Effect of Visceral Disease Site on Outcomes in Patients with Metastatic Castration-Resistant Prostate Cancer Treated with Enzalutamide in the PREVAIL Trial

Short title: Enzalutamide for mCRPC with Visceral Disease

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Microabstract

We assessed outcomes from men with metastatic castration-resistant prostate cancer that had spread to the liver and/or lungs in the PREVAIL clinical trial of enzalutamide in patients who had not received docetaxel chemotherapy. Compared with placebo, enzalutamide lengthened the time it took for the cancers to grow (according to changes in scans), prostate-specific antigen to rise, or patients to require chemotherapy.

Abstract

Purpose: The placebo-controlled PREVAIL trial of the oral androgen-receptor inhibitor enzalutamide for chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) was unique as it included patients with visceral disease. This analysis was designed to describe outcomes for the subgroup of men from PREVAIL with specific sites of visceral disease to help clinicians understand how these patients responded to enzalutamide prior to chemotherapy.

Patients and Methods: Prespecified analyses examined the coprimary endpoints of radiographic progression-free survival (rPFS) and overall survival (OS) only. All other efficacy analyses were post hoc. The visceral subgroup was divided into liver or lung subsets. Patients with both liver and lung metastases were included in the liver subset.

Results: Of the 1717 patients in PREVAIL, 204 (12%) had visceral metastases at screening (liver only or liver/lung metastases, n = 74; lung only metastases, n = 130). In patients with liver metastases, enzalutamide was associated with an improvement in rPFS (hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.22-0.90) but not OS (HR, 1.04; 95% CI, 0.57-1.87). In patients with lung metastases only, the HR for rPFS (0.14; 95% CI, 0.06-0.36) and OS HR (0.59; 95% CI, 0.33-1.06) favored enzalutamide over placebo. Patients with liver metastases had worse outcomes than those with lung metastases, regardless of treatment. Enzalutamide was well tolerated in patients with visceral disease.

Conclusions: Enzalutamide is an active first-line treatment option for men with asymptomatic or mildly symptomatic chemotherapy-naïve mCRPC and visceral disease. Patients with lung-only disease fared better than patients with liver disease, regardless of treatment.

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Keywords: androgen receptor inhibitor; survival analysis; chemotherapy-naïve; phase III

Abbreviations: AE = adverse event; CRPC = castration-resistant prostate cancer; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FACT-P = Functional Assessment of Cancer Therapy–Prostate questionnaire; HR = hazard ratio; IQR = interquartile range; mCRPC = metastatic castration-resistant prostate cancer; NYR = not yet reached; OS = overall survival; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival.

Introduction

Nearly all patients with recurrent prostate cancer or *de novo* metastatic disease treated with androgen deprivation therapy eventually develop castration-resistant prostate cancer (CRPC), the lethal form of this disease.[1,2] Survival of patients with metastatic CRPC (mCRPC) is usually < 3 years, with > 26,000 deaths predicted in the United States alone in 2016.[3-7] Patients with mCRPC with visceral disease, most commonly in liver and/or lung, are thought to have a particularly poor prognosis, and the presence of liver metastases is associated with the shortest survival.[3,4,8,9]

During the drug development process, patients with mCRPC have been previously categorized by docetaxel chemotherapy exposure, the first drug to improve overall survival (OS) for men with mCRPC in phase III trials.[10,11] Studies of systemic agents in the post-docetaxel setting have generally included men with visceral disease.[12-14] However, phase III trials in the pre-docetaxel setting have excluded these patients because of the widespread belief that docetaxel, rather than an investigational agent is the preferred treatment option for patients with visceral disease given their poor prognosis.[15,16] The PREVAIL phase III trial of the oral androgen-receptor inhibitor enzalutamide versus placebo in men with asymptomatic or minimally symptomatic chemotherapy-naïve mCRPC challenged this view by enrolling patients with visceral disease, provided they were otherwise eligible based on performance criteria (ie, an Eastern Cooperative Oncology Group Performance Status [ECOG PS] of 0 or 1 and a score of 0-3 on Brief Pain Inventory Short Form question 3).[5] PREVAIL was designed with the expectation that minimally symptomatic men with good ECOG PS would be followed carefully with imaging studies and could receive an investigational therapy or placebo and still receive chemotherapy after discontinuing the study medication.

In PREVAIL, enzalutamide significantly improved OS and radiographic progression-free survival (rPFS) relative to placebo in the overall population of men with chemotherapy-naïve mCRPC.[5] A prespecified subgroup analysis of PREVAIL data revealed that treatment with enzalutamide reduced the risk of the composite endpoint of radiographic progression or death by 72% (hazard ratio [HR], 0.28; 95% confidence interval [CI], 0.16-0.49) but not risk of death (HR, 0.82; 95% CI, 0.55-1.23) in patients with visceral disease, defined as a combined population with baseline disease in the liver and/or lung, with or without metastases to the bone or lymph nodes.[17] Outcomes for patients with lymph node–only disease were also analyzed in this subgroup analysis.[17] The current analysis of PREVAIL determines how outcomes with enzalutamide versus placebo treatment were affected by the specific site of visceral disease (ie, liver metastases vs. lung-only metastases). Moreover, this analysis provides information on the natural history of chemotherapy-naïve patients with mCRPC and liver or lung-only visceral disease treated in the placebo arm.

Patients and Methods

Study Design and Participants

The PREVAIL study design, eligibility criteria, and conduct have been fully described elsewhere.[5] Patients were randomized to either oral enzalutamide 160 mg/day or placebo until the occurrence of unacceptable adverse events, or confirmed radiographic progression *and* the initiation of chemotherapy or an investigational agent. The study was approved by the independent review board at each participating site, and was conducted in compliance with the ethical principles originating in or derived from the provisions of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonisation. All patients provided written informed consent before participating in the trial.

