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Enzalutamide in Castration-Resistant Prostate Cancer Patients With Visceral Disease in the Liver and/or Lung: Outcomes From the Randomized Controlled Phase 3 AFFIRM Trial

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Abstract

BACKGROUND—Patients with metastatic castration-resistant prostate cancer (mCRPC) and visceral metastases have a worse prognosis than those with nonvisceral metastases. Treatment with the androgen receptor inhibitor enzalutamide in the phase 3 AFFIRM trial led to significant improvements in outcomes for patients with mCRPC. We analyzed efficacy with enzalutamide among AFFIRM patients with visceral disease.

METHODS—Patients with liver and/or lung metastases at baseline were selected for prespecified overall survival (OS) and exploratory post hoc analyses, including prostate-specific antigen (PSA) response and time to PSA and radiographic progression.

RESULTS—In patients with liver metastases ($n = 92$), enzalutamide was associated with lower risk of radiographic progression (hazard ratio [HR], 0.645; 95% confidence interval [CI], 0.413–1.008), improved 12-month OS (37.7% vs 20.6%) and radiographic progression-free survival (rPFS) (11.6% vs 3.0%) rates, and higher PSA response rates (35.1% vs 4.8%) than placebo. Enzalutamide-treated patients with lung metastases ($n = 104$) showed improvements in median OS (HR, 0.848; 95% CI, 0.510–1.410), substantially reduced risk of radiographic progression (HR,

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Author contributions: Drs. Loriot, de Bono, Forer, Hirmand, and Scher were responsible for the study methodology. Dr. Forer was responsible for the software, validation, formal analysis, and data curation. Dr. de Bono was responsible for the investigation. Drs. Loriot, Fizazi, de Bono, and Scher provided study resources. Drs. Loriot, de Bono, and Scher wrote the original draft. Drs. Loriot, de Bono, and Hirmand provided supervision. All authors were responsible for conceptualization and writing, editing, and approving the final draft.

Conflict of Interest Disclosures: Dr. Loriot reports honoraria from Astellas, Bayer, Ipsen, Janssen, OncoGenex, and Sanofi, and advisory roles for Astellas, Bayer, and Ipsen. Dr. Fizazi reports honoraria from and advisory role for Astellas. Dr. de Bono reports honoraria from and advisory roles for Astellas and Medivation. Mr. Forer and Dr. Hirmand are employees of Medivation and receive salaries and stock options. Dr. Scher's institution has received research funding from Medivation, and he reports advisory roles for AstraZeneca, Bristol-Myers Squibb, Celgene, Chugai Academy for Advanced Oncology, Endocyte, Endo/Orion, Exelixis, Ferring Pharmaceuticals, Genentech, Janssen, Novartis, Pfizer, Sanofi-Aventis, and Takeda Millennium.

0.386; 95% CI, 0.259–0.577), improved 12-month OS (65.1% vs 55.3%) and rPFS (30.9% vs 8.2%) rates, increased time to PSA progression (HR, 0.358; 95% CI, 0.204–0.627), and better PSA response rates (52.1% vs 4.9%) compared with placebo-treated patients. No increase in treatment-related adverse events was observed for visceral compared with nonvisceral metastases cohorts.

CONCLUSION—Across multiple end points, patients with visceral metastases had better outcomes with enzalutamide than with placebo.

Keywords

visceral metastasis; lung; liver; metastatic castration-resistant prostate cancer; enzalutamide

INTRODUCTION

Prostate cancer is the second most common malignancy in men worldwide (1,095,000 cases in 2012) and the most common male malignancy in the United States (220,800 new cases estimated in 2015).^{1,2} An estimated 22% of patients in the United States and a majority of patients in northeast China diagnosed with prostate cancer have locally advanced or metastatic disease at presentation.^{3,4} Patients with metastatic disease are typically treated first with androgen deprivation therapy (ADT) by bilateral orchiectomy (ie, castration) or luteinizing hormone-releasing hormone agonists/antagonists. Patients with metastatic disease at diagnosis who are treated with ADT often develop a castration-resistant phenotype within 1–3 years.^{5,6} Furthermore, median survival time for patients with metastatic castration-resistant prostate cancer (mCRPC) is often less than 3 years with currently available treatments.^{7–9}

