disease reported at least one adverse event (AE) regardless of grade or causality. In the nonvisceral and visceral subgroups, the incidence of common AEs and specific AEs was similar to that observed in the full safety population (Table 4).

As in the full safety population, patients with nonvisceral or visceral disease receiving enzalutamide had a higher incidence of grade 3 or higher events than those receiving placebo (42.3% vs 37.3%, nonvisceral subgroup, and 48.0% vs 35.8%, visceral subgroup); however, median exposure to study drug was much longer in the enzalutamide group than the placebo group (median difference in length of time on enzalutamide relative to placebo of 12.1 mo in the nonvisceral subgroup and 10.2 mo in the visceral subgroup). In the nonvisceral subgroup, incidence of AEs leading to treatment discontinuation (5.6% enzalutamide vs 5.3% placebo) or death (3.5% vs 3.7%, respectively) was comparable between groups and consistent with that observed in the full population.

Discussion

Enzalutamide added to ADT at the time of progression provided clinically significant benefit in men with chemotherapy-naïve metastatic prostate cancer, either with or without visceral disease, low- or high-volume bone disease, or lymph node only disease. Our results suggest that enzalutamide is an active treatment in this prostate cancer population, irrespective of the location and extent of baseline disease.

On all primary and secondary outcomes, enzalutamide demonstrated clinically significant benefit in patients with nonvisceral disease, who represent both the majority of patients in PREVAIL (88%) and a population of patients commonly treated by urologists and medical oncologists. Nearly half of the nonvisceral subgroup had lymph node disease at study entry and 85% had bone metastases (a rate similar to that of the visceral disease subgroup). The extended duration of therapy (16.8 mo) and rPFS (14.1 mo) in patients receiving enzalutamide in the

nonvisceral disease subgroup suggests long-term disease control in patients without visceral disease. In the subset of patients with lymph node only disease (13% of patients, nonvisceral subgroup), median rPFS was 10.4 mo longer with enzalutamide than with placebo. Another clinically important finding in patients with nonvisceral only disease was the 16.8-mo delay in median time to initiation of cytotoxic chemotherapy, although the study did not specify when chemotherapy was to be initiated; thus, this finding represents the collective decisions of patients and their treating physicians. The decrease in risk of PSA progression and improvement in radiographic response with enzalutamide provide additional evidence of clinical benefit. Furthermore, the benefit on time to degradation of FACT-P scores suggests that enzalutamide treatment may prolong quality of life.

Although patients with more extensive baseline bone metastases generally had shorter rPFS and OS, patients with nonvisceral disease who also had extensive bone disease achieved a similar rPFS and OS benefit with enzalutamide as those with less extensive disease. A consistent rPFS and OS benefit was observed in patients with visceral disease who had three or fewer bone metastases, whereas patients with visceral disease who had 4 or more bone metastases had improved rPFS but not OS. It is well established that patients with mCRPC display a high risk for bone metastases, which contribute significantly to reduced quality of life and shorter survival due to bone-related complications [4]. Our results suggest that enzalutamide provides meaningful benefit to patients with mCRPC who present with either limited or widespread bone disease.

Enzalutamide demonstrated a favorable safety profile that was similar between patients with or without visceral disease and similar to that reported previously for the full safety population [13]. The most common AEs included fatigue,

back pain, constipation, and arthralgia. Incidence of AEs leading to discontinuation of enzalutamide was low (6%) in both visceral and nonvisceral disease subgroups, suggesting good tolerability over an extended treatment duration. The incidence of hypertension was higher with enzalutamide than with placebo in both the nonvisceral (14% vs 4%) and visceral (11% vs 4%) subgroups. As described previously [13], hypertension in this study was most often reported in patients with a prior history of hypertension and was generally managed with standard therapies. Enzalutamide was not associated with a higher incidence of seizure in this study (one patient [0.1%] in each treatment group). In an earlier phase 3 study (AFFIRM) of enzalutamide in men with mCRPC who had previously received chemotherapy, 0.6% of enzalutamide-treated patients experienced a seizure [15].

Conclusions

In our study, enzalutamide provided meaningful clinical benefit to men with chemotherapy-naïve mCRPC, with or without visceral disease, low- or high-volume bone disease, or lymph node only disease. Patients without visceral disease particularly benefitted from enzalutamide, an active therapy with good tolerability that allowed for a long duration of treatment. Similar benefit was observed for patients with visceral disease who also had low-volume metastases to bone.