Presence of visceral disease (liver and/or lung) was determined radiographically (computed tomography scan or magnetic resonance imaging) by the treating physician and did not require confirmation by biopsy. For all efficacy analyses, the visceral subgroup was divided into liver and lung subsets. Patients with both liver and lung metastases were included in the liver subset because of the previously described inferior survival outcomes of patients with liver versus lung-only involvement.[3,4,8,9]

The coprimary endpoints of rPFS and OS were prospectively evaluated in the liver and lung subsets along with the exploratory analysis of the following endpoints (all were secondary endpoints in PREVAIL except where indicated): time to initiation of chemotherapy, time to prostate-specific antigen (PSA) progression, time to decline on the Functional Assessment of Cancer Therapy–Prostate questionnaire (FACT-P; exploratory endpoint), confirmed PSA response (≥ 50% PSA decline from baseline), and best overall tissue response determined by investigator assessment using Response Evaluation Criteria In Solid Tumors version 1.1. The coprimary endpoint rPFS was defined as time from randomization to first objective evidence of radiographic disease progression assessed by a blinded independent central review facility or death from any cause within 168 days after treatment discontinuation, whichever occurred first.

Statistical Analysis

The Kaplan-Meier product limit method was used to estimate distributions of the time to events. Hazard ratios and their 95% CIs were estimated using an unstratified Cox regression model. A two-sided, unstratified log-rank test was used to compare rPFS and OS between enzalutamide and placebo. The primary analysis was by intention-to-treat, defined as those

patients with measurable disease at screening who were then randomized to one of the treatment arms.

Cochran-Mantel-Haenszel score tests were used to compare the proportion of enzalutamide- and placebo-treated patients with a confirmed ≥ 50% reduction in PSA from baseline to PSA nadir and objective response, with corresponding two-sided 95% CIs calculated using the Clopper-Pearson method.

Incidence data were used to assess the safety and tolerability of enzalutamide and placebo. To adjust for differences in duration of study treatment between the enzalutamide and placebo groups, adverse events (AEs) were also evaluated using event-rate calculations (events per 100 patient-years).

The results presented herein are based on a cutoff date of September 16, 2013, except for rPFS, which was based on a data cutoff date of May 6, 2012.

Results

Patients and Treatment

In PREVAIL, 1717 patients were randomized to treatment: 872 to enzalutamide and 845 to placebo (Figure A1, appendix). Overall, 204 patients had visceral disease at baseline: 98 (11%) in the enzalutamide group and 106 (13%) in the placebo group (Table 1). Among patients with visceral disease, liver metastases (in 36% of patients) were less frequent than lung metastases (in 64% of patients). Six patients (0.7%) in the enzalutamide group and three (0.4%) in the placebo group had both liver and lung metastases and were included in the liver subset.

In the visceral subgroup, patient demographics and disease characteristics were generally similar between treatment arms (Table 1). Liver and lung subsets were well balanced between each other and the full population with respect to patient age, ECOG PS, median Gleason score, baseline levels of hemoglobin and albumin, baseline pain, and presence of bone disease. A greater proportion of patients in the liver subset than those in the lung subset and full population had more than 20 bone metastases (Table 1). Patients with liver metastases also had higher baseline levels of lactate dehydrogenase, alkaline phosphatase, and PSA than those with lung metastases and those in the full population.

In both the liver and lung subsets, duration of treatment was longer with enzalutamide than placebo (Table 2). However, duration of enzalutamide and placebo treatment was shorter in the liver subset than the lung subset and full population.

Efficacy

Coprimary endpoints

Treatment with enzalutamide versus placebo reduced the risk of radiographic progression or death by 56% in patients with liver metastases and by 86% in patients with lung metastases (Figure 1). The HR in the lung subset (0.14) was similar to that in the full population (0.19).[5] The HR in the smaller subset of patients with liver metastases favored enzalutamide (0.44), although the magnitude of benefit was less than in the lung subset or the full population. In both treatment groups, median rPFS was shorter in patients with liver metastases than in those with lung metastases.

Treatment with enzalutamide versus placebo was not associated with a reduced risk of death in the subsets of patients with liver and/or lung metastases (Figure 2). In the liver subset, median OS was 18.9 months (interquartile range [IQR], 10.7-26.2) with enzalutamide and 14.8 months (IQR, 8.9-not yet reached [NYR]) with placebo, both considerably shorter than that observed in either the lung subset or full population.[5] Median OS with enzalutamide in the lung subset (32.4 months; IQR, 20.9-NYR) was identical to that of patients in the full population receiving enzalutamide (32.4 months; IQR, 22.0-NYR[5]), and indicated some improvement in median OS over placebo (26.0 months; IQR, 14.8-NYR) in this subset of patients.

A post hoc test of the interaction between treatment and visceral status was not significant for rPFS (P = .2231) or OS (P = .4755).

Secondary and exploratory endpoints

In both the liver and lung subsets, treatment with enzalutamide versus placebo was associated with improvements in all secondary endpoints (Figure 3), including delaying time to initiation of chemotherapy (by approximately 15 and 18 months, respectively), which was similar to that in the full population (approximate delay of 17 months). In both visceral subsets, treatment with enzalutamide was associated with delaying time to PSA progression. Confirmed PSA response rates (≥ 50% decline) with enzalutamide were 51% in the liver subset (0% with placebo) and 94% in the lung subset (3% with placebo). In the full population, PSA response rates were 78% with enzalutamide and 3% with placebo.[5] The small subset of patients with liver metastases fared worse than those with lung metastases, who had benefits on secondary endpoints consistent with the full population. Enzalutamide did not delay time to FACT-P decline in the visceral subsets versus placebo, which was not the case in the full population.[5]

In patients with measurable disease at baseline, best overall soft-tissue response rate with enzalutamide was 29% (10 of 34 patients) in the liver subset and 73% (27 of 37 patients) in the lung subset and 3% (1 of 30 patients) and 0% (0 of 50 patients), respectively, with placebo. Six patients with visceral disease—two (6%) with liver metastases and four (11%) with lung metastases—achieved a complete response with enzalutamide. Radiographic images showing the disappearance of liver and lung lesions in two patients with a complete response to enzalutamide are shown in Figure A2 (appendix).