Visceral metastases are found in approximately 22%–30% of patients with mCRPC^{10–13} and are associated with unfavorable outcomes.^{14,15} Historically, patients with visceral (liver and lung) involvement have been considered a single group; however, several recent studies have shown the prognostic significance of spread to these sites differs, with spread to the liver associated with inferior survival.^{11,14,16}

Enzalutamide is an oral androgen receptor (AR) inhibitor.^{17,18} It binds competitively to the AR ligand-binding domain and inhibits AR translocation to the cell nucleus, recruitment of AR cofactors, and AR binding to DNA.¹⁸ Preclinical studies demonstrated that enzalutamide had a higher affinity for AR in vitro than other AR antagonists such as bicalutamide and flutamide^{16,17}; in xenograft models, enzalutamide induced tumor regression in model systems where bicalutamide showed agonist effects.¹⁷

In phase 1/2 clinical trials, enzalutamide was associated with tumor responses and had a favorable safety profile,¹⁸ which led to the phase 3 multinational AFFIRM trial in patients (N = 1199) with mCRPC previously treated with docetaxel.¹⁹ At the interim analysis, enzalutamide reduced risk of death by 37% relative to placebo ($P < .001$). Consequently, the independent data and safety monitoring committee recommended that the study be halted and unblinded and patients receiving placebo offered enzalutamide.¹⁹

In the present study, we performed prespecified secondary and post hoc analyses of outcomes in AFFIRM patients with visceral disease, who were considered separately (liver vs lung); efficacy and safety are reported using early indicators of response and later indicators of disease progression, as outlined in Prostate Cancer Working Group 2 (PCWG2) recommendations.²⁰

PATIENTS AND METHODS

Study Population

Eligibility criteria for AFFIRM were previously described in detail.¹⁹ In brief, patients were eligible if they had histologically or cytologically confirmed prostate cancer, had castrate levels of testosterone, had received docetaxel treatment, and had progressive disease as defined by PCWG2 criteria.²⁰ All patients provided written informed consent to participate in the study.

Study Design and Treatment

AFFIRM was an international, randomized, double-blind, placebo-controlled phase 3 study (NCT00974311) comparing the efficacy of enzalutamide versus placebo in men with mCRPC following docetaxel therapy.¹⁹ Review boards of all participating institutions approved the study, which was conducted according to the provisions of the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Conference on Harmonization. After stratification according to Eastern Cooperative Oncology Group (ECOG) Performance Status (0 or 1 vs 2) and mean pain score (0–4 vs 4), patients were randomly assigned 2:1 to enzalutamide capsules 160 mg/day or matching placebo. Use of prednisone or other glucocorticoids during treatment was permitted but not required. Study drug was administered until further systemic treatment was initiated after disease progression. The primary study endpoint, overall survival (OS), and all secondary endpoints were previously defined.¹⁹

For the current prespecified secondary and post hoc analyses, the cohort of patients with established visceral metastases in the liver or lung at baseline was selected independently of skeletal or nodal involvement. These cohorts were compared with the remaining population of patients without specific liver or lung metastases, who may have presented with bone and/or nodal involvement and/or metastases at alternative soft-tissue sites; the latter cohort is hereafter termed the nonvisceral metastases cohort. As liver metastases have been previously identified to have a strong correlation with negative outcomes,^{11,14,16} in the prespecified analysis of OS comparing patients with liver versus lung metastases independent of treatment arm and in the exploratory post hoc analyses, patients with both liver and lung metastases were included solely in the liver metastases cohort.