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Table 1 – Baseline patient and disease characteristics

Baseline characteristics	Nonvisceral Subgroup (n = 1513)		Visceral Subgroup (n = 204)		Overall ITT Population (n = 1717)	
	Enzalutamide (n = 774)	Placebo (n = 739)	Enzalutamide (n = 98)	Placebo (n = 106)	Enzalutamide (n = 872)	Placebo (n = 845)
Age, yr, median (range)	71 (44–93)	71 (42–93)	73 (43–88)	71 (53–89)	72 (43–93)	71 (42–93)
Gleason score ≥8 at initial diagnosis, %	51.2	53.0	45.7	48.0	50.6	52.4
ECOG PS grade = 0, %	67.8	70.1	60.2	63.2	67.0	69.2
Baseline pain 0–1 on BPI-SF Q3, %	66.8	68.3	61.9	61.9	66.2	67.5
Baseline use of corticosteroids,%	3.7	4.3	6.1	3.8	4.0	4.3
Baseline use of bone targeting agents, %	25.3	27.3	27.6	26.4	25.5	27.1
Prior antiandrogen use, %	87.6	85.9	83.7	89.6	87.2	86.4
Prior radical prostatectomy, %	25.7	27.5	27.6	20.8	25.9	26.6
Median PSA, ng/mL	51.1	42.3	80.0	70.4	54.1	44.2
Median LDH, IU/L	184.0	184.0	188.0	201.0	185.0	185.0
Bone disease, %	85.4	82.0	81.6	79.2	85.0	81.7
Lymph node, %	49.0	50.6	59.2	56.6	50.1	51.4
Soft-tissue disease, %*	54.1	53.9	100	100	59.3	59.6

*Lymph node, visceral, or other.

BP-SF Q3 = Brief Pain Inventory Short Form Question 3; ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat; LDH = lactate dehydrogenase; PS = performance status; PSA = prostate-specific antigen.

Table 2 – Radiographic progression-free survival and overall survival by extent and location of disease at baseline

	<4 Bone Metastases				≥4 Bone Metastases				Lymph Node Only		All Patients	
	Nonvisceral		Visceral		Nonvisceral		Visceral					
	ENZA (n = 393)	PBO (n = 377)	ENZA (n = 48)	PBO (n = 49)	ENZA (n = 381)	PBO (n = 362)	ENZA (n = 50)	PBO (n = 57)	ENZA (n = 87)	PBO (n = 108)	ENZA (n = 872)	PBO (n = 845)
Median OS, mo	NYR	NYR	32.4	NYR	28.0	26.0	18.9	18.3	NYR	NYR	32.4	30.2
	HR, 0.644 (95% CI, 0.47–0.89)		HR, 0.518 (95% CI, 0.25–1.07)		HR, 0.695 (95% CI, 0.55–0.88)		HR, 1.134 (95% CI, 0.69–1.86)		HR, 0.681 (95% CI, 0.35–1.32)		HR, 0.706 (95% CI, 0.60–0.84) $p < 0.0001$	
Median rPFS, mo	14.1	5.2	NYR	3.6	NYR	4.0	10.9	3.9	14.1	3.7	NYR	3.9
	HR, 0.159 (95% CI, 0.11–0.23)		HR, 0.130 (95% CI, 0.05–0.35)		HR, 0.185 (95% CI, 0.13–0.26)		HR, 0.479 (95% CI, 0.24–0.95)		HR, 0.092 (95% CI, 0.04–0.19)		HR, 0.186 (95% CI, 0.15–0.23) $p < 0.0001$	

CI = confidence interval; ENZA = enzalutamide; HR = hazard ratio; NYR = not yet reached; PBO = placebo.

Table 3 – Secondary efficacy outcomes in the nonvisceral subgroup

Endpoint	Enzalutamide (n = 774)	Placebo (n = 739)	HR (95% CI)
Median time to initiation of cytotoxic chemotherapy, mo (95% CI)	28.4 (25.8–NYR)	11.6 (10.0–13.1)	0.356 (0.31–0.42)
Median time to PSA progression, mo (95% CI)*	11.3 (11.1–13.8)	2.8 (2.8–2.9)	0.169 (0.15–0.20)
Median time to decline in the FACT-P total score, mo (95% CI)†	11.2 (11.1–13.9)	5.6 (5.3–5.6)	0.626 (0.54–0.73)
Confirmed change in PSA			
Patients with ≥1 postbaseline PSA assessment, n (%)	765 (98.8)	684 (92.6)	
PSA decline of ≥50% from baseline, n/total N (%)	597/765 (78.0)	25/684 (3.7)	
PSA decline of ≥90% from baseline, n/total N (%)	362/765 (47.3)	8/684 (1.2)	

*PSA progression defined by PCWG2 criteria.