Safety

The incidence of any AE, grade 3 or 4 AEs, and serious AEs in the visceral subgroup were similar to those in the full study population (Table A1, appendix). The incidence rate of the most common AEs of fatigue, back pain, constipation, and arthralgia were each lower with enzalutamide than placebo; among specific AEs, rates of hypertension (11 vs. 8 per 100 patient-years) and cardiac AEs (19 vs. 15 per 100 patient-years) were higher with enzalutamide, which was consistent with findings in the full population (Table A1, appendix).

Subsequent Therapies

More patients in the placebo arms of the nonvisceral and visceral subgroups received chemotherapy (either docetaxel or cabazitaxel) as the first subsequent therapy after progression (Table 3).

Discussion

The PREVAIL trial included patients with visceral disease who were asymptomatic or minimally symptomatic, had ECOG PS of 0 or 1, and were chemotherapy naïve. Men in the placebo arm also represent the first prospectively followed group with CRPC and visceral disease stratified by specific anatomical site to be reported.

It is important for clinicians to understand how the subgroup of men with baseline visceral disease located at common sites of metastasis did with second-line hormone therapy prior to chemotherapy. A prior analysis showed that enzalutamide versus placebo reduced the risk of rPFS but not OS in the 204 PREVAIL patients with baseline visceral disease at any site.[17] Our analysis extends these findings by assessing enzalutamide efficacy specifically by the site of metastasis. Although patients with liver metastases had delayed radiographic progression and improvements on all progression and response endpoints, including complete responses in two (6%) patients, enzalutamide treatment did not improve OS in that subset. The lack of an effect on survival may have been because of the small number of patients with liver metastases in PREVAIL.

We focused on subsets of patients with liver and lung metastases because these were the most common sites of visceral disease, and we determined that these sites affected rPFS and OS, as well as secondary and exploratory endpoint measures. Patients with liver metastases had a distinctly worse outcome than those with lung metastases. Moreover, patients with lung-only visceral metastases had outcomes similar to patients without any visceral metastases and the overall PREVAIL study population.[5] These findings confirm the poorer prognosis associated with liver metastases regardless of enzalutamide or placebo treatment, which is consistent with prior reports for other agents.[3,4,8,9] We observed that a significant proportion of patients in the visceral and nonvisceral placebo arms were able to receive treatment with chemotherapy after progression on study, supporting the initial reasoning that placebo use in this population would not prevent subsequent treatment with chemotherapy.

Our results suggest a need to better understand the underlying biology of metastatic tumors with a predilection to the liver that leads to inferior treatment responses and outcomes in CRPC patients regardless of the treatment prescribed. For those with lung-only metastases, improvements in rPFS, OS, and secondary endpoints were similar to those observed in the overall PREVAIL population. These findings suggest that the category of “visceral disease” should be divided into lung-only and liver and not analyzed separately, at least in this population of chemotherapy-naïve men with mCRPC.

There is limited information on efficacy outcomes for chemotherapy-naïve mCRPC patients with visceral disease treated with systemic therapies other than chemotherapy. In the TAX 327 study, docetaxel plus prednisone improved survival compared with mitoxantrone plus prednisone in men with mCRPC.[10] An updated survival analysis that combined all patients who received chemotherapy in TAX 327 showed that patients with visceral disease (liver or lung sites not specified), who comprised 23% of the overall study population, died earlier than those without visceral disease.[18] A subsequent retrospective analysis that evaluated outcomes by site of visceral disease showed PSA response rates of 22% and 31% in patients with liver or lung metastases and radiographic response rates of 6% and 7%, respectively.[4] In comparison, patients with liver or lung metastases treated with enzalutamide in our analysis had PSA response rates of 51% and 94% and radiographic response rates of 29% and 73%, respectively. Complete responses were observed in individual patients with liver (6%) or lung (11%) metastases. Although the TAX 327 and PREVAIL trial populations and designs are not directly comparable and they were conducted more than a decade apart, our analysis suggests that enzalutamide has substantial clinical activity in chemotherapy-naïve patients with mCRPC with visceral disease, regardless of the site of visceral involvement.

Several strengths and limitations of our analysis should be noted. PREVAIL was the first phase III study of chemotherapy-naïve mCRPC men with minimal or no symptoms to include patients with visceral disease. Liver and lung subsets were prospectively defined in terms of number and sites of involvement as recommended by the Prostate Cancer Clinical Trials Working Group 2.[19] However, because presence of visceral disease (liver and/or lung) was determined radiographically by the treating physician and did not require confirmation by biopsy, it is possible that some of the lesions were not accurately attributed. While enzalutamide was effective in chemotherapy-naïve mCRPC patients with visceral disease, it is likely that other agents that target androgen receptor signaling, such as abiraterone acetate, may also be efficacious. This assertion remains unresolved as the COU-302 study excluded men with visceral disease.[15] Finally, the total number of patients with liver or lung metastases was small compared with the nonvisceral subgroup, and PREVAIL was not designed or powered to detect treatment differences within these subsets. Our interpretations of results must therefore be considered exploratory.

Conclusions

Our analysis has relevance for clinical practice by addressing a knowledge gap in the literature regarding the outcomes of men with asymptomatic or minimally symptomatic mCRPC and visceral disease involving the liver and/or lung who were treated with enzalutamide or placebo. Enzalutamide is a reasonable therapeutic option in such patients and appears to be well tolerated, with a safety profile similar to that observed in the full PREVAIL population. Because of the poorer outcomes in patients with liver metastases than in those with lung metastases observed in this and other studies,[3,4,8,9] it is critical to identify tumor and microenvironment influences that may be responsible. Elucidating the biological differences between metastatic sites of CRPC may enable the development new drug combinations that further improve upon the efficacy of enzalutamide.