Outcomes measured included confirmed post-therapy prostate-specific antigen (PSA) changes, including the proportion of patients with a 50% or greater decline from baseline, objective response rate (ORR) in measurable soft-tissue disease (best overall radiographic response per Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1]²¹),

time to PSA progression, radiographic progression-free survival (rPFS) (per RECIST v1.1 for soft-tissue disease and PCWG2²⁰), and OS.

Statistical Analysis

Primary endpoint—Survival times were calculated from start of therapy to patient status at the data cutoff date of September 25, 2011. Hazard ratios (HRs) were determined using the Cox regression model (with treatment as the only covariate) without stratification and are relative to enzalutamide, with values <1 favoring enzalutamide.

Secondary endpoints—The proportion of patients with 50% or greater decline in PSA and best overall radiographic response rates were analyzed using the Cochran-Mantel-Haenszel mean score test stratified by 2 randomization stratification factors (ECOG Performance Status and mean pain score). Time to PSA progression and rPFS were based on the earliest contributing event censored at the date of last assessment and were analyzed using the log-rank test and Cox regression model.

Exploratory analyses—The PSA response rate, overall radiographic response, time to PSA progression, rPFS, and OS were evaluated for patients with visceral liver and/or lung metastases receiving either enzalutamide or placebo. The interaction between enzalutamide treatment and presence of visceral metastases (liver and/or lung) were examined for rPFS and OS. These were unplanned post hoc analyses, with no adjustments for multiple comparisons.

RESULTS

Patients

Of 1199 patients randomized in AFFIRM (n = 800 enzalutamide, n = 399 placebo), 278 (23.2%) had liver and/or lung metastases at baseline (Fig. 1). Of these, 97 (34.9%) had liver metastases, 152 (54.7%) had lung metastases, and 29 (10.4%) had both liver and lung lesions; patients with both liver and lung metastases were included only in the liver metastases subgroup. In the full population, there was a numerically higher proportion of patients from the liver and lung subgroups in the enzalutamide (11.5% [92/800] and 13.0% [104/800]) versus placebo (8.5% [34/399] and 12.0% [48/399]) groups.

The liver metastases cohort generally had more adverse prognostic factors than the nonvisceral and lung metastases cohorts (Table 1). In contrast, the lung metastases cohort showed baseline characteristics comparable to those of the nonvisceral metastases cohort, with the exception of number of bone metastases, which were higher in patients with lung metastases.

Median duration of study drug treatment for the nonvisceral metastases cohort was 9.3 (range, 0.1–23.2) months for those receiving enzalutamide (n = 604) and 3.1 (range, 0.2–19.6) months for those receiving placebo (n = 317). The duration in the liver metastasis cohort was lower, with 4.0 (range, 0.0–17.5) months for the enzalutamide group and 2.7 (range, 0.2–20.7) months for the placebo group. In contrast, the duration in the lung

metastasis cohort was similar to that in the nonvisceral metastases cohort: 8.3 (range, 0.4–21.2) months and 3.5 (range, 0.2–17.0) months, respectively.

Efficacy

PSA and objective tumor response—A significantly higher proportion of patients with liver disease showed a 50% or greater PSA decline with enzalutamide than with placebo (35.1% vs 4.8%; 95% confidence interval [CI], 16.2%–44.6%), as did those with lung disease (52.1% vs 4.9%; 95% CI, 35.2%–59.3%) (Fig. 2; Table 2). Similarly, enzalutamide was associated with an increase in ORR compared with placebo in both the liver and lung metastases cohorts.

Time to PSA progression—In the liver metastases cohort, median time to PSA progression was modestly shorter with enzalutamide than with placebo. In the lung metastases cohort, enzalutamide considerably improved time to PSA progression compared with placebo (HR, 0.358; 95% CI, 0.204–0.627) (Table 2).