†FACT-P decline defined as ≥10-point decrease in total score.

CI = confidence interval; FACT-P = Functional Assessment of Cancer Therapy–Prostate; HR = hazard ratio; NYR = not yet reached; PCWG2 = Prostate Cancer Working Group; PSA = prostate-specific antigen.

Table 4 – Most common and specific adverse events

Adverse Events	Nonvisceral Subgroup (n = 1511)		Visceral Subgroup (n = 204)		Overall Safety Population (n = 1715)	
	Enzalutamide (n = 773)	Placebo (n = 738)	Enzalutamide (n = 98)	Placebo (n = 106)	Enzalutamide (n = 871)	Placebo (n = 844)
Any adverse event, n (%)	750 (97.0)	689 (93.4)	94 (95.9)	98 (92.5)	844 (96.9)	787 (93.2)
Any adverse event leading to treatment discontinuation, n (%)	43 (5.6)	39 (5.3)	6 (6.1)	12 (11.3)	49 (5.6)	51 (6.0)
Most common adverse events, n (%)*						
Fatigue	282 (36.5)	192 (26.0)	28 (28.6)	26 (24.5)	310 (35.6)	218 (25.8)
Back pain	210 (27.2)	163 (22.1)	25 (25.5)	24 (22.6)	235 (27.0)	187 (22.2)
Constipation	167 (21.6)	125 (16.9)	26 (26.5)	20 (18.9)	193 (22.2)	145 (17.2)
Arthralgia	160 (20.7)	123 (16.7)	17 (17.3)	12 (11.3)	177 (20.3)	135 (16.0)
Specific adverse events, n (%)						
Hypertension	106 (13.7)	31 (4.2)	11 (11.2)	4 (3.8)	117 (13.4)	35 (4.1)
Any cardiac adverse event	76 (9.8)	59 (8.0)	12 (12.2)	7 (6.6)	88 (10.1)	66 (7.8)
ALT increased	6 (0.8)	3 (0.4)	2 (2.0)	2 (1.9)	8 (0.9)	5 (0.6)
Seizure	1 (0.1)†	0	0	1 (0.9)	1 (0.1)†	1 (0.1)

*****Included in this category are adverse events that were reported in the overall safety population in ≥10% of patients in the enzalutamide group at a rate that was ≥2% higher than that in the placebo group.

†This seizure occurred after the data cutoff date. ALT = alanine aminotransferase.

Figures

Fig. 1 – Kaplan-Meier estimates of (A) rPFS and (B) OS in the overall population and in the nonvisceral and visceral subgroups.

CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival; rPFS = radiographic progression-free survival.