Clinical Practice Points

What is already known about this subject? Enzalutamide significantly decreases the risk of radiographic progression and death, delays the initiation of chemotherapy, and improves health-related quality of life in chemotherapy-naïve men with asymptomatic or minimally symptomatic metastatic prostate cancer progressing on androgen-deprivation therapy.

What are the new findings? The PREVAIL trial of the oral androgen-receptor inhibitor enzalutamide versus placebo was unique in that it did not exclude patients with visceral

disease. Our analysis revealed that enzalutamide improved radiographic progression-free survival in patients with liver and/or lung disease.

How might it impact on clinical practice in the foreseeable future? Enzalutamide may be considered to be an active first-line treatment option in patients with metastatic castration-resistant prostate cancer, including those with visceral involvement, delaying the need for chemotherapy.

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Author Contributions

H.M. was responsible for the conceptualization and methodology of the study. J.J.A., S.C., Y.L., C.N.S., J.S.D.B., B.T., J.C., T.W.F., T.B.D., D.P., D.F., S.B.N., H.M., T.M.B., and C.S.H. were responsible for the investigation. J.J.A., S.C., Y.L., C.N.S., J.S.D.B., B.T., J.C., T.W.F., T.B.D., D.P., D.F., S.B.N., H.M., T.M.B., and C.S.H. validated the data. D.P. and D.F. provided the formal analysis, software, and data curation. J.J.A., S.C., Y.L., C.N.S., J.S.D.B., B.T., J.C., T.W.F., T.B.D., D.P., D.F., S.B.N., H.M., T.M.B., and C.S.H. wrote, revised, and approved the manuscript.

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Appendix Captions

Table A1. Summary of AEs in the PREVAIL visceral subgroup (liver and lung subsets combined) and full population.

Figure A1. PREVAIL CONSORT diagram.

Figure A2. Example of complete responses in metastatic castration-resistant prostate cancer patients with a (A) liver lesion and (B) lung lesion at baseline.

Figure Legends

Figure 1 Kaplan-Meier Estimates of Radiographic Progression-Free Survival in Patients with Metastatic Castration-Resistant Prostate Cancer Who Participated in the Phase III PREVAIL Trial and Had Metastatic (A) Liver or (B) Lung Disease

Abbreviations: CI = confidence interval; HR = hazard ratio; IQR = interquartile range; NYR = not yet reached.

Figure 2 Kaplan-Meier Estimates of Overall Survival in Patients with Metastatic Castration-Resistant Prostate Cancer Who Participated in the Phase III PREVAIL Trial and Had Metastatic (A) Liver or (B) Lung Disease

Abbreviations: CI = confidence interval; HR = hazard ratio; IQR = interquartile range; NYR = not yet reached.

Figure 3 Secondary Efficacy Outcomes in the PREVAIL Visceral Subgroups and Full Population

Abbreviations: chemo = chemotherapy; CI = confidence interval; ENZA = enzalutamide; FACT-P = Functional Assessment of Cancer Therapy–Prostate questionnaire; IQR = interquartile range; mets = metastases; NYR = not yet reached; PBO = placebo; PSA = prostate-specific antigen.

Table 1
Click here to download Table: PREVAIL visceral_CGUC Table1_121216.docx

Table 1 Baseline Patient and Disease Characteristics in the PREVAIL Visceral Subgroups and Full Population

Parameter	Liver Metastases		Lung Metastases		Full Study Population	
	Enzalutamide (n = 40)	Placebo (n = 34)	Enzalutamide (n = 58)	Placebo (n = 72)	Enzalutamide (n = 872)	Placebo (n = 845)
Age, median (IQR), years	74.0 (70.0-81.5)	70.0 (65.0-75.0)	73.0 (66.0-78.0)	71.0 (65.0-76.5)	72.0 (66.0-78.0)	71.0 (65.0-77.0)
ECOG PS, n (%)						
0	22 (55)	23 (68)	37 (64)	44 (61)	584 (67)	585 (69)
1	18 (45)	11 (32)	21 (36)	28 (39)	288 (33)	260 (31)
Baseline pain score on BPI-SF Q3, n (%)[a]						
0-1	22 (56)	24 (73)	38 (66)	41 (57)	569 (66)	567 (68)
≥ 2	17 (44)	9 (27)	20 (35)	31 (43)	290 (34)	273 (33)
Median lactate dehydrogenase, U/L (IQR)	204.5 (176.5-307.0)	218.5 (190.0-324.0)	180.5 (154.0-212.0)	190.0 (170.0-221.0)	185.0 (164.0-218.0)	185.0 (164.0-217.0)
Median alkaline phosphatase, U/L (IQR)	112.0 (77.5-168.0)	126.5 (77.0-298.0)	91.5 (71.0-119.0)	89.0 (70.0-131.0)	94.0 (70.0-138.0)	86.0 (68.0-126.0)
Median PSA, ng/mL (IQR)	83.9 (35.5-259.1)	104.3 (30.5-289.7)	70.2 (16.5-152.2)	51.2 (13.7-156.3)	54.1 (17.7-130.9)	44.2 (17.0-132.2)
Median hemoglobin, g/L (IQR)	128.5 (116.5-137.0)	127.0 (120.0-134.0)	130.0 (121.0-137.0)	130.0 (124.0-139.0)	130.0 (123.0-138.0)	131.0 (123.0-138.0)