Radiographic PFS—Enzalutamide extended median rPFS by 2.6 months (HR, 0.505; 95% CI, 0.377–0.676) (Fig. 3A) and increased the 12-month rPFS rate by 15.3% (21.5% vs 6.2%) relative to placebo in patients with liver and/or lung metastases (Fig. 3A). At 6 months, 61.1% and 17.8% of enzalutamide and placebo-treated patients in the overall population were still on drug, with 24.8% and 4.5%, respectively, still on drug at 12 months. Radiographic PFS also improved in patients with nonvisceral metastases receiving enzalutamide versus placebo (HR, 0.360; 95% CI, 0.304–0.425; 12-month rPFS rate, 36.0% vs 9.5%). A post hoc test of the interaction between enzalutamide treatment and visceral status was not significant ($p = 0.1947$) for rPFS. Enzalutamide improved rPFS in both visceral metastases cohorts, but to a greater extent in patients with lung metastases than in those with liver metastases (Fig. 4A, B; Table 2).

Overall survival—Median duration of follow-up to determine survival status in AFFIRM was 14.4 months.¹⁹ Enzalutamide extended median OS by 3.9 months (HR, 0.806; 95% CI, 0.574–1.132) (Fig. 3B) and increased the 12-month OS rate by 11.1% (52.1% vs 41.1%) relative to placebo in patients with liver and/or lung metastases. Overall survival was also improved in patients with nonvisceral metastases receiving enzalutamide versus placebo (HR, 0.562; 95% CI, 0.457–0.692; 12-month OS rate, 73.2% vs 57.1%) (Fig. 3B). Irrespective of whether patients received enzalutamide or placebo, median OS times were shorter in patients with liver and/or lung metastases than in patients with nonvisceral metastases (Fig. 3B). A post hoc test of the interaction between enzalutamide treatment and visceral status was not significant ($p = 0.1437$) for OS.

To address the impact of metastatic disease distribution, OS was compared in patients with lung versus liver metastases. Patients with liver metastases had shorter OS (median, 7.7 months; 95% CI, 5.8–9.8 months) than those with lung metastases alone (median, 16.5 months; 95% CI, 13.8 months to estimate not met; HR, 1.991) (Fig. 3C). Compared with placebo, enzalutamide was associated with improvement in median OS of 3.3 months in patients with liver metastases and 1.2 months in patients with lung metastases (Fig. 4C, D;

Table 2). Enzalutamide was also associated with a 17.1% increase (37.7% vs 20.6%) in 12-month OS rate in patients with liver metastases and a 9.8% increase (65.1% vs 55.3%) in patients with lung metastases (Table 2).

Safety

In this post hoc analysis, the total number of treatment-emergent adverse events (AEs) was comparable among all 3 subgroups, with 97.7% of patients with nonvisceral metastases, 97.6% of patients with liver metastases, and 100% of patients with lung metastases presenting with at least 1 treatment-emergent AE of any grade. The proportion of patients who discontinued treatment due to an AE was comparable between the visceral (8.6%) and nonvisceral (8.3%) metastases cohorts.

Observed AEs in both enzalutamide- and placebo-treated patients with liver or lung metastases were broadly similar to those in patients with nonvisceral metastases (Table 3), with some differences. Fatigue was more common in enzalutamide-treated patients with liver or lung metastases than in those treated with placebo, whereas no similar trend was seen in the nonvisceral cohort. Liver function test abnormalities were not common in enzalutamide- or placebo-treated patients in any of the visceral metastases subgroups.

DISCUSSION

The primary analysis of AFFIRM demonstrated that patients with visceral metastases had worse outcomes than patients with nonvisceral metastases, but benefited from treatment with the AR inhibitor enzalutamide.¹⁹ These data are extended here to evaluate the relationship between specific metastatic sites (liver vs lung) and efficacy and safety findings from AFFIRM. The results with enzalutamide confirm that the prognosis of patients with liver and lung disease were distinctly different; however, clinical benefit was observed in both cohorts, including in the proportion of patients with a 50% or greater PSA decline, ORR, and length of rPFS and OS.