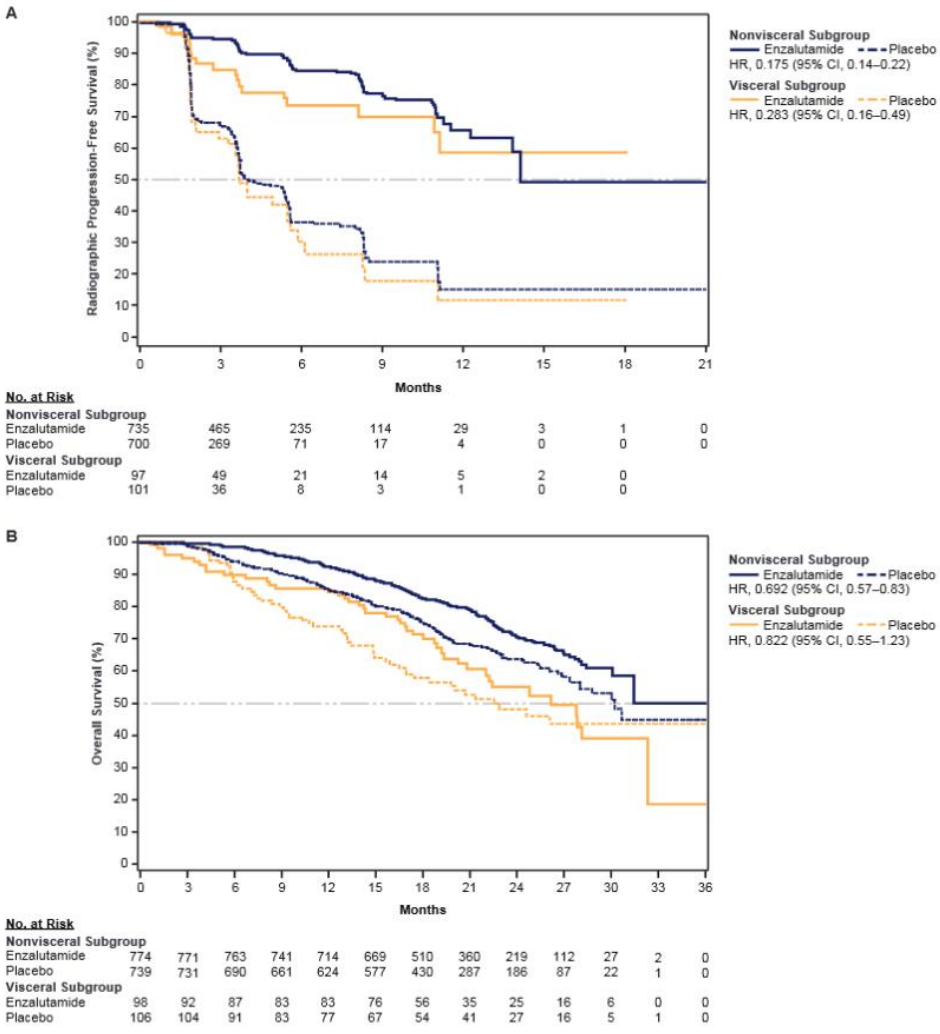


Fig. 2 – Kaplan-Meier estimates of rPFS (A) and OS (B) by number of bone metastases at screening (<4 vs ≥4).

CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; mets = metastases; OS = overall survival; rPFS = radiographic progression-free survival.