Median albumin, g/L (IQR)	37.5 (36.0-41.5)	37.0 (35.0-39.0)	39.0 (36.0-41.0)	38.0 (36.0-40.0)	38.0 (36.0-40.0)	39.0 (36.0-40.0)
Median Gleason score (IQR)	8.0 (7.0-9.0)	7.0 (7.0-9.0)	7.0 (7.0-8.0)	7.0 (7.0-9.0)	8.0 (7.0-9.0)	8.0 (7.0-9.0)
Gleason score ≥ 8 at initial diagnosis, n (%)[a]	22 (56)	15 (47)	21 (38)	34 (49)	424 (51)	423 (52)
Bone disease, n (%)	34 (85)	27 (79)	46 (79)	57 (79)	741 (85)	690 (82)
> 20 bone metastases, n (%)	10 (25)	13 (38)	7 (12)	14 (19)	145 (17)	150 (18)
Measurable soft-tissue disease, n (%)	34 (85)	30 (88)	37 (64)	50 (69)	396 (45)	381 (45)
Baseline use of corticosteroids, n (%)	3 (7.5)	2 (5.9)	3 (5.2)	2 (2.8)	35 (4.0)	36 (4.3)
Prior antiandrogen use, n (%)	36 (90)	31 (91)	46 (79)	64 (89)	760 (87)	730 (86)
Prior radical prostatectomy, n (%)	12 (30)	8 (24)	15 (26)	14 (19)	226 (26)	225 (27)

Abbreviations: BPI-SF Q3 = Brief Pain Inventory Short Form question 3; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IQR = interquartile range; PSA = prostate-specific antigen.

[a]Some patients had missing baseline values. Percentages were calculated based on all patients with baseline values.

Table 2
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Table 2 Duration of Study Drug Treatment in the PREVAIL Visceral Subgroups and Full Population

Parameter	Liver Metastases		Lung Metastases		Full Study Population[a]	
	Enzalutamide (n = 40)	Placebo (n = 34)	Enzalutamide (n = 58)	Placebo (n = 72)	Enzalutamide (n = 871)	Placebo (n = 844)
Duration of treatment, months						
Median (IQR)	9.6 (3.6-17.6)	3.4 (2.1-4.4)	15.5 (10.6-20.4)	3.9 (2.1-6.9)	16.6 (10.1-21.1)	4.6 (2.8-9.7)
Mean (SD)	10.5 (8.15)	4.8 (4.67)	15.6 (8.21)	5.3 (4.32)	15.8 (7.64)	7.0 (6.05)
Patients with ≥ 12 months of treatment duration, %	32	8.8	55	4.2	68	18
Treatment ongoing at data cutoff date, %	20	0	36	2.8	42	7.2
Median OS follow-up, months (IQR)	22.9 (17.4-27.2)	25.1 (20.5-27.8)	22.8 (18.2-29.2)	23.6 (20.9-27.5)	22.2 (18.5-26.7)	22.4 (18.5-26.4)

Abbreviations: IQR = interquartile range; OS = overall survival; SD = standard deviation.

[a]One patient in each treatment group was enrolled but never treated.

Table 3
Click here to download Table: PREVAIL visceral_CGUC Table3_121216.docx

Table 3 All Subsequent Postbaseline Antineoplastic Therapy Use for Metastatic Castration-Resistant Prostate Cancer in PREVAIL

Parameter	Nonvisceral Subgroup (n = 1513)		Visceral Subgroup (n = 204)	
	Enzalutamide (n = 774)	Placebo (n = 739)	Enzalutamide (n = 98)	Placebo (n = 106)
Patients with ≥ 1 postbaseline therapy listed below, n (%)	307 (40)	516 (70)	44 (45)	78 (74)
Antineoplastic therapy, n (%)				
Abiraterone acetate	157 (20)	340 (46)	22 (22)	45 (43)
Cabazitaxel	40 (5.2)	93 (13)	11 (11)	17 (16)
Docetaxel	255 (33)	412 (56)	31 (32)	67 (63)
Enzalutamide	5 (0.6)	29 (3.9)	4 (4.1)	8 (7.5)
Sipuleucel-T	11 (1.4)	7 (0.9)	1 (1.0)	3 (2.8)
Patients taking ≥ 1 investigational drug, n (%)	38 (4.9)	69 (9.3)	4 (4.1)	12 (11)