While median data and HRs provide valuable exploratory insights into enzalutamide treatment effects, statistical findings should be viewed conservatively given the post hoc nature of these analyses and small sample sizes, particularly for the patient cohort with liver metastases. Additionally, patients were not prospectively stratified based on the type of metastasis.

In this exploratory analysis, compared with placebo, enzalutamide reduced risk of death by 19.4% and risk of progression by 49.5% and improved 1-year survival rates by 11.1% and 1-year rPFS rates by 15.3% in patients with visceral liver and/or lung metastases; greater efficacy was observed with regard to progression in patients with lung metastases (15.2%, 61.4%, 9.8%, and 22.7%, respectively) than in patients with liver metastases (30.3%, 35.5%, 17.1%, and 8.6%, respectively). This is consistent with data presented as part of exploratory analyses of mCRPC patients with visceral metastases treated with abiraterone acetate plus prednisone (vs prednisone alone as an active comparator).¹¹

Although our analyses show that patients with visceral metastases benefit from enzalutamide, metastatic disease distribution may affect its efficacy, particularly in patients with liver metastases. Enzalutamide-treated patients with lung metastases saw improvements in both early indicators of response (ie, PSA and tumor response) and later indicators of disease progression, including a 15.2% reduction in risk of death and an 9.8% increase in 1-year OS rate (65.1% vs 55.3% with placebo). Men with liver metastases gained more modest benefit with enzalutamide, although enzalutamide was associated with a 30.3% reduction in risk of death and 17.1% increase in 1-year OS rates (37.7% vs 20.6% with placebo). These findings are consistent with a retrospective analysis of the phase 3 TAX 327 study of docetaxel plus prednisone or mitoxantrone plus prednisone, which found that patients with liver metastases had shorter OS than patients with lung metastases, who in turn had shorter OS than patients with nodal disease only.¹⁶

Similarly, in exploratory analyses of patients with mCRPC treated with abiraterone acetate plus prednisone (vs prednisone alone as an active comparator),¹¹ the median OS was markedly smaller in patients with liver metastases (7.3 months) than in those with lung metastases (13.9 months) in the abiraterone plus prednisone arm and also in the prednisone-alone arm (4.0 months and 7.9 months, respectively). Further analyses using larger populations that account for specific patient and tumor biology characteristics and extent of metastatic spread may help elucidate the factors contributing to outcomes in this severely ill population.

Emerging data suggest that specific histological characteristics, tumor microenvironments, and molecular aberrations in visceral metastatic tumor tissues are associated with resistance mechanisms and survival outcomes.^{22–24}

Therapeutic options remain limited for mCRPC patients with visceral metastases. Typically, such patients have been excluded from enrolling in phase 2 and 3 clinical trials of new therapies such as radium-223 dichloride and sipuleucel-T,^{25,26} and ipilimumab has performed poorly in patients with visceral metastases or more significant disease burden.^{27,28} However, cabazitaxel plus prednisone may represent a therapeutic option; this regimen was shown to prolong OS (15.1 vs 12.7 months) and rPFS (2.8 vs 1.4 months) versus prednisone plus mitoxantrone in mCRPC patients who had progressed on docetaxel, 24.9% (188/755) of whom had visceral metastases at baseline, and efficacy with cabazitaxel was reported even in patients progressing after abiraterone.^{12,29,30} Given the prolonged survival times associated with the use of novel therapeutics in patients with prostate cancer, it is likely that the number of patients with visceral metastases will continue to increase in clinical practice,³ making alternative therapeutic options increasingly critical.

In AFFIRM, patients in the visceral metastases cohort did not demonstrate any notable increases in treatment-emergent AEs compared with the nonvisceral metastases cohort, and patient discontinuation due to AEs was comparable between the visceral and nonvisceral metastases cohorts.