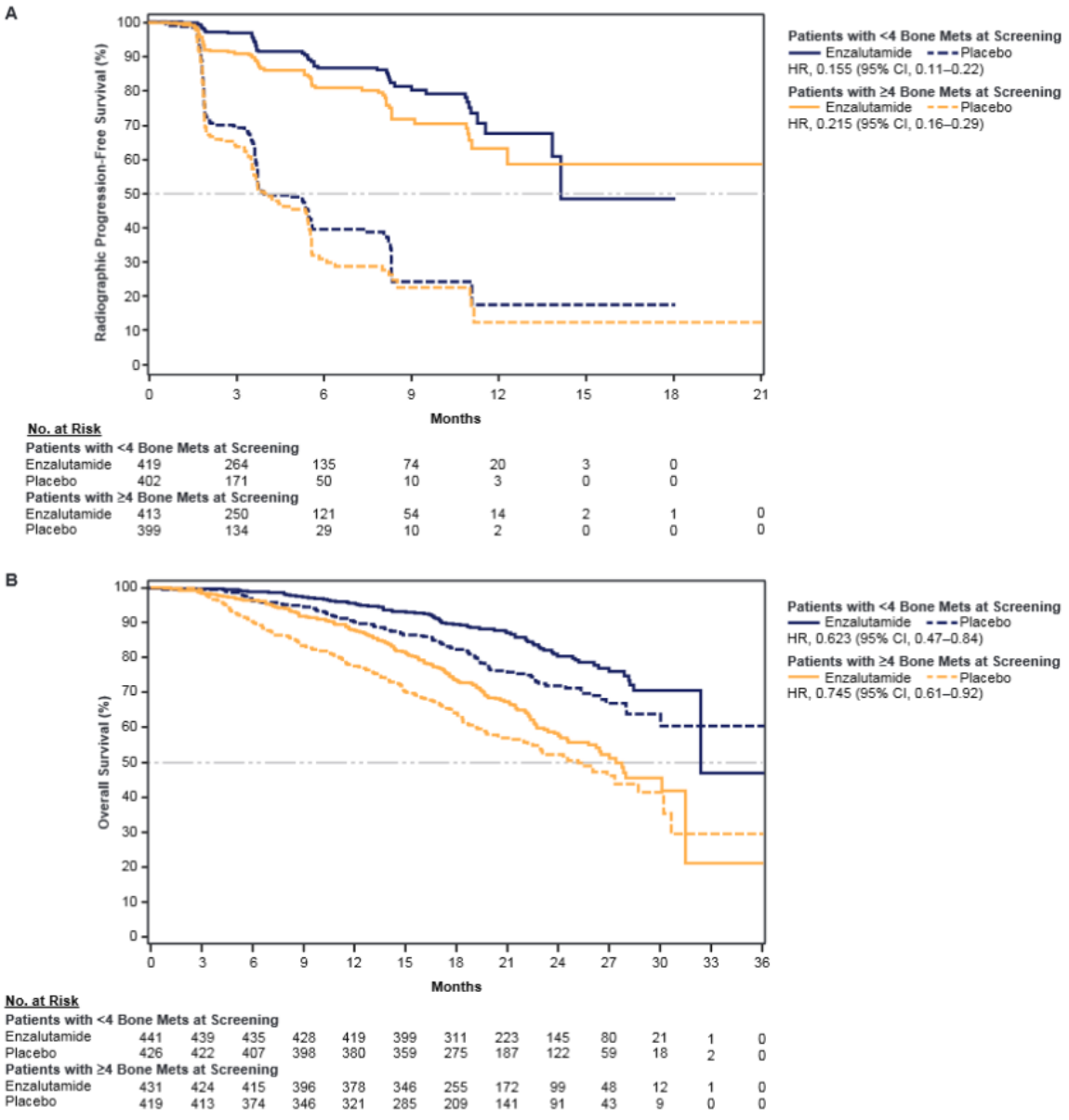
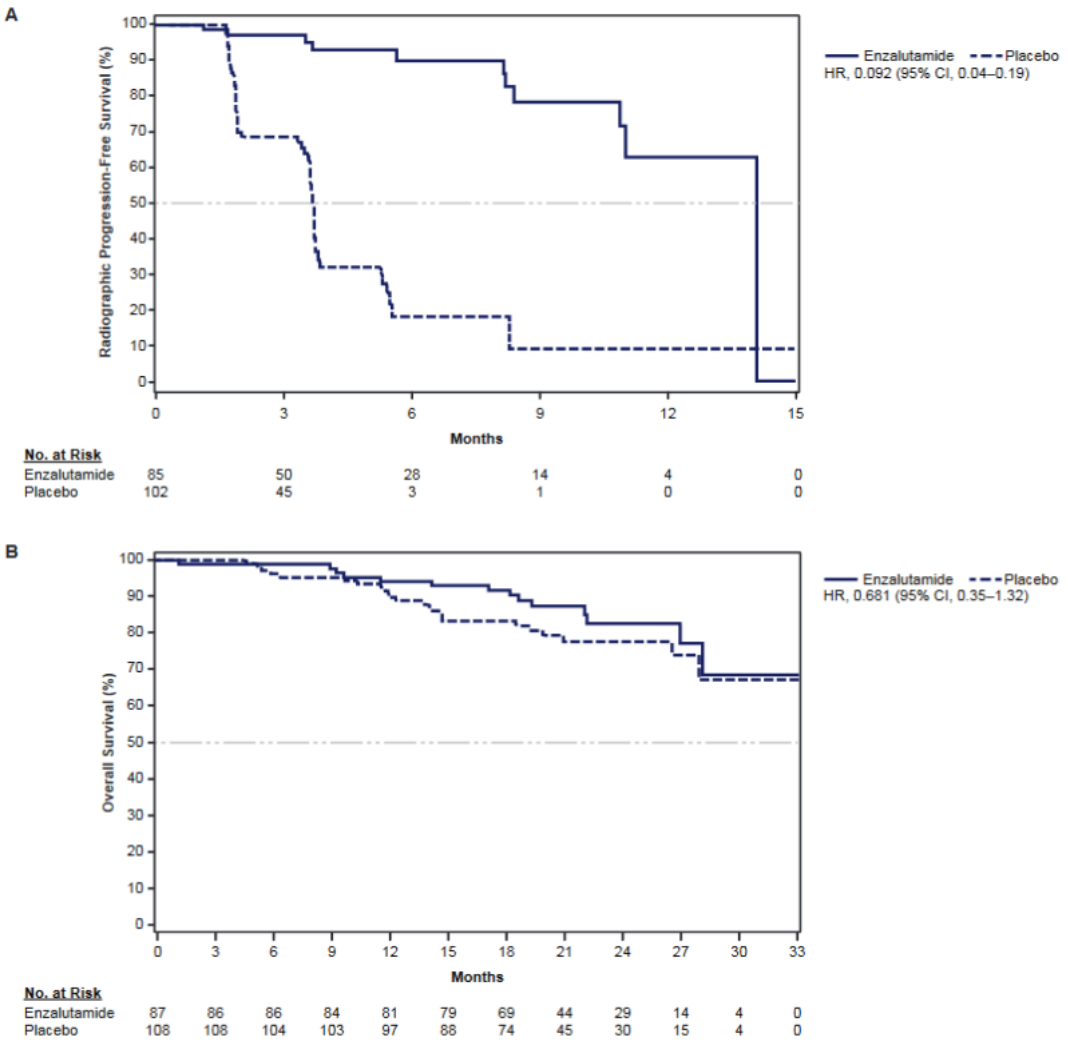
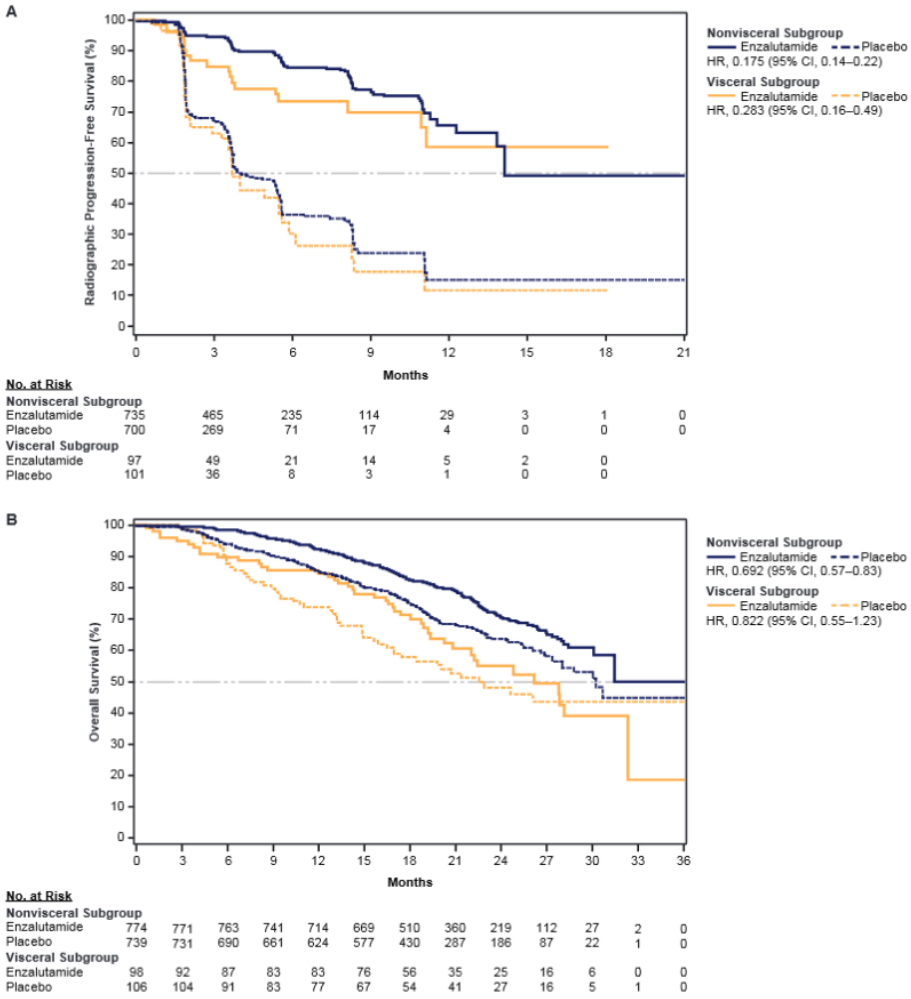


Fig. 3 – Kaplan-Meier estimates of (A) rPFS and (B) OS in the subgroup of patients with lymph node only disease.

CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival; rPFS = radiographic progression-free survival.



Supplementray Figure 1



Supplementray Figure 2