Figure 1

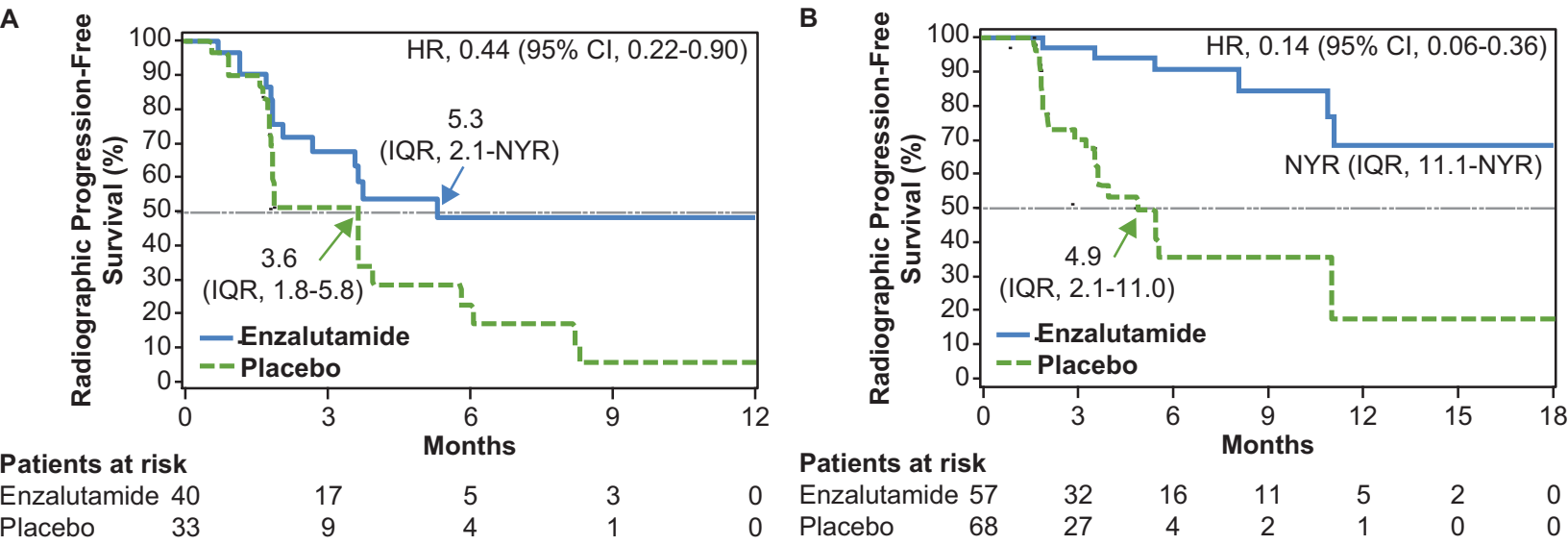
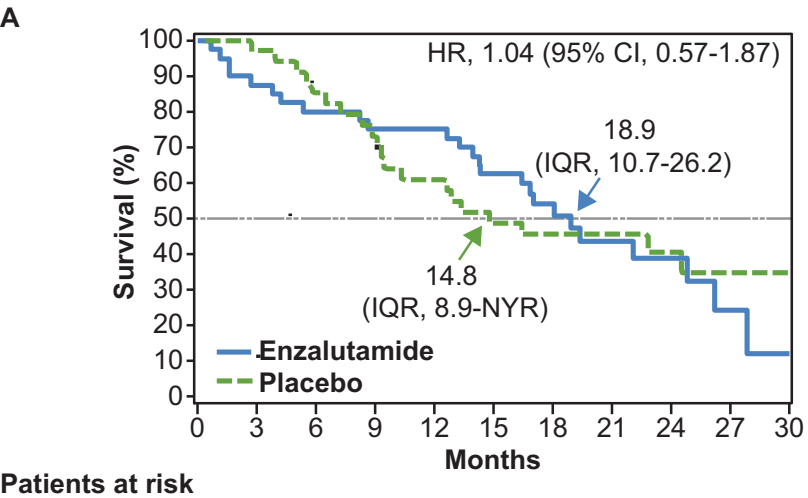

A
Radiographic Progression-Free Survival (%)
HR, 0.44 (95% CI, 0.22-0.90)
5.3
(IQR, 2.1-NYR)
3.6
(IQR, 1.8-5.8)
Enzalutamide
Placebo
Months
Patients at risk
Enzalutamide 40 17 5 3 0
Placebo 33 9 4 1 0
B
Radiographic Progression-Free Survival (%)
HR, 0.14 (95% CI, 0.06-0.36)
NYR (IQR, 11.1-NYR)
4.9
(IQR, 2.1-11.0)
Enzalutamide
Placebo
Months
Patients at risk
Enzalutamide 57 32 16 11 5 2 0
Placebo 68 27 4 2 1 0 0

Figure 2


A
HR, 1.04 (95% CI, 0.57-1.87)
18.9
(IQR, 10.7-26.2)
14.8
(IQR, 8.9-NYR)
Enzalutamide
Placebo
Survival (%)
Months
Patients at risk
Enzalutamide 40 35 32 30 30 25 16 9 6 3 0
Placebo 34 33 28 24 20 16 14 11 8 5 0

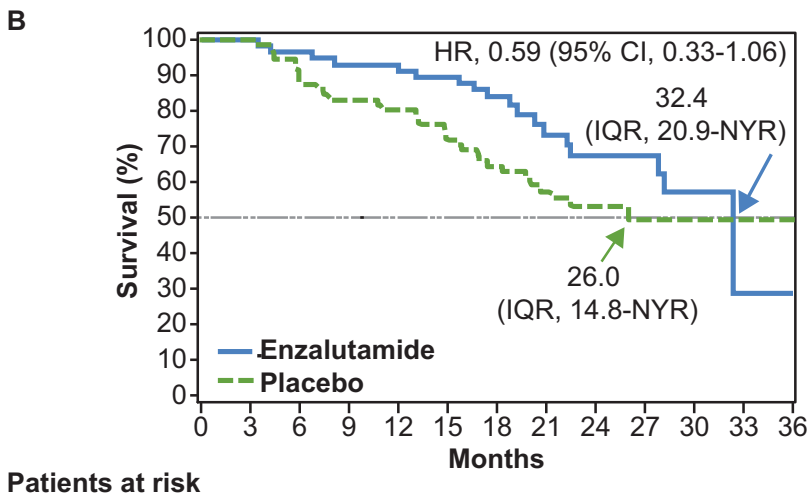
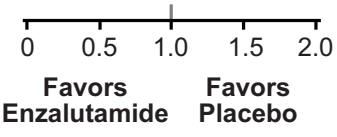

B
HR, 0.59 (95% CI, 0.33-1.06)
32.4
(IQR, 20.9-NYR)
26.0
(IQR, 14.8-NYR)
Enzalutamide
Placebo
Survival (%)
Months
Patients at risk
Enzalutamide 58 57 55 53 53 51 40 26 19 13 6 0 0
Placebo 72 71 63 59 57 51 40 30 19 10 5 1 0