Patients with both liver and lung metastases at baseline were included in the liver only cohort because of the strong correlation of liver metastases with negative outcomes. While it

was possible to identify patients with measurable liver or lung metastases at baseline, others may have had subclinical metastases or lesions that developed during the trial. Further, among patients in the nonvisceral metastases cohort, a small percentage had nonliver, nonlung visceral tumors that were difficult to localize to specific organs. The relatively stringent inclusion and exclusion criteria of this randomized clinical trial may limit potential interpretation and general applicability of these data. However, another phase 3 trial testing enzalutamide against placebo in patients with earlier stages of mCRPC (PREVAIL) also included a subgroup of patients with visceral metastases, and evidence of enzalutamide efficacy was reported.⁸

In conclusion, these data strongly suggest that patients presenting with visceral metastases in the liver versus lung should be assessed independently given the differential prognosis and response to treatment observed based on the site of visceral disease. Improvements observed with enzalutamide compared with placebo in the visceral metastases cohort highlight the fact that visceral metastases per se should not routinely be used as an exclusion criterion in clinical trials, as this subset of patients can still benefit from treatment.

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Figure 1.

CONSORT diagram. Nonvisceral disease refers to patients without visceral liver or lung disease who may have presented with bone and/or nodal involvement and/or disease at alternative soft-tissue sites.

Figure 2.

Waterfall plots showing PSA change from baseline for patients with (a) liver and (b) lung metastases. The 29 patients presenting with metastases in both the liver and lung were included in the liver metastases cohort only. Dashed lines represent 50% and 90% decline in PSA from baseline. Abbreviation: PSA, prostate-specific antigen.

Figure 3.

Kaplan-Meier curves for (a) radiographic progression-free survival in patients with nonvisceral versus visceral metastases treated with either enzalutamide or placebo, (b) overall survival (OS) in patients with nonvisceral versus visceral metastases treated with either enzalutamide or placebo, and (c) OS in patients with visceral metastases in liver versus lung. The 29 patients presenting with metastases in both the liver and lung were included in the liver metastases cohort only. Dashed lines represent medians. Abbreviations: CI, confidence interval; ENZA, enzalutamide; NA, not available; NM, estimate not met; PBO, placebo; visc, visceral.

Figure 4.

Kaplan-Meier curves for (a) radiographic progression-free survival (rPFS) in patients with visceral liver metastases treated with enzalutamide versus placebo, (b) rPFS in patients with visceral lung metastases treated with enzalutamide versus placebo, (c) overall survival (OS) in patients with visceral liver metastases treated with enzalutamide versus placebo, and (d) OS in patients with visceral lung metastases treated with enzalutamide versus placebo. The 29 patients with visceral metastases in both the liver and lung are included in the liver metastases cohort only. Dashed lines represent medians. Abbreviations: CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; NM, estimate not met; PBO, placebo.

Table 1

Baseline Disease Characteristics

	Nonvisceral mCRPC		Visceral Liver and/or Lung mCRPC		Liver mCRPC		Lung mCRPC	
	ENZA (n = 604)	PBO (n = 317)	ENZA (n = 196)	PBO (n = 82)	ENZA (n = 92)	PBO (n = 34)	ENZA (n = 104)	PBO (n = 48)
Median age, y	69	69	69	69	68	69	70	70
Median Gleason score at initial diagnosis	8.0	8.0	8.0	8.0	8.0	8.0	7.0	7.0
ECOG Performance Status = 2, %	8.3	6.9	10.2	12.2	14.1	14.7	6.7	10.4
BPI-SF Q3, mean pain score 4, %	27.3	28.4	31.1	30.5	37.0	38.2	26.0	25.0
Median PSA, ng/mL	108.8	128.3	104.2	126.9	126.8	155.6	93.5	110.8
Median hemoglobin, g/L	121.0	121.0	117.0	116.5	117.0	113.5	116.5	119.0
Median alkaline phosphatase, U/L	108.0	105.0	137.0	119.5	155.0	150.5	123.0	102.0
Median lactate dehydrogenase, U/L	203.5	213.0	226.5	224.5	270.5	267.5	201.0	197.5
>20 bone metastases at screening, %	37.4	37.5	38.8	39.0	35.9	35.3	41.3	41.7

Abbreviations: BPI-SF Q3, Brief Pain Inventory-Short Form question 3; ECOG, Eastern Cooperative Oncology Group; ENZA, enzalutamide; mCRPC, metastatic castration-resistant prostate cancer; PBO, placebo; PSA, prostate-specific antigen.