Figure 3

	Patients, n ENZA/PBO	Median, mo (IQR) ENZA	Median, mo (IQR) PBO	Hazard Ratio (95% CI)
Time to initiation of chemo - liver mets	40/34	20.7 (10.4-NYR)	5.5 (3.2-15.4)	0.37 (0.19-0.71)
Time to initiation of chemo - lung mets	58/72	26.0 (15.0-NYR)	8.5 (5.0-15.0)	0.25 (0.15-0.43)
Time to initiation of chemo - full population	872/845	28.0 (15.3-NYR)	10.8 (4.9-28.8)	0.35 (0.30-0.40)
Time to PSA progression - liver mets	40/34	8.3 (5.6-11.1)	3.0 (2.8-3.7)	0.25 (0.11-0.56)
Time to PSA progression - lung mets	58/72	14.5 (8.3-24.8)	2.8 (2.8-3.7)	0.11 (0.06-0.22)
Time to PSA progression - full population	872/845	11.2 (5.7-NYR)	2.8 (2.8-4.6)	0.17 (0.15-0.19)
Time to FACT-P decline - liver mets	40/34	22.0 (2.8-NYR)	3.0 (1.0-11.1)	0.47 (0.22-1.00)
Time to FACT-P decline - lung mets	58/72	11.1 (2.7-22.1)	5.6 (2.8-13.8)	0.65 (0.37-1.15)
Time to FACT-P decline - full population	872/845	11.3 (2.8-NYR)	5.6 (2.7-16.6)	0.62 (0.54-0.72)



Appendix

Table A1 Summary of AEs in the PREVAIL Visceral Subgroup (Liver and Lung Subsets Combined) and Full Population

Parameter	Visceral Subgroup, n (%)		Full Study Population, n (%)[a]	
	Enzalutamide (n = 98)	Placebo (n = 106)	Enzalutamide (n = 871)	Placebo (n = 844)
AE, n (%)				
Any AE	94 (96)	98 (93)	844 (97)	787 (93)
Any grade 3-4 AE	47 (48)	38 (36)	374 (43)	313 (37)
Any serious AE	35 (36)	33 (31)	279 (32)	226 (27)
Most common AEs[b]				
Fatigue	28 (29)	26 (25)	310 (36)	218 (26)
Back pain	25 (26)	24 (23)	235 (27)	187 (22)
Constipation	26 (27)	20 (19)	193 (22)	145 (17)
Arthralgia	17 (17)	12 (11)	177 (20)	135 (16)
Specific AEs				
Hypertension	11 (11)	4 (3.8)	117 (13)	35 (4.1)
Cardiac AEs	12 (12)	7 (6.6)	88 (10)	66 (7.8)
Alanine aminotransferase elevation	2 (2.0)	2 (1.9)	8 (0.9)	5 (0.6)
Seizure	0	1 (0.9)	1 (0.1)[c]	1 (0.1)
AE, event rate per 100 patient-years of exposure				
Fatigue	28.8	50.0	29.9	43.0
Back pain	26.1	53.9	23.6	42.5
Constipation	25.3	40.4	18.5	28.4
Arthralgia	20.9	23.1	18.6	29.5
Hypertension	11.3	7.7	10.8	6.6
Cardiac disorders	19.2	15.4	10.3	14.8

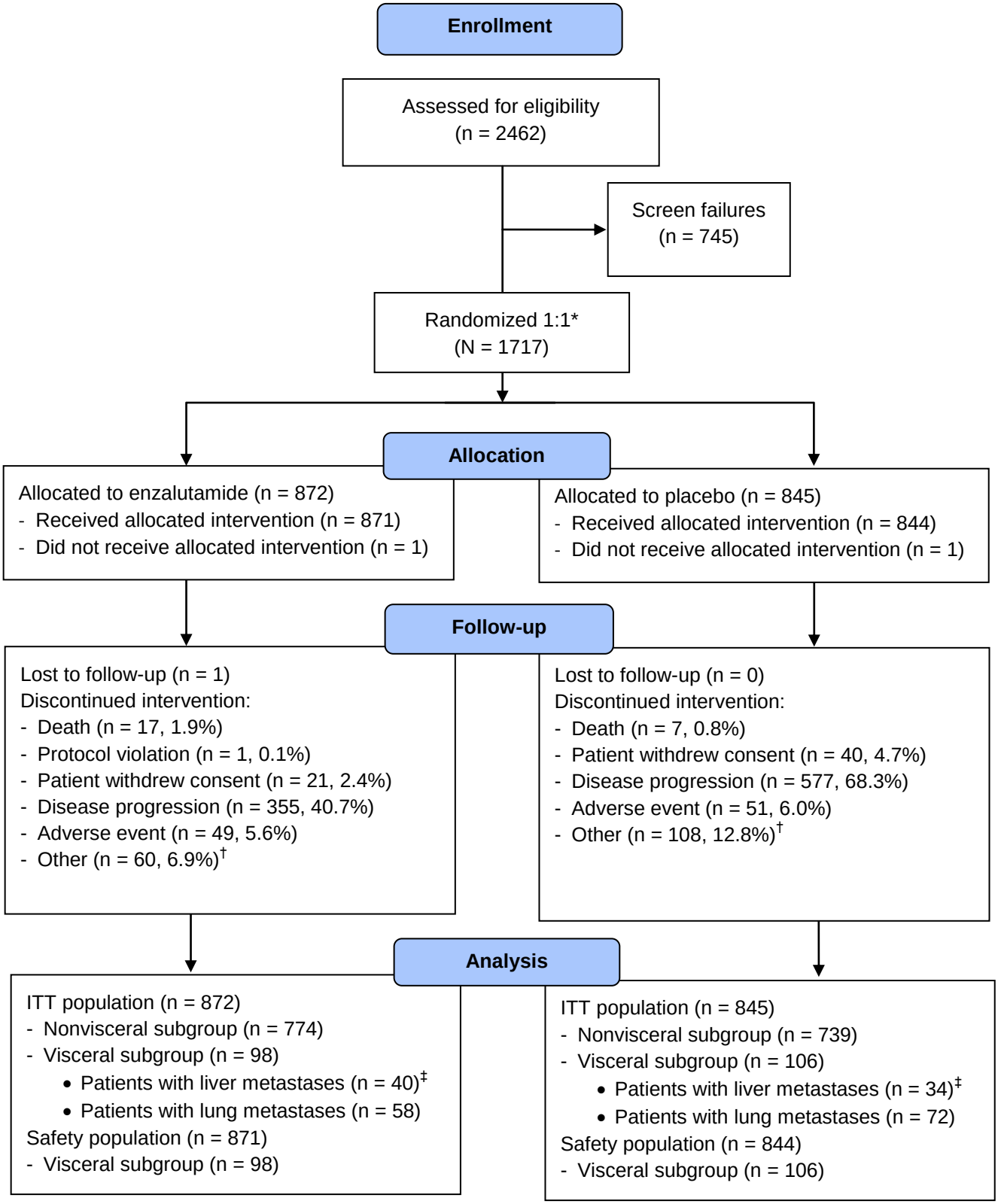
Abbreviation: AE = adverse event.

[a]One patient in each treatment group was enrolled but never treated.

[b]At least 20% on enzalutamide and ≥ 2% more than placebo in the safety population.

[c]This seizure occurred after the data cutoff date.

Figure A1 PREVAIL CONSORT Diagram



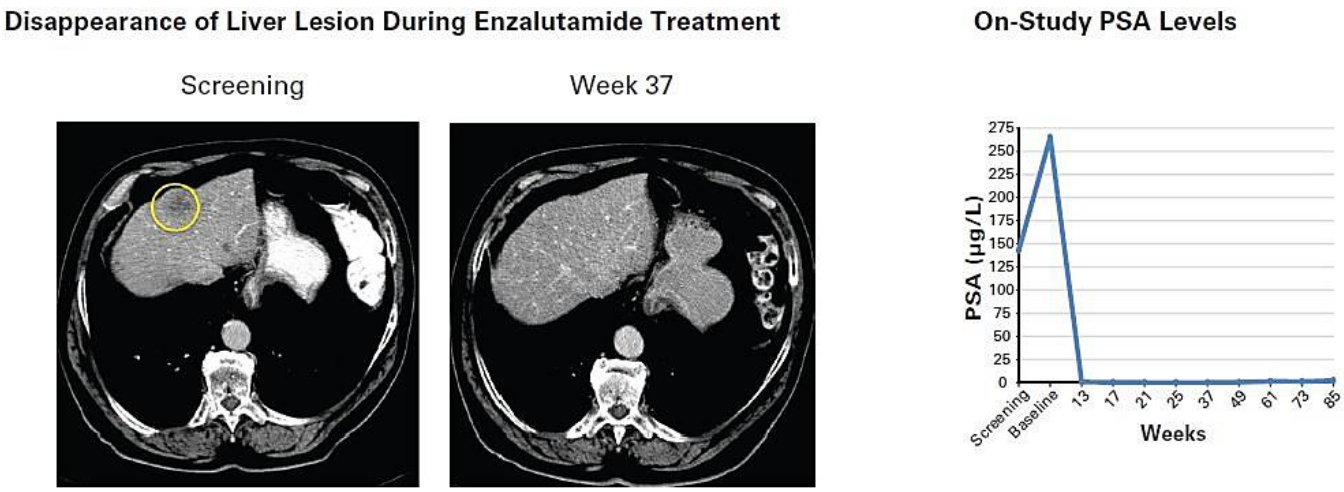
*Randomization was stratified by study site.

†Majority discontinued due to rising prostate-specific antigen.

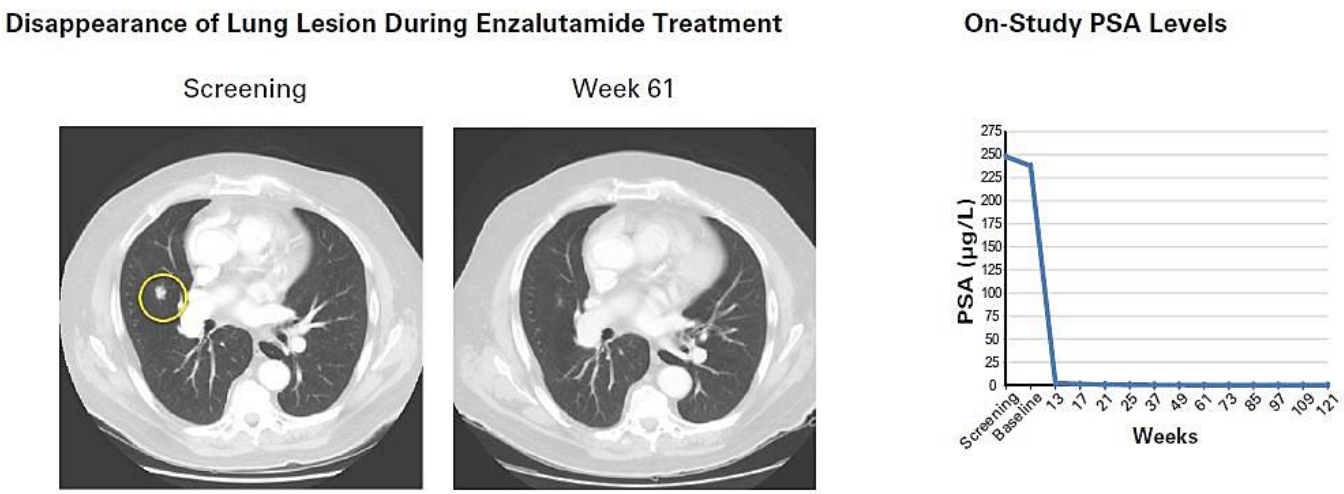
‡Liver only or liver and lung metastases.

Figure A2 **Example of Complete Responses in metastatic Castration-Resistant Prostate Cancer Patients with a (A) Liver Lesion and (B) Lung Lesion at Baseline**

A



B



Abbreviation: PSA = prostate-specific antigen.