NOTE: Baseline disease characteristics are shown for patients with nonvisceral metastases, patients with visceral liver metastases, and patients with visceral lung metastases. Patients with metastases in both liver and lung (n = 29) are included in the liver metastases subgroup.

Table 2

Efficacy Outcomes

	Liver mCRPC ^a		Lung mCRPC ^a	
	ENZA (n = 92)	PBO (n = 34)	ENZA (n = 104)	PBO (n = 48)
50% or greater decline in PSA, % (n/N) [95% CI]	35.1 (26/74) [24.4–47.1]	4.8 (1/21) [0.1–23.8]	52.1 (49/94) [41.6–62.5]	4.9 (2/41) [0.6–16.5]
ORR, % (n/N) [95% CI]	14.9 (13/87) [8.2–24.2]	3.3 (1/30) [0.1–17.2]	29.3 (24/82) [19.7–40.4]	6.3 (2/32) [0.8–20.8]
Median time to PSA progression, months [95% CI]	5.6 [4.5–8.3] HR, 0.456 [0.193–1.078]	14.2 [2.8–14.2]	8.3 [5.6–8.5] HR, 0.358 [0.204–0.627]	3.7 [2.9–4.8]
Median rPFS, months [95% CI]	2.9 [2.8–4.9] HR, 0.645 [0.413–1.008]	2.8 [2.7–3.2]	13.9 [10.1–NM]	5.3 [2.8–6.7] HR, 0.386 [0.259–0.577]
12-month rPFS rate, %	11.6	3.0	30.9	8.2
Median OS, months [95% CI]	9.0 [6.4–10.7] HR, 0.697 [0.436–1.114]	5.7 [4.2–9.5]	17.0 [13.5–NM]	15.8 [8.5–NM] HR, 0.848 [0.510–1.410]
12-month OS rate, %	37.7	20.6	65.1	55.3

Abbreviations: CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; NM, estimate not met; ORR, objective response rate; OS, overall survival; PBO, placebo; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.

NOTE: Efficacy outcomes are shown for patients with visceral liver metastases and patients with visceral lung metastases. Patients with metastases in both liver and lung (n = 29) are included in the liver subgroup. The ORR includes fewer patients, as it only includes those with measurable soft-tissue metastases at screening.

^aHRs (for descriptive purposes) are shown for enzalutamide versus placebo for both patient subgroups.

Table 3**Treatment-Emergent Adverse Events**

Adverse Event	Nonvisceral mCRPC		Visceral Liver and/or Lung mCRPC		Liver mCRPC		Lung mCRPC	
	ENZA (n = 604)	PBO (n = 317)	ENZA (n = 196)	PBO (n = 82)	ENZA (n = 92)	PBO (n = 34)	ENZA (n = 122)	PBO (n = 59)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Reported in 10% of Patients								
Nausea	205 (33.9)	126 (39.7)	60 (30.6)	41 (50.0)	33 (35.9)	20 (58.8)	27 (26.0)	21 (43.8)
Fatigue	205 (33.9)	99 (31.2)	64 (32.7)	17 (20.7)	32 (34.8)	8 (23.5)	32 (30.8)	9 (18.8)
Constipation	148 (24.5)	85 (26.8)	40 (20.4)	25 (30.5)	16 (17.4)	15 (44.1)	24 (23.1)	10 (20.8)
Anorexia	152 (25.2)	77 (24.3)	48 (24.5)	27 (32.9)	24 (26.1)	9 (26.5)	24 (23.1)	18 (37.5)
Back Pain	151 (25.0)	75 (23.7)	43 (21.9)	20 (24.4)	21 (22.8)	4 (11.8)	22 (21.2)	16 (33.3)
Diarrhea	129 (21.4)	56 (17.7)	42 (21.4)	14 (17.1)	17 (18.5)	5 (14.7)	25 (24.0)	9 (18.8)
Arthralgia	122 (20.2)	58 (18.3)	33 (16.8)	13 (15.9)	15 (16.3)	3 (8.8)	18 (17.3)	10 (20.8)
Hot flush	139 (23.0)	33 (10.4)	23 (11.7)	8 (9.8)	13 (14.1)	4 (11.8)	10 (9.6)	4 (8.3)
Vomiting	100 (16.6)	67 (21.1)	30 (15.3)	21 (25.6)	18 (19.6)	12 (35.3)	12 (11.5)	9 (18.8)
Anemia	86 (14.2)	65 (20.5)	29 (14.8)	11 (13.4)	12 (13.0)	6 (17.6)	17 (16.3)	5 (10.4)
Asthenia	99 (16.4)	52 (16.4)	41 (20.9)	15 (18.3)	19 (20.7)	4 (11.8)	22 (21.2)	11 (22.9)
Bone pain	92 (15.2)	58 (18.3)	19 (9.7)	10 (12.2)	8 (8.7)	5 (14.7)	11 (10.6)	5 (10.4)
Pain in extremity	95 (15.7)	45 (14.2)	25 (12.8)	18 (22.0)	8 (8.7)	6 (17.6)	17 (16.3)	12 (25.0)
Edema peripheral	89 (14.7)	40 (12.6)	30 (15.3)	12 (14.6)	12 (13.0)	7 (20.6)	18 (17.3)	5 (10.4)
Musculoskeletal pain	93 (15.4)	34 (10.7)	16 (8.2)	6 (7.3)	3 (3.3)	3 (8.8)	13 (12.5)	3 (6.3)
Weight decreased	78 (12.9)	30 (9.5)	16 (8.2)	11 (13.4)	9 (9.8)	3 (8.8)	7 (6.7)	8 (16.7)
Headache	76 (12.6)	16 (5.0)	17 (8.7)	6 (7.3)	5 (5.4)	2 (5.9)	12 (11.5)	4 (8.3)
Urinary tract infection	41 (6.8)	21 (6.6)	22 (11.2)	7 (8.5)	9 (9.8)	5 (14.7)	13 (12.5)	2 (4.2)
Dyspnea	51 (8.4)	30 (9.5)	28 (14.3)	9 (11.0)	9 (9.8)	4 (11.8)	19 (18.3)	5 (10.4)
Hematuria	36 (6.0)	12 (3.8)	16 (8.2)	6 (7.3)	5 (5.4)	5 (14.7)	11 (10.6)	1 (2.1)
Pyrexia	41 (6.8)	19 (6.0)	13 (6.6)	9 (11.0)	6 (6.5)	3 (8.8)	7 (6.7)	6 (12.5)
Liver function test abnormalities								
AST increased	4 (0.7)	2 (0.6)	1 (0.5)	1 (1.2)	1 (1.1)	1 (2.9)	0	0

Adverse Event	Nonvisceral mCRPC		Visceral Liver and/or Lung mCRPC		Liver mCRPC		Lung mCRPC	
	ENZA (n = 604)	PBO (n = 317)	ENZA (n = 196)	PBO (n = 82)	ENZA (n = 92)	PBO (n = 34)	ENZA (n = 122)	PBO (n = 59)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ALT increased	3 (0.5)	2 (0.6)	1 (0.5)	0	1 (1.1)	0	0	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ENZA, enzalutamide; mCRPC, metastatic castration-resistant prostate cancer; PBO, placebo.